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Biotechnology for control of growth and product quality in meat production: implications and acceptability

Proceedings of an International Symposium,
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P. van der Wal, G.M. Weber & F.J. van der Wilt (Editors)

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The work of the **chairmen and discussion moderators** greatly contributed to the symposium and made the drafting of the conclusions of the various sessions possible on the spot.

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The technical assistance of the **staff of the American Society of Animal Science and of Wageningen Agricultural University** in preparing and organizing the symposium has been of great importance and was accordingly appreciated.

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SCOPE OF THE SYMPOSIUM

Meat producing animals have, since their domestication, changed dramatically in their capacity for providing high quality products in an efficient way. Systematic breeding proved to be a successful tool in selecting for physiologically more efficient animals.
Biotechnology offers for the first time opportunities for controlling the efficiency of growth and the quality of the products in a more direct and selective way. A range of interrelated technologies is emerging, affecting the same endogenous mechanisms. In several symposia it has been demonstrated that the technologies have unprecedented potential for efficient, safe and sustainable production of animal products, provided that the proper choices are made.
The participation of the scientific world seems to be more needed then ever in plotting the right course through this field of promising possibilities, while avoiding the pitfalls in the road to the future. An adequate communication with both producer and consumer is essential for playing this role in an effective and credible way.

The implications and the acceptability of the emerging technologies, have been analyzed for swine production in an international symposium in Wageningen in the Netherlands in December 1988. Research in the field has intensified since, and has increasingly covered other meat producing animals as well.
Participants and sponsors of the Wageningen symposium felt that a follow up, largely based on the same organizational approach, should cover these recent developments.
The European Association for Animal Production (EAAP) and the American Society of Animal Science (ASAS) decided to adopt the symposium as a joint venture, together with their Australasian counterpart (AASAS). Support for the concept has been received from the European Community (EC-DG XII), the Food and Drug Administration of the USA (FDA-CVM), the United States Department of Agriculture (USDA) and from the Biotechnology Industry.

An international scientific consensus on relevant questions and answers on key issues for public and regulatory acceptance of the new technologies forms the main objective of the symposium. Such a scientific consensus is probably a prerequisite for harmonizing standards in international trade and for providing a sound base for consumers perception. The symposium offers as well an opportunity for identifying targets for int ernational cooperation in research, which is increasingly necessary for meeting the challenge of these technologies adequately.

To facilitate intense scientific communication among participants, a compact symposium is organized , with a limited number of invited participants.
For the scientific coherence of the program, it is focused on biotechnologies affecting the somatotropin axis. Three approaches are here under development, viz. via genetic impact, via the administration of the constituents of the axis (somatotropin, its releasing factor, insulin like growth factors) and via immunomodulation of these factors.
Because of the common denominator in the mode of action these technologies show commonalities in impact on efficacy and safety aspects as well. The program puts special emphasis on safety for man, target animals and environment and on the perception of these key aspects in acceptability. The socioeconomic implications are discussed from various points of view.

SESSION I
PERSPECTIVES OF INTRODUCING BIOTECHNOLOGY IN MEAT PRODUCTION

* Introductory Statement
* Perspectives for introduction
* Technical perspectives
* Global regulation and acceptability

SUMMARISED AND ADOPTED CONCLUSIONS FROM PAPERS AND DISCUSSION

ON

PERSPECTIVES OF INTRODUCING BIOTECHNOLOGY IN MEAT PRODUCTION

Chairman:

A. A. M. van Agt, *Head Delegation of the European Communities to the United States*

Conclusions drafted and presented:

P. van der Wal, *Agricultural University Wageningen*

- *The **demand for more and better food will rapidly be increased** by the expected growth of the world population to 15 billion in the first half of the next century. The available acreage of land for food production is limited and overused already in many regions.*

  Biotechnology is an indispensable tool for meeting the resulting challenges for food production by:
  - *Increasing the efficiency in using land and its products.*
  - *Improving product quality and safety of food.*
  - *Decreasing the threat for environmental pollution with nitrates, methane and carbon dioxide.*

- *An* **effective control of the Somatotropin -IGF axis** *in food producing animals can lead to a more efficient production of better, in particular leaner products. Potentially effective strategies to achieve these objectives are:*
  - *Intrinsic: Advanced marker assisted breeding and production of transgenic animals.*
  - *Extrinsic: Administration of Somatotropins, Growth Hormone releasing Factors (GRF) or Insulin like Growth Factors (IGF). Immunomodulation of the potency of these constituents.*

- *A* **global approach to regulation and acceptability** *aspects is necessary:*
  - *For creating mutual confidence between consumers and producers.*
  - *To remove unjustified trade barriers.*
  - *To promote uniform control of use of new technologies.*

- *In a global approach a* **common reference point for governments, producers, industry and consumers** *can be found in the FAO / WHO Codex Alimentarius Commission.*

  Providing advice and assistance in developing countries in this field is of particular relevance, especially in the area of livestock production where these countries can benefit greatly.

INTRODUCTORY STATEMENT

A.A.M. van Agt

Head of Delegation of the Commission of the European Communities to the United States, Washington D.C., USA

It is my pleasure to chair the introductory session of this important international conference. Faced with the formidable expertise of the speakers who will be following me. I shall not make any attempt to introduce the scientific and technical aspects of biotechnology in animal production; but will seek, rather, to set these in a wider context.

It is a particular pleasure to participate in a conference whose programme chairman is our conference president, Dr. Charles Hess. Prior to his summons to Washington by the present administration, Dr. Hess was Dean of the University of California at Davis, an internationally reputed centre for agricultural research. I am tempted to say it is probably the second-best agricultural university in the world; for if I wasn't wearing my "European" hat, I would recall that in my native land, we have an Agricultural University at Wageningen whose reputation and excellence are second to none, and whose skills underpin the quality and competitiveness of Dutch agricultural exports, which in so many sectors are indisputably the finest of the world - but I digress. If you want to know more about Wageningen, ask Peter van der Wal.

In fact our statisticians tell me that the European Community is number two in agricultural exports, behind the United States - but to quote the slogan of a well-known American car-hire firm, "We're Number 2 - we try harder". Incidentally, on agricultural imports, we are number 1 - but let me not spoil the atmosphere of this friendly conference by discussing who is more agriculturally protectionist - especially not in this delicate final week of the GATT negotiations.

Dr. Hess amongst his many new duties co-chairs a ***US-EC Task Force on Biotechnology Research,*** which held its first meeting here in Washington just three months ago. That Task Force was the brainchild of European Commission Vice-President Filippo Pandolfi, and of President Bush's Science Advisor Dr. Allan Bromley. The success of the first meeting has underlined the growing extent of our common interest in scientific exchange and collaboration, particularly in a fast-moving, inter-disciplinary field such as biotechnology. The natural internationalism of scientific endeavour is a model which we should seek to extend into other fields of international relations and cooperation, by no means limited to EC and US, but extending to the wider global community. It is one of the strengths of this conference that so many different nations are represented here today.

The subject of our conference is one which has been associated with controversy, and no doubt will continue to be so. It represents one of the leading edges where the impressive progress of science and technology comes into contact, possibly into conflict, with traditional agricultural practices and with the conservatism and natural suspicion of the consumer. Many of our fellow-citizens, on ***both sides of the Atlantic, are ambivalent about biotechnology,*** and it is important for political leaders to be aware of that ambivalence, and to address it constructively.

On the positive side, nobody considering the long-term, global balance of food supply and demand can doubt the ***vital need for a continuing, sustained effort of agricultural research and biotechnology.*** The latest population projections from the United Nations indicate that, over the next century, the human population may rise to over 14 billion - two-and a-half times our current population. Over the next decade, each year will see an addition of 90 to 100 million people. In both agricultural and health care, biotechnology represents our best hope for coping with these inescapably increasing demands. We are degrading our planet with a current population of 5.7 billion people, many of them living in deplorable conditions of health and nutritional status: how are we to cope with a doubled population, if not by a massive development and application of our knowledge of living systems and their responsible, sustainable management?

In this conference, we bring together many people from diverse backgrounds - politicians, scientists, regulators, consumers. Many of us carry several of these labels simultaneously. Let us not forget the other essential partner with whom the farmer has to work, and on whose efforts we depend: the food animal. The ***cow*** in particular is ***a most remarkable example of biotechnology***: one of the Commission's early study reports describes her as a ***"mobile, edible, self-reproducing fermenter".*** Throughout much of human history, we have depended on ruminants, on the cellulase enzymes in the microbes of the rumen, to give us access to that great proportion of the world's biomass which is produced as cellulose. As the prophet Isaiah precisely expressed it, "All flesh is grass". In the cow or elsewhere, we can admire nature as our exemplar in biotechnology; we can learn much from her, and we can seek continually to improve upon or to adapt her, to shape the world and its flora and fauna more precisely to human needs. But we need also to reflect upon limits and constraints.

In Europe, we are currently considering whether and how we should update the 1976 Convention on the **welfare of animals** kept for farming purposes, to take account of modern technological developments. For these tools are sharp, and if misapplied they could be unacceptably hurtful. I am pleased to note that a later session of this conference is devoted to the safety and welfare of the animal; and this is not unrelated to the topic of Session Five, on Social and Consumer Acceptance.

A well-known brand of French cheese is "La Vache Qui Rit": the Laughing Cow. At a practical level, of course the good farmer has every interest in keeping his animals healthy in body and contented in spirit. But as the success of that brand name suggests, the consumer, too, is increasingly interested in the methods and conditions of production of his food. From what we have seen of biotechnology so far, there is no reason to fear that it will raise any new issues of animal welfare, and indeed ample potential for it to improve welfare if properly used. But biotechnology must certainly observe all the existing laws and constraints, and precisely because it is a new and powerful technology, it raises concerns and suspicions which the scientist should not too hastily dismiss as irrational.

I have emphasised the ***beneficial potential of biotechnology,*** our essential need for it; yet at the same time, as with any powerful technology, we have to learn how to manage it, to maximise the benefits, and to ***identify and limit any unwanted side effects.***

This societal learning is a slow business. The scientists and innovators will be impatient of restraint and delay, and indeed both global human needs and our economic interest in

competitiveness argue for maximum speed. Biotechnology's safety record is so far excellent. But we have to carry public opinion with us. At an aggregate level, of course there is a continuing and worldwide progressive accumulation of knowledge, and a resultant continuous stream of innovations seeking to come on the market. Yet not every innovation will succeed, as commercial entrepreneurs know too well; and not every innovation **should** succeed, if it goes beyond the limits of welfare and acceptability.

The "limits of acceptability" is a vague phrase, for which I do not apologize; the reality is volatile, and acceptability may be influenced by many factors. Among the most important of the ***factors affecting acceptance are trust, confidence and understanding.*** These factors cannot be bought. They must be earned, patiently, through habits of ***comprehensible communication, transparency and dialogue.***

I am delighted to see that this commitment is obviously shared by the organisers of this conference, and I congratulate them on that. This conference comes at a time of great international negotiations on trade, with the inevitable accompanying tensions; it comes at a crucial time for the acceptability of new biotechnological methods in agriculture; it is held in the capital city of the most powerful nation on earth. It is therefore very much in the spotlight of public attention, and will command a worldwide audience. If the performance of the coming speakers and the participation of the audience can live up to these high hopes and expectations, this conference can do a great deal of good.

PERSPECTIVES OF INTRODUCING BIOTECHNOLOGY IN MEAT PRODUCTION

Charles E. Hess,

U.S. Department of Agriculture, Washington, D.C., U.S.A.

Summary and Conclusions

The world has a constant need for more and better food. This is a simple and yet easily forgotten fact. The USDA Economic Research Service projects that world population will reach 7,2 billion by 2010. Population is increasing; prime agricultural land is not. More and more, we will rely on technology for necessary increases in productivity.

Previously existing methods of gene transfer have been used for thousands of years to alter animals to better serve human needs. The new techniques of biotechnology involve no radical departure from historical practices, but simply enable animal breeders to do the same things they have always done - but more quickly, easily, and surely. It is reasonable to expect that the new tools will continue to be used in this same way.

In 1965, Nobel laureate Francois Jacob observed: "A revolution in science is not simply an accumulation of data, a harvest of results, a change in the landscape. It is a change in the way people think, in the way they look at things. It is a change in vision itself."

That kind of change of vision is what we want to bring about. My own experience has been that the more people understand about science the more they feel positive about it - and the better they can "view things in their true relation." What we need to "see clearly," is that the communication of that knowledge is up to us.

When the public is knowledgeable and informed, the word biotechnology in connection with food should not raise a red flag of fear, but rather conjure up thoughts of lower food costs, safer food, more nutritious food supplies, and a healthier environment.

***Keywords**: Biotechnology, meat production, perspective, policy.*

Introduction

The dialogue in this symposium will go a long way toward building an international scientific consensus on the key issues facing the development and adoption of biotechnology for animal production. As members of professional societies, regulatory agencies, government, commodity groups, and trade associations, it is part of our responsibility to get ideas out on the table where they can be examined in the light of day.

In opening this important symposium by talking about "Perspectives of Introducing Biotechnology in Meat Production", I want to remind you that in the dictionary, one of the

definitions of "perspective" is "the ability to see clearly; the capacity to view things in their true relation". That is the kind of vision I hope we can bring to our discussions this week.

Animal production and biotechnology

Since the late 1970's, global production of meat products has increased by approximately 26 percent, and in general, prospects for the future continue to point to large meat supplies, with slight increases in production. In the April-June 1990 issue of USDA's National Food Review (13:2), Vocke reports that as incomes increase in countries around the world, so does the demand for a higher quality diet, often including animal products.

In the United States, animal products have always been a mainstay of the diet. The National Academy of Sciences 1988 publication "Designing Foods: Animal Product Options in the Marketplace" states that about 36 percent of the food energy - and between 36 and 100 percent of each of the major nutrients - in the U.S. food supply come from animal products.

For centuries, people have sought to improve animals and the food products from them by selecting and breeding only the best. Throughout history, humans have taken advantage of genetic diversity and genetic exchange through breeding to develop animals that grow bigger, produce more, provide leaner and better quality products, use resources more efficiently, show increased fecundity, or demonstrate resistance to disease and stress.

The various tools placed at our disposal by biotechnology do not change these purposes. Instead, they offer new techniques for modifying biological traits in a much more directed manner than is possible with conventional animal breeding. The new tools also enable us to ask questions and find answers in a way that was not possible in the past.

Externalities

Yet, if biotechnology offers us such wonderful possibilities, why do we hold symposia such as this one to continue to discuss its implications and acceptability?

Over the years, I have concluded that if we truly want to understand the motivating forces at work in improving animal agriculture and its products, we need to go beyond a simple preoccupation with science. There are powerful outside forces - what the economists call "externalities" - which often have both positive and negative effects upon agricultural research and its use.

These externalities affect not only the way in which we do our work, but what work we decide to do. Research and production policies are not formulated in any pure and solitary test tube. They spring from the messy and often disorderly real world of conflicting demands and unclear choices. We no longer operate - in fact, we probably never really did - in isolation from an increasingly concerned public. Our course is continually influenced by the changing winds of public opinion and national and agricultural policy.

PERSPECTIVES FOR INTRODUCTION

There are a variety of public concerns which we must address and take into account if we are to "see clearly" what the perspectives are for introducing biotechnology in meat production and to understand the impact of these larger issues.

Environment

Having just observed the 20th anniversary of Earth Day this year, the environment is very much in our collective consciousness. More and more, we are aware of its influence on us, as well as our own impact on it.

One example which is causing a certain amount of amusement in the press is the role of livestock in global climate change. Along with flooded rice fields and termites, livestock is one of the major agricultural contributors of methane into the environment. This could be an important factor in greenhouse gas accumulation because methane traps 20 times more heat energy than carbon dioxide. To help alleviate this, it may be possible to genetically modify ruminant micro-organisms to shunt methane into energy (thus improving animal production efficiency) rather than releasing it as a gas.

Furthermore, through tools such as genetic engineering and embryo transplants, animals can be bred to be stress-resistant, thereby enabling them to live in different or less hospitable climates. This ability may become even more important as we get a better understanding of the potential impacts of global climate change, and it is already relevant in some of the less developed nations which experience droughts and other climate extremes.

Another environmental example which springs to mind involves bovine somatotropin (bST). Excellent progress has been made by using biotechnology to produce commercial quantities of growth hormones and other proteins which are essentially identical to substances naturally produced in the animal. Bovine somatotropin can improve the efficiency of dairy cows by improving the milk-to-feed ratio by 5 to 15 percent.

The use of bST does not necessarily mean more milk. It can mean the same amount of milk with fewer cows - and therefore fewer waste disposal problems. This helps alleviate ground water contamination. In Holland, for example, the disposal of animal manure is a major problem, and one which could be helped through the environmentally beneficial effects of bST.

Competitiveness

Fewer cows would also mean fewer feed requirements and lower production costs, thus helping farmers to compete in world markets. The way for any country to remain competitive in the international marketplace is to reduce production costs and enhance product quality, and we need every ounce of careful management and efficient resource use we can muster to make this possible. We will have to compete on the basis of our technology - including biotechnology. In addition, as we increase efficiency in a free market system, the ultimate beneficiary is the consumer who will enjoy food at a lower cost.

Another example in which the tools of biotechnology are being used to increase efficiency is the ability to predetermine the sex of offspring. This offers the livestock industry greater flexibility and faster genetic improvement of offspring. Scientists working for USDA's Agricultural Research Service (ARS) at Beltsville are making good progress in accurately predicting sex ratios by the analysis of the DNA of sorted sperm, thus moving us closer to a practical method for sexing livestock semen.

Disease diagnosis and prevention

In the search for efficiency of production, biotechnology is useful in the improved diagnosis, control, and eventual eradication of animal diseases. The Office of Technology Assessment (OTA) of the U.S. Congress calculates that animal diseases cost American agriculture $17 billion each year.

One way of applying biotechnology to animal health is through improved diagnostic tools. Specific and unique segments of the chromosomal DNA from disease-causing organisms have been identified, cloned, and produced in large numbers. These labelled DNA fragments, or probes, can be used to determine the presence of disease organisms in animal tissues or fluids. More sensitive and rapid than conventional isolation and typing methods, these probes have been successfully applied to various important livestock diseases such as anaplasmosis, a disease of cattle which causes deaths, abortions, and weight loss - and leptospirosis, a disease which causes abortion and other reproductive failures in cattle and swine. Earlier diagnosis right on the farm, rather than sending specimens to distant laboratories, means many important diseases will be discovered at the earliest stages, when they can be treated without large applications of drugs and chemicals.

Control of disease is also important in improving the safety of the food supply. ARS research demonstrates that it is possible to identify swine with a genotype that is resistant to trichinosis. With further research, this genotype could be incorporated into domestic swine populations.

Health and nutrition

These possibilities lead us into health and nutrition. No where else is there a clearer demonstration of the impact of externalities - in this case public opinion/choice - on an industry, or on the science supporting that industry, than the current public obsession with diet and health. Look at the impact of the concern over cholesterol on the sale of eggs or the amount of shelf space devoted to lowfat milk. This is both a challenge and an opportunity.

I mentioned earlier the many nutrients in the food supply - a major portion of the dietary protein, calcium, phosphorous, essential amino acids, trace minerals and vitamins - that come from animal products. But they also contribute more than half the total fat, nearly three-fourths of the saturated fatty acids, and all of the cholesterol - dietary components that may increase the risk of heart disease and cancer for some individuals.

Dr. Perry Adkisson, Chancellor of the A&M University System, and this year's Hatch Lecturer at the recent meeting of the National Association of State Universities and Land Grant Colleges (NASULGC) in Kansas City, MO, spoke on the topic "Warning: Eating May be Harmful to Your Health." He urged animal and plant scientists to work more closely with nutritionists and physicians to design foods for health. Earlier, I referred to the National Academy of Sciences report on "Designing Foods: Animal Product Options in the Marketplace." It suggests a research agenda to turn the *challenge* of the growing recognition of the important role of diet in human health into an *opportunity* to design and market foods which address health concerns. Biotechnology holds great promise for the development of foods to meet dietary and health goals by improving the nutritional attributes of animal products.

Another naturally occurring hormone that has been produced, porcine somatotropin (pST), may help to improve human health, while at the same time lowering the farmer's cost of production. Porcine somatotropin not only improves the feed efficiency in hogs by 15 to 35 percent - but, perhaps more importantly in this age of health consciousness, it increases protein deposition and reduces fat deposition, allowing pST-treated hogs to provide consumers with leaner cuts of pork. This ability to produce lean pork has enormous implications for improving human health by reducing dietary fat and cholesteról.

Animal genome mapping

As was emphasized in the study put out in 1987 by the National Research Council's Committee on a National Strategy for Biotechnology in Agriculture, gene mapping is essential as the foundation for genetic manipulation. Thus far, however, identifying, isolating, or mapping genes of significance to animal agriculture has received less attention than has been given to plant genome mapping.

ARS and the Cooperative State Research Service (CSRS) are attempting to remedy that. They have provided funds to establish a U.S. Committee on Conservation of Animal Germplasm, with subcommittees on Germplasm Conservation and Mapping the Animal Genome.

The mapping of animal genomes (85 percent of those in cattle and swine are identical to those in the human) will permit evaluation of genes that regulate animal traits and enable farmers to produce quality animals in an efficient, competitive, and environmentally sensitive way.

Policy context

These are only a few examples of what biotechnology could mean for animal agriculture. But what can we do to ensure that biotechnology reaches its full potential? I would like to conclude by discussing two concepts which are key to the future of biotechnology - effective regulation and public acceptance.

Effective regulation

From one perspective, effective regulation and public acceptance are two ways of saying the same thing. In my experience, people fear the unknown. Thus, we must ensure that our systems of oversight are as visible as possible, so that the public has a chance to understand what we are doing to ensure their safety and protect the environment.

In the United States we are working on a uniform scope for our coordinated framework of regulatory oversight and are developing guidelines for field testing genetically modified organisms. We view these as critical steps in developing a regulatory structure based on sound scientific principles, in which oversight is commensurate with the level of risk.

One goal of these discussions is to strengthen public confidence that science is being pursued safely and that the products of agricultural biotechnology, like the products of other technologies, meet the three accepted regulatory criteria of safety, efficacy, and quality. But an equally important goal of these scope discussions is to ensure that we do not create a burdensome system of oversight for biotechnology which stifles innovation and requires scientists to provide unnecessary paperwork on projects we already know, through long experience, are really very safe.

This is a difficult balance to achieve, but I am confident we in the United States will continue to make it work. I hope the European Community and the rest of the world will join us in this endeavour, and avoid injecting non-scientific elements into the regulatory framework for biotechnology, The effects of establishing a fourth criterion - socio-economic need - for bST and possibly other products would be profoundly negative, not just on animal biologics, but on all biotechnology research.

Would private firms, or for that matter, governments, pursue research programs if the resulting products might be rejected because of perceived social or economic concerns? My bet is that most would not and that many promising advances would be lost to society. While we must take social and economic issues into account, we cannot allow them to bring the advancement of science and technology to a grinding halt.

Adding a fourth criterion would also inevitable lead to continued trade disputes as each new product comes up for review. The U.S. goal in the current Uruguay round of talks on the General Agreement on Tariffs and Trade (GATT) is to help build a global trading system in which merchants of all nations can sell agricultural products, including safe and effective products of biotechnology, with a minimum of restriction and with every transaction subject to the same rules. Such a system of harmonized standards would be a strong incentive for research and development of biotechnology.

Public acceptance

To my mind, the single most critical issue confronting biotechnology is the anxiety of a concerned public. And unfortunately, that is often based upon the *perception* of risk rather than the *reality*. Take the recent spate of food scare stories - alar or bST. Here you have public policy being created by actresses and PR firms.

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Part of the answer to this barrage is to improve public education programs to counteract, or better yet, prevent, misinformation. For example, in the area of food safety we need to get across the story that where problems such as microbial contamination and disease-producing bacteria exist, biotechnology offers some exciting new tools for preventing and detecting them - and it can improve food quality at the same time.

As scientists and end users of technology, it is part of our role to get across to the public the facts it needs to make informed decisions in areas like this - to help people look at the big picture - the long term - and weigh the benefits and costs. We must help the public to understand that a genetically engineered cow is still a cow, and that this research is being conducted by responsible scientists operating under a strict and credible system of safety guidelines in the pursuit of biotechnology's benefits.

Our ability to responsibly tap the full potential of technology depends more than we might like to admit on public support - whether it be social, financial, or political. That is why we must recognize and take into account the "external" issues I have outlined.

Fortunately, in the United States, we have a Secretary of Agriculture, Clayton Yeutter, and a President, George Bush, who have a deep appreciation for the role of science. They consistently emphasize research, education, and technology as the means by which agriculture can produce in a socially, economically, and environmentally responsible way.

In fact, in the recent 1990 Farm Bill, there is included a $73 million National Initiative for Research on Agriculture, Food, and the Environment. Of that total, $20 million is directed to research on animal systems, including the genome mapping I mentioned earlier.

Looking at the future, an OTA staff paper on transgenic animals suggests that economic incentives are likely to dictate the order in which different advances are made, with agricultural animals such as livestock and poultry near the front of the line. And in the near term, research will focus on traits involving a single gene - because it is technically simpler than work involving complex traits influenced by more than one gene.

TECHNICAL PERSPECTIVE OF BIOTECHNOLOGY FOR CONTROL OF GROWTH AND PRODUCT QUALITY IN MEAT PRODUCTION

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Summary

Producing leaner, high quality meat to satisfy consumer demands and improve public health is a great challenge to animal agriculture. The same biological propensity for humans to deposit fat makes it difficult to achieve quantum improvements in animal composition. Fortunately, new technologies for identifying, examining and transferring genes have increased our understanding of biological processes and provided unprecedented ability to modify these processes. Administration of exogenous somatotropin to finishing pigs causes desirable changes in performance and composition. Treated pigs grow faster, while eating less, resulting in an increased gain to feed ratio typically around 10%. Additionally, carcasses from these pigs have greatly decreased adipose mass and increased muscle mass. Somatotropin plays a major role in endocrine regulation of growth and development, although many of its important functions are probably indirect, acting through the insulin-like growth factors (IGFs) or through modulation of other endocrine axes. Recently, research has shown that many tissues make as well as respond to IGFs and the view is increasingly accepted that the effects of IGFs are mediated by both endocrine and paracrine effects. There is considerable evidence that the IGF axis is the main point of integration between endocrine control of growth and nutritional status. Both protein and energy intake influence circulating IGF levels emphasizing the importance of adequate nutrition when using somatotropin. Physiological effects of IGF are further modulated by the IGF binding proteins which may provide an additional mechanism regulating IGF because they have different patterns of hormone or nutrient dependence. Regulating other components of the somatotropin axis may be as useful to enhance efficiency and leanness as well as administration of exogenous somatotropin. To be acceptable for use somatotropin must also be safe for target animals and cost effective. Furthermore, meat products from the animals, in order to be acceptable to consumers, must be healthful as well as palatable. Research about animal safety has led to important discoveries about links between the immune system and somatotropin. It appears that somatotropin may enhance function of macrophages and polymorphonuclear neutrophils. While it is abundantly clear that food products from somatotropin treated animals are safe for human consumption consumer acceptance of these products will be determined by perceptions of safety and the actual quality of the products.

Keywords: *Biotechnology, meat production, technical perspective.*

Introduction

In the past decade, at least 8 major reports on public health have recommended reducing dietary fat intake in the United State (NRC, 1988). A consensus of these reports is to reduce animal fat consumption by 20 to 25%. This goal has clearly been taken to heart (no pun intended) by consumers. The tremendous marketing appeal of "Lite," the number of low fat products being introduced and the financial health of the diet industry are all clear evidence of this. Surveys by commodity groups indicate that up to three out of four consumers trim additional fat from meat products when they get home (NLS&MB, 1987) and this is despite a greater amount of fat trimming by retailers (AMI, 1989). Producing leaner, high quality meat to satisfy consumer demands and improve public health is a great challenge to animal agriculture.

The same biological propensity for humans to deposit fat makes it difficult to achieve quantum improvements in animal composition. Fortunately, new technologies for identifying, examining and transferring genes have increased our understanding of biological processes and provided unprecedented ability to modify these processes. The benefits to society of this biotechnology applied to medicine are apparent every day as increased health and quality of life. For agriculture, biotechnology offers the necessary tools to alter the composition of animal products. Production of commercial quantities of somatotropin offers the potential to improve leanness and at the same time has increased our understanding of how this endogenous protein regulates metabolism. However, both technical and social challenges lie ahead before somatotropin can be used commercially. The purpose of this paper is to provide an overview of what somatotropin does, some recent advances regarding its mode of action, and to identify some of the technical obstacles to its practical application.

Effects of Administering Exogenous Somatotropin to Pigs

It is apparent that administration of exogenous somatotropin to finishing pigs causes desirable changes in performance and composition. Treated pigs grow faster while eating less resulting in an increased gain to feed ratio typically around 10% (Chung et al., 1985; McLaren et al., 1987; Boyd and Bauman, 1989). Additionally, carcasses from these pigs have greatly decreased adipose mass and increased muscle mass (Grebner et al., 1987; Novakofski et al., 1988). Increased leanness is the most dramatic change in somatotropin treated animals. Figure 1 illustrates the magnitude of somatotropin effects on subcutaneous fat thickness relative to the fat thickness in commercial pigs. Control pigs in this experiment were about average. In comparison, pigs treated with even moderate levels of somatotropin by daily administration were leaner than 95% of commercial hogs as indicated in Figure 1, tenth rib fat depth distribution in commercial pork.

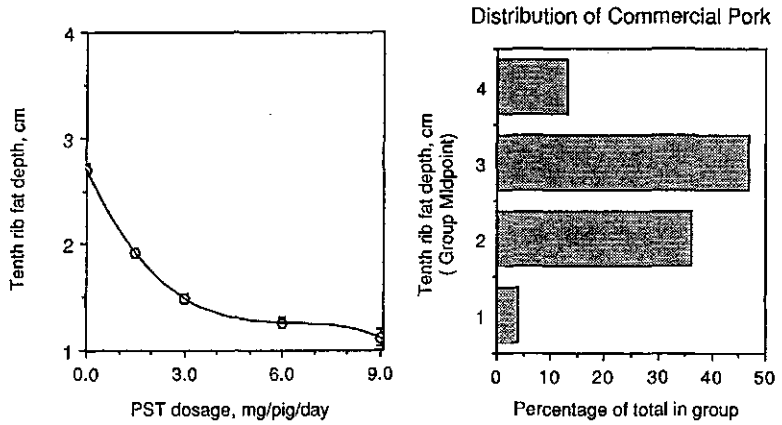

Figure 1. Comparison of fat reduction resulting from somatotropin treatment (Novakofski et al., 1988) with the distribution of fat in commercial hogs (DeVol et al., 1988b).

Mechanisms of Somatotropin Action

Somatotropin plays a major role in endocrine regulation of growth and development, although many of its important functions are probably indirect, acting through the insulin-like growth factors or through modulation of other endocrine axes.

Control of endogenous somatotropin

Somatotropin is an endogenous polypeptide secreted by the anterior pituitary gland (Millard, 1989). Regulation of somatotropin secretion is complex and is under both positive and negative control as well as feedback modulation (Figure 2). Areas of the brain such as the amygdala and hippocampus may modulate somatotropin secretion depending on circadian rhythms and/or stress. The hypothalamus produces both a somatotropin release stimulating

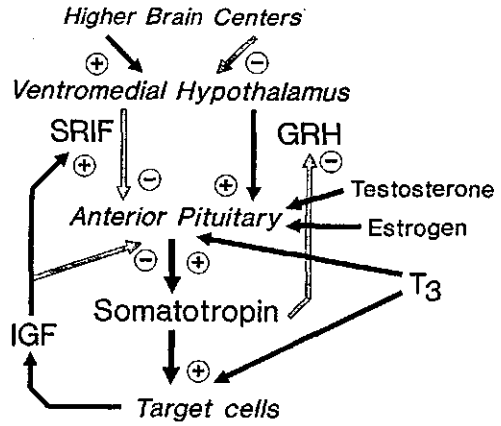

Figure 2. Regulation of somatotropin release.

hormone (GRH) and a release inhibitor (somatostatin or SRIF). In the hypothalamus, GRH and somatostatin secretion are neurally regulated by serotonin, dopamine and catecholamine. Hypothalamic factors are under negative feedback by somatotropin or other components of this axis. In addition to direct regulation of the pituitary, several other endocrine systems modulate somatotropin secretion or peripheral effects. Thyroid hormones affect both somatotropin secretion and the sensitivity of target cells (Wolf et al., 1989). Depending on level, oestrogen can either augment the somatotropin axis by increasing secretion or impair the axis by reducing peripheral responses. Testosterone does not have an acute effect on somatotropin secretion but it can function to "imprint" the pituitary or hypothalamus with a male pattern of somatotropin secretion or to "imprint" tissues to have male response patterns (Jansson et al., 1984).

The Insulin-like growth factors

Hypophysectomy of young animals or congenital defects of the pituitary results in individuals with short stature, indicating the role of somatotropin in normal growth. However, in some biological and nutritional conditions, somatotropin levels are not related to development of stature, or long bone growth indicating somatotropin is not a direct mediator of growth. For example, in protein/calorie deficiency, somatotropin levels may be elevated, presumably to facilitate use of stored lipid, although growth is reduced. Similarly in some smaller animal strains, somatotropin levels maybe the same or higher than in large or normal sized individuals (Guyda and Rappaport, 1989).

Research into these questions as well as others led to the discovery of the insulin-like growth factors (IGF-I and IGF-II) which are the major endocrine class directly regulating growth. IGFs stimulate proliferation and differentiation of many cell types. Furthermore, they stimulate protein synthesis and production of connective tissue or bone matrix and play a role in adipose tissue development. Levels of IGF in the circulation are controlled by somatotropin and insulin and are dependent on both protein and calorie intake (Figure 3), emphasizing the importance of proper nutrition in maximizing response to exogenous somatotropin.

Unlike most peptide hormones IGFs are not stored in a single tissue or organ. In the classic view of this axis, IGF-I is produced by the liver in response to somatotropin stimulation when nutritional conditions are suitable for growth of the animal. The IGF is bound to carrier proteins in the blood and carried to peripheral tissues by the circulation in classic endocrine fashion (Froesch et al., 1985). Recently, research has shown that many tissues make as well as respond to IGFs. This has resulted in an important change in our views of how somatotropin as well as the IGF's function in regulation.

Endocrine and paracrine IGF

The view is increasingly accepted that the effects of IGF's mediated by paracrine production may be as important as the endocrine effects of circulating IGF (Holly and Wass, 1989). It has been estimated that the liver generates about 1/2 to 2/3 of the growth hormone

dependent circulating IGF-I (D'Ercole et al., 1984). IGFs are made in response to somatotropin in both muscle and adipose tissue, which are the economic targets of somatotropin. Furthermore, somatotropin and IGF play a role in modulating immune function, which is a particularly important consideration when evaluating the effects of exogenous somatotropin on animal health.

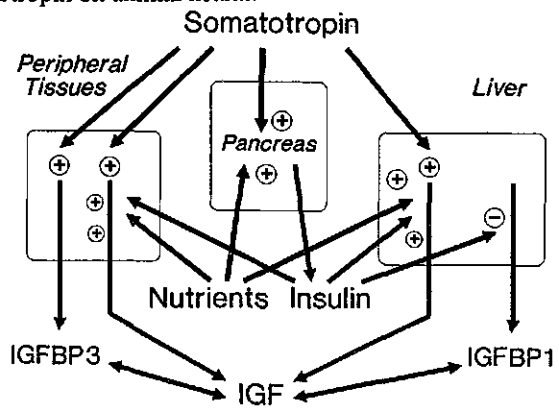

Figure 3. Interaction of somatotropin and nutrient status to control IGF and IGF binding proteins.

Endocrine effects are mediated by a hormone secreted into the circulatory system. A paracrine mechanism differs from an endocrine mechanism in that the hormone or factor produced mediates events within the same tissue rather than in a different organ and is not transported in the circulation. Paracrine factors may be identical to endocrine factors and in the case of IGF's the distinction becomes less clear because in a given tissue part of the effects produced may be endocrine and part may be paracrine. Paracrine mechanisms have been postulated in somatic tissues for many years and are used to explain such examples as hypertrophy of a single muscle group in weight lifters.

Modulation of IGF

Considerable information is available regarding regulation of circulating levels of IGF-I (Froesch et al., 1985; Guyda and Rappaport, 1989). Blood levels typically parallel circulating levels of somatotropin. However, in some species (rats) during fasting or diabetic conditions, IGF-I levels are decreased unrelated to somatotropin. Similarly, IGF-I mRNA levels in the liver and in most tissues which have been examined are typically responsive to somatotropin (Hynes et al., 1987; Mathews et al., 1986). Hypophysectomy reduces serum IGF to about 3% of normal and reduces tissue IGF content to between 12% and 79% of normal levels. Hypophysectomy reduces IGF content or IGF mRNA level more in the liver than in tissues such as adipose tissue (D'ercole et al., 1984; Yang and Novakofski, 1990) which suggests that the liver is particularly sensitive to somatotropin.

Somatotropin probably regulates paracrine IGF levels as well as circulating IGF concentration. Isgaard et al. (1986) infused somatotropin directly into epiphyseal cartilage. There was enhanced growth at the site of somatotropin infusion relative to the contra-lateral control cartilage which would also have been affected by any increase in circulating somatotropin or any hepatic IGF resulting from the infused somatotropin. Kasser et al.

(1989) performed an intriguing experiment in which rats were infused with somatotropin either subcutaneously (which would expose the periphery to higher somatotropin levels) or by an intraperitoneal route (which would preferentially expose the liver to higher somatotropin levels). The subcutaneous route of administration gave a greater growth response at high doses of somatotropin, indicating that IGF production by peripheral tissues may also be important in the response to somatotropin. These and similar experiments (Isaksson et al., 1986; Schlecter et al., 1986) provide strong evidence for a somatotropin mediated paracrine IGF mechanism.

Although the classic concept of the IGF axis emphasizes the role of somatotropin for normal growth, it is important to remember that somatotropin accounts for only about one-third of growth potential in most animal species. Hypophysectomized animals still attain two-thirds of normal size. Growth in hypophysectomized animals may in part be the result of non-somatotropin mediated IGF production (both paracrine and endocrine).

Similarly, paracrine IGF may also be modulated by pathways not involving somatotropin. Compensatory hypertrophy of muscle induces a 2-3 fold increase in IGF-I mRNA levels above control values (DeVol et al., 1988a). This increase is seen in hypophysectomized as well as intact animals indicating that somatotropin is not involved in the response. Paracrine IGF production clearly plays a role in growth of white adipose tissue (Gaskins et al., 1990) as well as growth of brown adipose in response to cold (DeVol et al. 1988c). Non-somatotropin related modulation of IGF-I by oestrogen has been described in the uterus (Murphy et al., 1987).

Integration of nutrition and endocrine regulation of IGF

There is considerable evidence that the IGF axis is the main point of integration between endocrine control of growth and nutritional status. Both protein and energy intake influence circulating IGF levels (Isley et al., 1983). The dependence of somatotropin response on adequate nutrition is clear although the relationship of somatotropin and nutrition is complex. The energy effect is partially, but not completely, mediated by insulin since diabetic animals have low IGF (Phillips et al., 1985) but insulin is not sufficient to restore IGF in protein deficient animals (Maiter et al., 1989). Treatment with additional somatotropin does not overcome the effects of nutrient restriction (Merimee et al., 1982) indicating separate paths for the effects of somatotropin and nutrition. Supporting this idea at the molecular level, both somatotropin and insulin affect IGF-I transcription independently (Johnson et al., 1989).

The mechanism of nutrition effects on IGF have not been investigated as extensively as the effects of somatotropin. As in the case of somatotropin modulation, changes in liver IGF are relatively sensitive to nutrition. Liver levels were reduced 8 fold in fasted rats compared to fed rats while muscle IGF was reduced less than 3 fold from the fed state (Lowe et al., 1988). Levels of IGF-I mRNA in adipose were also modulated less than liver during fasting (Yang and Novakofski, 1990).

It is likely that a part of the nutrient dependence of IGF is indirectly related to the regulation of nutrient availability by insulin and somatotropin. Insulin modulates glucose

and amino acid uptake while somatotropin modulates lipogenesis and lipolysis which determines availability of fatty acids as an alternative fuel to glucose. Furthermore, somatotropin and insulin also have indirect influences on peripheral metabolism that may be more important than direct effects. Somatotropin has relatively small effects on lipolysis but it has a large effect on tissue sensitivity to lipolytic hormones. For example, *in vivo* lipolytic responsiveness is increased 6 to 7 fold in somatotropin treated animals while normal glucose clearance requires higher insulin release (Novakofski et al., 1988; Sechen et al., 1990). Similarly, blood levels of T_3 are elevated in somatotropin treated animals, although changes in T_3 are normal following TRH challenge (Brenner et al., 1988).

IGF binding proteins

Physiological effects of IGF are further modulated by the IGF binding proteins. Circulating IGF complexed to binding proteins is probably not recognized by receptors and is thought to be inactive (Holy and Wass, 1989). Somatotropin also has circulating binding or carrier proteins. However, meat animals appear to have only relatively low affinity somatotropin binding proteins in contrast to humans that also have high affinity proteins (Baumann, 1990). There are several IGF binding proteins which may provide a mechanism for fine tuning IGF because they have different patterns of hormone or nutrient regulation.

There are three distinct plasma IGF binding proteins (IGFBP), which have been well characterized, although meat animal binding proteins may have different properties (McCusker et al., 1990). IGFBP-1 (also called somatotropin independent BP) and IGFBP-2 are highest in fetal circulation while IGFBP-3 (also called somatotropin dependent BP) is highest postnatally (Yang et al., 1989). IGFBP-1 is expressed exclusively in the liver while IGFBP-3 is made in many tissues. IGFBP-1 is unaffected by nutrition or somatotropin but it is inversely related to insulin concentration and it changes more rapidly than IGF in response to changes in insulin. In contrast IGFBP-3 is increased by somatotropin, IGF-I, insulin and other growth factors (Clemmons et al., 1989).

Depending on physiological conditions, the IGFBP's can enhance or inhibit the physiological effects of IGF. For example, during fasting when total IGF-I declines slowly, IGFBP-I increases rapidly as insulin decreases. This blunts response to IGF-I, effectively decreasing IGF function faster than IGF concentration. Conversely, IGFBP-3 increases concurrently with IGF-I in response to somatotropin and this would moderate the acute effects of increasing IGF, but would also prolong these effects by delaying removal and degradation of the IGF binding protein complex.

Challenges and Opportunities Regarding Somatotropin

It is clear that somatotropin can affect desirable changes in efficiency and composition. However, to be useable, somatotropin must also be safe for target animals and cost effective. Furthermore, meat products from the animals must be acceptable for consumers as well as healthful and they must be palatable.

Delivery systems

Because somatotropin is a protein it is not orally active. This is clear from both direct test and the continued need to inject short stature children being treated with human somatotropin. A method to continuously deliver somatotropin would make it easier to use, although it is an open debate whether a delivery system will be required for cost effectiveness or commercial success.

Daily administration is fast, efficacious and does not stress the pigs. Within a few days, animals adapt to the point where many will not even get up if they are lying down. However, it does require labour on a daily basis. The usefulness of delivery systems or devices will depend on the duration and kinetics of delivery. Longer delivery time will reduce labour inputs although such devices will likely be more expensive and because agriculture is a very efficient business the real technical challenge of making a delivery system is keeping the cost low.

Development of delivery systems is mostly proprietary research by different corporations although some important considerations and general approaches are apparent. First, the amount of material needed for even relatively long delivery is not large. A one month dose could weigh less than 1/2 g assuming a 3 mg/day dose and a 25% concentration of active ingredient. Second, the most desirable delivery system would mimic the pulsatile nature of endogenous release or daily treatment. Next best would be a zero order device that would release somatotropin at a constant rate. Real world devices or systems will probably perform less well than the ideal.

For the purpose of discussion, these products can be discussed as delivery systems or devices. Systems are absorbable formulations to control delivery kinetics. These might include layered solid state products that dissolve slowly as a result of various polymer coatings. Liquid delivery systems are likely to resemble those for antibiotics, and might be composed of a suspension, an emulsion or possibly liposomes. Delivery devices are non-absorbable structures and may potentially provide longer release than formulation. Although not practical for production use, the Alzet Osmotic Pump (Alza, Palo Alto, CA) is a device that has been used experimentally.

Somatotropin and the immune system

To be approved for use, somatotropin must be safe for target animals. Research into this area has led to important and far reaching discoveries about regulation of the immune system. Five years ago, researchers at the University of Illinois discovered an important link between the immune system and somatotropin.

It has been known for years that the size of the thymus gland in both humans and animals becomes smaller with age, and it was thought that this process was irreversible. However, experiments suggested that administration of somatotropin might permit the thymus gland to grow again in aged animals (Kelley et al., 1985). Only remnants of the thymus gland could be detected in control aged rats (equivalent to a 54 year-old human). However, aged rats that had been implanted with somatotropin secreting pituitary cells regenerated their thymus

glands to the point that they were indistinguishable from those of young rats. Furthermore, the capability of T lymphocytes to grow, an aspect of the immune response that deteriorates during aging, was significantly improved. It now appears that the real cellular target for the action of somatotropin may be the macrophage (Davila et al., 1990; Edwards et al., 1991).

These experiments provided the impetus to study whether somatotropin affects the immune system of farm animals. Initial experiments concentrated on studying phagocytic cells of pigs because these types of cells are critically important for destroying many types of bacterial and fungal pathogens. Porcine somatotropin that had been shown to increase growth rate and reduce carcass fat also increased the capability of macrophages to produce a superoxide anion free radical (Edwards et al., 1988). This molecule plays an important role in the killing of bacteria by porcine macrophages. It has now been shown in pigs, cattle and humans (University of Illinois faculty and graduate students!) that recombinant somatotropin increases the secretion of superoxide anion by another type of phagocytic cell know as the polymorphonuclear neutrophil (Fu et al., 1991). In pigs, these somatotropin-treated cells appear to be more efficient in killing *Escherichia coli in vitro*. Lymphocytes from somatotropin treated dairy cattle are also more responsive to mitogen stimulation (Burton et al., 1991).

Other experiments have challenged young pigs with *Pasteurella multocida* or bacterial toxin causing turbinate atrophy (Dau, 1989). These experiments indicate that disease does not prevent somatotropin effects on efficiency or composition. Immune response was not enhanced by somatotropin in these animals, indicating that either young animals already have maximally functioning immune response or that the challenges were sufficiently severe to overcome any enhancement.

Value based marketing systems

It is important that producers be rewarded appropriately for the benefits of using somatotropin. Current livestock purchasing practices are based primarily on a subjective evaluation of merit and have led to pricing on the "average". Unfortunately, good animals are penalized and poor ones are rewarded by average pricing. Average pricing also amounts to "buying pounds" so there is little reward for producing animals with better composition. Because of this, only improved efficiency resulting from somatotropin would be rewarded and improved composition would not.

Increased use of "value based marketing" would address this type of problem. Actual value of an animal is based on the ***quantity*** and ***quality*** of retail products that are produced. Grading systems are designed to assess or predict yield and quality of retail products. Most evaluation technologies can account for 60-80% of variation in composition so there is considerable interest in developing more flexible grading systems that are rapid and accurate.

Even conventional grading approaches may have to be modified for use with somatotropin treated animals. Most technologies to estimate composition are based on the fact that animal growth is allometric; ie. growth of all parts is proportional to other parts over narrow ages or sizes. Therefore, a small number of measures of fat and lean can be used to

predict whole animal composition. However, if the proportionality of growth between parts is changed the accuracy of prediction is degraded.

Product quality and consumer acceptance

In order for somatotropin to be used in agriculture it must be acceptable to consumers. Somatotropin itself must be acceptable and this will depend on perception of safety. Problems such as the eosinophilia possibly caused by an "e peak" contaminant in specific commercial production lots of tryptophan have heightened concern about biotechnology among consumers and emphasize the need for both manufacturing care and consumer education. Acceptance will also be determined by the quality of products from somatotropin treated animals.

It is abundantly clear that food products from somatotropin treated animals are safe for human consumption (Juskevich and Guyer, 1990). In fact these products are probably more healthful because they are leaner. Neither somatotropin nor IGF proteins are orally active. They are proteins and are digested just as any other protein. Further, there are no biologically active proteolytic fragments of either protein.

Consumer perception of meat quality is a more difficult matter. Overall quality of meat is a matter of perception, a mental assessment of aggregate appearance and eating quality. If one doubts the contribution of appearance to the taste of meat quality, they need only contemplate the taste of green eggs. Many consumers perceive meat with less subcutaneous fat as being better so somatotropin will be positive in this aspect. Eating quality is a combination of texture, juiciness and flavours and these characteristics are not markedly effected by somatotropin. Tenderness is probably the most important quality parameter and an effect on tenderness can be measured. However, it is insignificant compared to the normal variation in pork tenderness (Figure 4). Similarly with good quality preparation, juiciness and flavour of meat from somatotropin treated animals is quite acceptable.

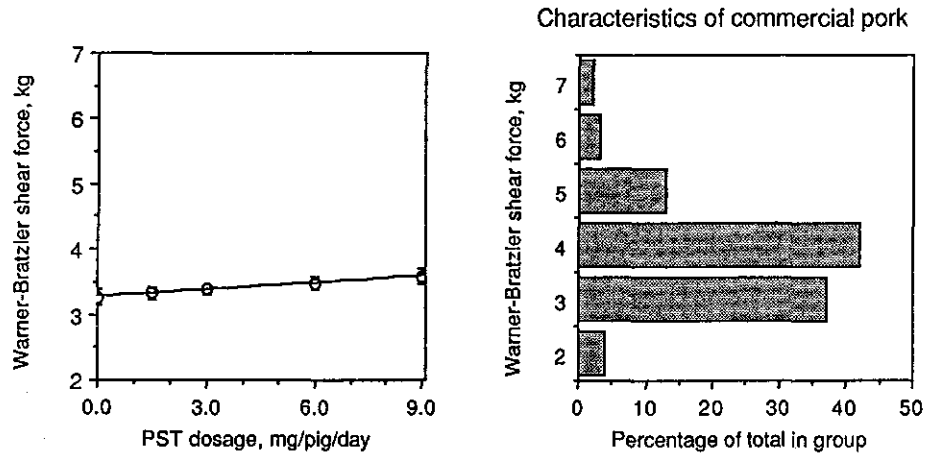

Figure 4. Comparison of change in tenderness resulting from somatotropin treatment (Novakofski et al., 1988) with the variation in tenderness in commercial pork (DeVol et al., 1988).

Future Approaches to Modifying Somatotropin

Regulating other components of the somatotropin axis may be as useful to enhance efficiency and leanness as administration of exogenous somatotropin. Several possibilities are suggested by looking at the somatotropin IGF axis. These can be divided into extrinsic and intrinsic strategies.

Extrinsic strategies could involve administration of axis components such as GRF or IGF instead of somatotropin. Treatment to modulate the potency of endogenous or exogenous somatotropin would be another possibility. This could be done by giving catecholamine such as the B agonists or thyroid hormones. Increasing binding protein levels (ie IGFBP-3) might also enhance somatotropin effects. Immunization against axis antagonists such as somatostatin or receptors mediating degradation pathways in non-target tissues are other possibilities.

Intrinsic strategies to modify the somatotropin axis would involve either augmented genetic selection or production of transgenic animals. Animals transgenic for axis components would be similar to animals treated with exogenous proteins or peptide. Transgenic methods also offer the possibility of enhancing intracellular transduction pathways or expression of various responsive genes. Using knowledge about the mechanism of somatotropin action might also permit marker assisted selection based on growth or muscle quality linked genes. Similarly, these methods could be used to maximize the interaction of somatotropin and nutrients in regulating IGF in order to reduce dietary protein requirements.

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GLOBAL APPROACH FOR THE REGULATION AND ACCEPTABILITY ASPECTS OF BIOTECHNOLOGY

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Summary

Biotechnology in Animal Production offers multiple opportunities for farmers and animal health specialists to have a wide range of technologies available for use, from traditional cross-breeding to biotechnologically produced vaccines and aids to production. There needs to be a global approach to the regulation and acceptability aspects of biotechnology to create an atmosphere of mutual confidence between producers, manufacturers and consumers, to remove unjustified technical barriers to trade, to promote uniform control of application of new biotechnology techniques, and to prevent concern and confusion amongst consumers as to whether the measures taken in one country are equivalent to those taken in another. In a global approach, recognition needs to be made of regional and national considerations, and a common reference point found. The work of FAO, and in particular the FAO/WHO Codex Alimentarius Commission, provides a focal point for governments, producers, industry and consumers, to work together in creating international rules for the acceptability of the use of biotechnology in animal production.

Keywords:*Biotechnology, global regulation, global acceptability*

Development of biotechnology

The development of biotechnology is the extension of a *continual process of traditional and modern technologies* to investigate and manipulate organisms at various levels, from the organism itself to the molecular level, and to make or modify biological products to meet particular needs. The main impetus for the current enthusiasm about biotechnology has been the development of recombinant DNA techniques during the 1970's and 1980's, which offer the possibility of moving any gene from any organism to any other organism.

Modern biotechnology, particularly genetic engineering, is an undertaking with far-reaching economic and social implications. In food and agriculture, as in other fields, it presents both opportunities and challenges. It represents new ways of solving old problems.

Modern biotechnologies provide opportunities to study and understand biological principles and processes, and constitute powerful tools, directly or as adjuncts to traditional technologies, for improved and sustained agricultural production and utilization. Biotechnology promises to improve agricultural productivity; decrease our dependence on pesticides and other potentially harmful chemicals by genetically redesigning plants and

animals to better resist natural and man-made enemies; improve safety, nutritional and other qualities of agricultural products; improve handling, storage and processing and most agricultural commodities; decrease our dependence on non-renewable resources; enhance our ability to harness marginal lands and other non-congenial agro-ecological settings for food production; conserve and judiciously exploit biodiversity; and increase our overall food, nutritional, and ecological security.

Biotechnology in Animal Production offers opportunities for the control of reproduction, selection and breeding, application to animal health and treatment of zoonotic diseases, improved feed and nutrition, and improved growth rates and production. None of these areas are new: Great strides have already been made using conventional breeding techniques, together with changes in diet and husbandry, to modify the characteristics of animals used in food production and the quality of their output. Changes in such diverse characteristics as maturity, fecundity and muscle distribution are observable in many domesticated animals compared both to their wild ancestors and to breeds commonly used a century or so ago.

Conventional breeding and selection techniques have enabled animal breeders to produce strains to meet producers' demands. This is especially marked in poultry where the industry has developed early maturing birds which, compared with the breeds used formerly, produce more eggs or can be taken to slaughter earlier. Also, strains of cattle are available to suit high or low intensity agricultural systems and the demands of those wishing to produce milk and/or beef. Milk yields have been improved when required and the fat content of milk and flesh altered to take account of changing demands. The changes introduced into cattle and poultry by the breeder have been parallelled in other commercially important species, and newer biotechnology techniques will enable even more rapid improvements in desirable traits.

Need for effective and realistic regulatory schemes

Despite its promise, biotechnology has been characterized by conflict ever since its inception; early work was followed almost immediately by intense scientific and public debate over the need for regulation. This is understandable, as biotechnology is a powerful new means of manipulating life and has profound moral, ethical and safety implications. It generates fear because of its potential misuse and the unknown threats it may pose to public health and the environment. This fear has to be overcome if biotechnology is to develop and be used productively. The creation of a climate of public trust is therefore one of the critical tasks to be undertaken so as to realize the great promises which biotechnology offers to industry, agriculture, health and other sectors. It is in this context that biosafety regulations have to be discussed, and consumer concerns addressed.

Given the nature of the potential contribution of biotechnology to economic and social development in the less advanced countries, the need and importance of effective and realistic regulatory schemes goes well beyond the moral imperative to safeguard individual and public health and the environment. First, the strengthening and further development of biotechnology in particular, and of science and technology in general, requires the support and trust of the general public. The existence of clear and comprehensive regulations to safeguard the general interest will be perceived as a sign that scientists are sincerely

concerned for the public at large and are not the self-serving and socially insensitive community they are often accused of being. Only when this happens will there be the continued support and flow of domestic resources which is a necessary conditions for sustained national technological development. Secondly, local safety regulations are needed so as to establish clear rules for international companies and research institutions. This, together with a framework for the legal protection of innovations in biotechnologies, is going to be one of the critical requisites for investment and location of production and research facilities in developing countries by these companies, an alternative which could be the most important means of gaining access to these technologies. Finally, there is the international trade dimension. Safety and sanitary regulations have been used to restrict access to given markets in the past and surely will eventually be used in this case also. The existence of them in developing countries can be an important bargaining element in negotiations for access to specific markets.

There needs to be a *global approach to the regulation and acceptability aspects* of biotechnology to create an atmosphere of mutual confidence between producers, manufacturers and consumers; to remove unjustified technical barriers to trade; to limit confusion in the minds of consumers as to whether the measures taken in one country are equivalent to those taken in another; and to improve productivity with net positive benefits in regard to the efficient use of limited natural resources. In a global approach, recognition needs to be made of regional and national considerations, and a common reference point found. Certain factors are common to all countries: aspects of human safety; interest in improved domestic and international trade in commodities produced with the aid of biotechnology; protection of the environment, balancing net benefits to agriculture and sustainable rural development; and adequate nutrition and access to safe food at reasonable prices.

Human health

In regard to human health, food safety and their relationship to broader concerns, a Joint FAO/WHO Expert Consultation on Assessment of Biotechnology in Food Production and Processing as Related to Food Safety was held in Geneva from 5-10 November 1990. Its report will be issued shortly. The Consultation noted that while significant changes can occur with the genetic modification of animal genomes, it would appear upon current review of known or suspected hazards that transgenic animals should not present significant food safety concerns. At least in mammals it should be emphasized that a normal healthy and productive animal is in effect an indication that food from that animal should generally be considered safe. The Consultation also considered that exact gene products that may be the result of transgenic modification should be fully characterized as either an existing substance or one which may be new or unique to the particular animal species. Assessment of the safety of products obtained from genetic manipulation in foods can be conducted in the same manner as is performed for other animal drugs and food additives.

Trade

Trade in safe animal products, produced with the aid of biotechnology, should not be subject to any increased barriers compared to trade in their "traditional" counterparts. Although countries have the right to take national measures necessary to protect public health, or animal health and welfare, and their environment, there is a growing consensus that such measures should be applied only to the extent necessary to protect human and animal health, and that these measures should be based on sound scientific principles. The objective is the development of a freer trading environment which is now recognized as an essential requirement for economic and social developments on a global level.

Benefits for sustainable agriculture and nutrition

Biotechnology in animal production can have potential net benefits for agriculture and its sustainable development and very importantly, for nutrition. Traditional selection and breeding has accomplished much in these areas, but biotechnology offers new opportunities to reduce dependence on chemicals used in animal production, and also perhaps, to reduce methane production by increasing conversion efficiencies. Consumer demands, especially in developed countries, are lending towards the need for a more diversified food supply and products which are lower in fat and other components. Lean meat, low-fat milk or cholesterol-reduced eggs are all achievable goals through biotechnology. Regional and national considerations which need to be recognized include: climate; type of agriculture; food patterns and habits; level of development including the degree of infrastructure such as laws and regulations, inspection and control systems, research and development, agricultural extension services; and social consideration and consumers' opinions.

Each of these *considerations have global and uniform validity,* providing a base for a global approach.

Climate, ranging from temperate to tropical, the type of agriculture, ranging from subsistence to intensely industrialized, and national food patterns and habits, will all tend to dictate which biotechnologies will be used in animal production, but not whether biotechnologies should be used or not. In fact, mutual recognition of the needs of other countries in their use of biotechnology in relation to their national or regional conditions will benefit the exchange of research information and information on the practical application of biotechnology; benefit trade in products, and provide an enhanced degree of consumer acceptance as consumers see applications which are relevant to their situations.

Biotechnology in developing countries vis-à-vis industrialized ones

Questions have been raised about the relative impact of the use of biotechnology in developing countries vis-à-vis industrialized ones. These questions relate to the proprietary ownership of many biotechnological processes and to the possibility that the technology gap between rich and poor countries will be further widened by the introduction of biotechnology. The differing degrees of infrastructure of developing countries also poses an

additional restraint of their ability to regulate the use of biotechnology. FAO is aware of these potential problems and is providing advice and assistance to developing countries, especially in the area of livestock production where these countries can benefit greatly from the use of new technologies. FAO also provides advice and assistance in establishing efficient, integrated food control programme, including elements of food legislation, standardization, inspection, analysis, and the management of such programmes. This work can only be enhanced by the development of a global approach to the regulatory aspects of biotechnology in animal production, which can then be applied specifically at the national level.

Social considerations and consumers' opinions

Social considerations and consumer's opinions have sometimes been seen as obstacles to global approaches in the acceptability of new processes for food production and manufacturing. A careful analysis of the situation reveals that this is not always the case. For example, the development of a major sector of the food industry, low-calorie foods, has been reliant on the judicious use of food additives despite concerns expressed by some specialized consumer organizations about the use of additives in general. In this case, consumer acceptance has been based on the confidence which the true consumer, the purchaser, has in the regulatory authorities concerned, and the desire to have access to these types of products. In the case of biotechnology applied to animal production, it is indeed possible that similar consumer acceptance can be found.

Factors such as climate and the type of agriculture will dictate many of the uses of biotechnology in animal production. The prevalence of diseases or insect pests will be one important factor, as will the price and availability of feed for the animals. Each local agricultural environment will have its own problems and its own means of overcoming them. Farmers and animal health specialists in all countries should have a wide range of technologies available for use, from traditional cross-breeding to biotechnologically produced vaccines and aids to production.

Global approach to regulation and acceptability of biotechnology

Elements of these regional and national considerations can be brought together to form a global approach to regulation and acceptability of biotechnology in animal production. This global regulation should be related to regulation of the products produced through its use and should be based on the definable differences between these products and their normal counterpart. Regulation of the processes and techniques used will develop in the light of national conditions.

Alternative narrow approaches will not work. Regulations aimed at rigidly restricting the application of biotechnology in animal production, simply because the technology is new or is not well understood, are not valid and will impede research and development in those parts of the world where unnecessarily strict controls are introduced. The assessment of safety, both to human and animal health and the environment, is a legitimate concern for governments and a legitimate object of regulation. It must however be *based in the scientific*

evaluation of the risks entailed in the use of biotechnology, in the same way that risks arising from the use of food additives or agricultural and veterinary chemicals are evaluated. Public concerns, based primarily on the lack of knowledge or lack of understanding of the process, cannot be the basis for decision making at the global level. Structural impediments in the form of food laws and regulations, should not confuse the scientific assessment of food safety with concerns for animal welfare or consumers' perceptions.

The *FAO/WHO Codex Alimentarius Commission* has initiated its consideration of the implications of biotechnology in the development of international standards for foods. Among the Commission's responses to this paper was the request to convene the Expert Consultation referred to above. The work of FAO, and in particular the FAO/WHO Codex Alimentarius Commission, will provide a focal point for governments, producers, industry and consumers, to work together in creating international rules for the acceptability of the use of biotechnology in animal production.

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D.A. Jonas and R.J. Rasaiah, 1990. "Biotechnology - Historical and Recent Developments", prepared for FAO and WHO for the Joint FAO/WHO Consultation on Assessment of Biotechnology in Food Production and Processing as related to Food Safety, Geneva, November 1990.

SESSION II
* BIOTECHNOLOGIES AFFECTING GROWTH AND PRODUCT QUALITY

* Advanced breeding; Gene transfer
* Immunomodulation
* GRF and ST in poultry and pigs
* ST in ruminants

SUMMARISED AND ADOPTED CONCLUSIONS FROM PAPERS AND DISCUSSION

ON

BIOTECHNOLOGIES AFFECTING GROWTH AND PRODUCT QUALITY

Chairman:

Dale E. Bauman, *Department of Animal Science, University of Cornell - USA*

Discussion moderators:

Roger Aston, *Peptide Technology Ltd. - Australia*

William J. Enright, *Department of Animal Nutrition and Physiology, TEAGASC, Grange Research Centre - Ireland*

- *Important **goals of animal production** are to increase nutrient use for lean tissue growth and reduce nutrient use for body fat deposition, with the overall result of increasing productive efficiency (gain per unit of feed). The excellent presentations in this session reviewed recent developments in **biotechnology** which have **potential to allow for unprecedented gains in the productive efficiency of farm animals**. These technologies also give us insight into the biology of growth in domestic animals and aid in our understanding of how animals regulate the use of nutrients for productive functions. For this reason, these technologies are frequently referred to as nutrient partitioning agents or metabolism modifiers.*

- *Presentations in this session **focused on the somatotropin axis**. This axis is clearly an important biological system in the **regulation of nutrient use** by animals, and manipulation of different regulatory elements of this axis offers the potential to improve animal efficiency. The changes which occur when the somatotropin axis is altered include an increase in the rate of lean accretion and a reduction in the rate of fat accretion. Depending on the magnitude of these reciprocal changes in lean and fat accretion, one can also observe alterations in average daily gain and feed intake. Overall, the net result of these changes is an unprecedented improvement in productive efficiency, especially of lean tissue.*

- *One way to alter the somatotropin axis is to directly **administer somatotropin** (ST) or growth hormone-releasing factor (GRF). Animal responses to exogenous ST and GRF, and factors affecting these responses were reviewed by McBride and Moseley for ruminants and by*

Bonneau for swine and poultry. A second approach to alter the somatotropin axis is by ***immunomodulation****. This is a relatively new approach and the possibilities and limitations were reviewed by Pell and co-workers. In general, this approach involves modification of an animal's immune system to produce long term changes in elements of the somatotropin axis. A third approach is to use* ***advanced breeding technologies and gene transfer*** *to improve the productive efficiency of animals; Smith and Brascamp reviewed the present status of this approach, including an evaluation of the specific techniques available to produce transgenic animals.*

- *While the potential for commercial use of these technologies is of* ***immediate interest,*** *their use in understanding the regulation of nutrient partitioning will likely be of* ***greater importance in the long term****. Indeed, throughout this session, authors related results to biological implications and concepts. While results to date do lead to important advances in knowledge, they have also highlighted our* ***lack of understanding in some areas****. For example, the dramatic responses in productive efficiency observed with use of exogenous ST in pigs clearly demonstrates that the components of the somatotropin axis which are downstream from ST have not yet been maximized. Yet responses in lean and fat accretion to ST treatment are quantitatively less in ruminants and negligible in poultry. There could be a nutritional explanation for the less dramatic response in ruminants (post-ruminal supply of amino acids) but that would not explain the lack of effect in poultry. Also, regarding immunomodulation of productive function, we know very little about the immune system of farm species and how it can be regulated with consistency and lack of variability between animals. Similarly, in the exciting area of gene manipulation and transfer in general, we still must identify the specific genes which are most appropriate to transfer and develop the technology to confidently regulate their site of insertion and tissue expression.*

- *In summary, there are technologies available to* ***significantly improve animal performance and quality****. Also, we have gleaned a tremendous amount of important basic information on the growth biology of farm animals through the development of these technologies. In the future, we will continue to make major strides through fundamental research and to convert this knowledge into applied technology for commercial use by the producer and to provide increasingly better quality animal products for the consumer.*

GENETIC IMPACT BY ADVANCED BREEDING TECHNOLOGIES AND GENE TRANSFER

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Summary

This paper reviews the prospects for enhancing animal breeding through cloning, selection by genetic markers, and transgenic animals, with special attention to genetic engineering. It is concluded that cloning has relatively little influence on the rate of genetic gain in nucleus herds but it could shorten the time interval between nucleus and commercial herds. Genetic markers in a selection program may increase the annual rate of genetic change as much as 30%. The contribution of transgenetics to animal improvement can be enhanced with cloning. To achieve continuing genetic improvement, one wishes to generate many animals identical with respect to the transgene but possessing the full genetic variation present in the stock.

In producing transgenic animals, the relative advantages of microinjection into the zygote, or of using embryonic stem cell and primordial germ cells as methods to introduce foreign DNA into the germ-line of animals are reviewed. Examples of genes which control growth and genes with potential for conferring disease resistance in poultry are briefly discussed. The advantage of selecting particular promoters to allow tissue specific or external control of expression of transgenes is addressed. Finally, a possible complication associated with genetic imprinting in transgenic animals is considered.

Keywords *: Meat production, gene transfer, advanced breeding*

Introduction

Quantitative genetics as an application of biotechnology in the past has contributed to improvement in animal production. Now application of new biotechnologies offer additional major improvements in livestock which could not be accomplished through traditional breeding methods. We wish to describe three new technologies; production of genetically identical animals by cloning (Bondioli et al., 1990), marker assisted selection (Stam, 1986; Lande & Thompson, 1990), and genetic engineering (Palmiter et al., 1982). These techniques will not replace present selection and improvement strategies of livestock; they will be incorporated into traditional breeding programs and some of the results will be additive.

Genetic engineering may be the most revolutionary of the three technologies because it offers to incorporate into the genome traits which do not exist in the base population and make subtle changes in other traits. Genetic engineering of animals has become a reality during the last 20 years through the isolation of specific genes of known function, and through our understanding of the role of regulatory elements that control expression of these genes. Until recently, the most common method of introduction of additional normal or modified genes into the germ-line has been by microinjection into the male pronucleus of the zygote. More recently, two alternative methods have been developed where instead of the zygote, embryonic stem (ES) cells or primordial germ cells are targeted. Now that the technology to produce transgenic animals has become routine in research institutions around the world, the potential practical impact on the breeding of livestock is revolutionary. However, we are currently constrained by the small number of genes that are known to be associated with specific traits and the lack of availability of efficient inducible promoters that allow us to activate these transgenes in a well controlled manner. Once we have this knowledge, the sorts of beneficial changes that can be introduced into domestic animals is limited only by our imagination.

The purpose of this paper is to briefly outline new technologies and discuss how cloning, genetic markers and genetic engineering may contribute to selection and improvement programs.

Current Breeding Programs

Current breeding programs in farm animals amount to the choice (selection) of the best parents to produce the next generation. This selection process is generally continuous, and selection decisions repeatedly are taken for subsequent batches of potential parents tested. Tests may include measurements on the potential parents themselves, sibs or progeny. At present, measurements generally concern performance traits like weight, body composition, fertility or scores of quality. Which potential parents are best is defined in a breeding goal, which generally specifies the effect of genetic changes in performance traits on overall economic merit of animals, herds or sections (Smith et al., 1986).

Two features of breeding programs should be pointed out in the context of the present paper. The first is that breeding programs are pyramidal in structure. The top of the pyramid is formed by breeding herds (nucleus herds) at which the actual selection and improvement takes place. The base of the pyramid consists of commercial herds using genetic material originating from the nucleus. Generally, multiplication levels exist to multiply the improved genetic stock, often by crossing different strains from the nucleus level. The organization of the pyramid influences the genetic lag between nucleus and base in the pyramid (Bichard,1971). Genetic improvement may be enhanced by diminishing this lag and by improving the efficiency of genetic change in the nucleus. This underscores another feature, essential for the animals in the nucleus; the existence of genetic variation. Without genetic variation, further improvement by selection is not possible. Smith (1984) summarized results of selection experiments and commercial selection programs in different species. He showed that one percent genetic improvement in overall economic merit seems a realistic figure for most farm animal species.

Implications of Advanced Techniques

Shorten the time lag

Cloning offers to reduce the time interval required for multiplication of animals from nucleus herds for use in commercial herds. Artificial insemination is a classic example of this. The cost effectiveness of cloning of embryos (Bondioli et at., 1990) together with embryo transfer varies among species. Cloning and embryo transfer in milk and meat production may prove useful only when they offer very superior stock, while there are more possible applications in dairy cattle. Sexing the embryos improves the usefulness of cloning in all species. Another point is that cloning would facilitate selection for special markets, because in principle only one embryo is needed meeting the special requirements.

New Selection Criteria

Presently selection decisions are based on performance traits. New selection criteria will arise based on physiological processes,regulation at the DNA-level of factors affecting performance traits, or because variation of coding genes or regulatory elements becomes known and exploitable. The use of genetic markers (Beckman & Soller, 1983) is a special case of the latter where DNA regulatory elements are not known, but polymorphic DNA-sequences appear to be associated with variation in performance. There are several suggestions for a large numbers of genetic markers (Jeffreys et at., 1985; Georges et al., 1990) and international programs have been initiated directed at genome maps for various species (e.g. for pigs Haley et al., 1990). Application of these new selection criteria looks very promising in principle for at least two reasons. First, while measurements of performance traits have normally reflected the joint effect of genetics and environment, some genetic markers may be free of environmental effects. Secondly, they may be measured on young animals and in both sexes. Some examples can be found in model approaches of Stam(1986) and Lande & Thompson (1990)allowing some 30% increase in rate of annual genetic change by the application of genetic markers.

Genetic Engineering

Smith et al (1987) and Kanis (1989) discussed the possibilities of transgenics in breeding programs. We wish to stress two aspects. In present breeding programs for nucleus stock, genetic variation is a prerequisite. This variation promises annual genetic improvements approaching 1% in overall economic merit. Based on expected time of development and testing of transgenic animals, Smith et al (1987)concluded that a founder transgenic animal has to be some 5 to 10% superior to competing non-transgenic parents. This implies that a transgene has to be introduced in a nucleus strain without loss of the existing genetic variation. Starting with one founder sire, the transgene can be incorporated by back crossing of transgenic animals on superior non-transgenic stock representing the required array of genetic variation. Of course, the transgene has to be carried over to each new generation. The

original stock is hemizygous, one generation is needed to produce homozygous transgenic stock, and this along with the backcrossing requires several years. Smith et al (1987) suggested that one should mate transgenic parents at an early stage of the program to identify potential unwanted side effects.

For commercial herds, transgenic animals probably must be hemizygous or homozygous for the transgene. Otherwise, the genetic variation at commercial level may impair sound management and marketing. In cross breeding systems, which dominate meat production, this implies that at least one of the parental stocks of commercial animals has to be homozygous. Where parental stock is crossbred, which is common in pigs, both grand parental stocks have to be homozygous.

The back-crossing procedure is not needed if techniques become available to produce various individuals identical with respect to the transgene but exhibiting the full genetic variation for further improvement.

Methods of Producing Transgenic Animals

Pronuclear injection

The potential offered by gene transfer was most dramatically illustrated by the "super mouse" in which high level expression of rat growth hormone (GH) caused a major increase in growth (Palmiter et al., 1982). In this particular example, rather than the natural regulatory regions being used to control expression of the growth hormone gene Palmiter used the mouse metallothionein (MT)promoter fused to the GH structural gene. This fusion gene allowed expression to occur not just in the pituitary gland but in several organs and tissues of the mouse. Another advantage of the MT promoter was that basal expression could be further increased by dietary supplementation with zinc or cadmium.

To produce the "super mouse" the MT-GH fusion gene was injected into the pronucleus of the zygote and the zygote transferred to a surrogate mother to allow development to term. The process of microinjection is very effective in the mouse. In our laboratory, approximately 50% of eggs injected produce progeny containing the transgene; about half the mice express the transgene.

The disadvantage of microinjection of DNA into the zygote is that there is no control of the site of integration or of the number of copies of a transgene that integrate into the genome of the host. In general multiple copies are inserted in a head to tail array. The result is an inherent variation in the degree of expression across the different transgenic lineages. However, this is not necessarily a problem if high level expression of a transgene is required.

Microinjection of DNA into a pronucleus also has been used successfully to produce transgenic pigs. Problems of visualizing the pronuclei because of opacity of the cytoplasm of pig ova was overcome by centrifugation (Wall et al., 1985). However, the efficiency of transferring genes into the germ-line of pigs is still low and varies from 0.31 to 1.73% (Pursel et al., 1990). Although a dramatic depression in backfat thickness was evident in MT-GH

transgenic pigs, unfortunately the enhanced growth rate typically observed in transgenic mice was not observed. There are a number of factors that appear to be relevant including the dietary requirements, appetite depression, and health problems associated with excess GH production in pigs (Pursel et al., 1990). The health problems and impairment of reproductive capacity are particularly severe in some animals and it must be concluded that uncontrolled overproduction of GH in pigs is unlikely to produce a superior pig. A similar conclusion can be made from studies in transgenic sheep (Rexroad et al., 1989).

Attempts have been made to express GH in a more controlled manner by using inducible promoters having very low basal activity such as the phosphoenolpyruvate carboxykinase (PEPCK) promoter. While PEPCK-GH fusion genes were useful in producing large mice and the promoter could be regulated by alteration of dietary carbohydrate and protein, the results in transgenic pigs was not ideal. Apart from a delayed onset of pathology, the performance mimicked that of the MT-GH transgenic pigs; most disappointingly, in contrast to the PEPCK-GH mouse there was no significant regulation afforded by manipulating the diet (Pinkert et al., 1990).

The results described above all indicate that continued overproduction of GH is detrimental to the animal. However, pigs injected with GH at specific periods throughout their growth phase remain healthy and have improved production traits (Etherton et al., 1986); therefore, it seems likely that effective external control of expression of the GH transgene is critical. In this regard, the results of experiments in which the bovine prolactin promoter has been used to direct transcription of the bovine GH gene in transgenic pigs are particularly encouraging (Polge et al., 1989). Basal activity of the promoter is low so that plasma levels of GH in the uninduced state are within the normal range of endogenous prolactin. A pulsatile secretion pattern of GH release can be induced by single injections of TRH. Most importantly, the transgenic pigs do not have the pathology typical of MT-GH and PEPCK-GH transgenic pigs. A recent report describing the use of a sheep MT rather than mouse MT promoter is also encouraging since this promoter is zinc inducible but has low basal activity (Shanahan et al., 1989).

An alternative approach to external control of gene expression is to use promoters which are controlled developmentally such as the alpha-fetoprotein and albumin promoters. The former is active in the liver only during early development, whereas the latter is active later when the alpha-fetoprotein promoter is developmentally switched off. Thus genes providing a growth advantage when overexpressed at a particular stage of development can be regulated by constructing the appropriate fusion gene. The DNA sequences necessary for skeletal muscle specific expression *in vivo* have recently been described by Chen et al (1990). Fusion genes in which these sequences are used as the promoter allows the expression of growth promoting genes to be targeted to skeletal muscle growth. Specific transgenes selected for improving production traits through developmentally or tissue specific expression have not been defined. However, identification of these genes and the use of very selective promoters will allow the generation of new genetic lines of livestock which lack the pathology caused by uncontrolled expression of transgenes.

Embryonic Stem Cells

The limitations imposed by microinjection; ie. the lack of control of the number of integrations and the site of integration can be avoided by using homologous recombination of DNA fragments into embryonic stem (ES) cells. ES cells are pluripotential cells isolated from the inner cell mass of blastocysts at the pre-implantation stage. The establishment of ES cell lines and their maintenance is well documented in the mouse (Robertson, 1987) and in the hamster (Doetschman et al., 1988). A challenge for reproductive biologists is the development of similar cell lines from livestock. To our knowledge only in the pig have ES cells been maintained through serial cultures (Piedrahita et al., 1988).

The advantage of ES cell lines for production of transgenic animals is that by homologous recombination genetic information can be altered in a controlled manner. For example, genes can be inactivated, replaced or mutated, or regulatory regions can be altered. The changes are introduced by transfecting, microinjecting, or infecting ES cells with DNA constructs having high homology with the chromosomal sequences to be modified. By specific selection techniques and by cloning, ES cells which have been modified by homologous recombination are isolated and then injected into blastocysts to produce chimeric offspring. Some of the offspring will be germ-line chimeras.

Once ES cell lines have been established from the embryos of economically important livestock and altered by homologous recombination they can be preserved indefinitely to be used as a resource to provide a stock of genetically identical animals. Importantly, as new discoveries are made the cells can be further modified to introduce additional desirable traits. ES cells can also be used for genetic selection *in vitro* by selection of lines having desired linkage patterns.

Primordial Germ Cells

The production of transgenic chickens is more difficult than the production of other transgenic animals because the early embryo is not readily accessible. When the fertilized egg is laid it consists of approximately 50,000 cells and microinjection of either DNA or ES cells to produce germ-line chimeras is very inefficient because only about 200 of the 50,000 cells in the egg are germ cells. The conventional approach is to use a retrovirus to deliver the transgene with the objective to infect every cell in the embryo. Although the efficiency of this approach is low it has been used successfully (Salter et al., 1986; Bosselman et al., 1989; Chen et al., 1990). Improved growth and acceleration of sexual development was observed following high level expression of bovine GH (Chen et al., 1990). Using similar methods transgenic chickens expressing the env gene have shown resistance to infection by avian leucosis virus (Salter & Crittenden, 1989; Chen et al., 1990). More recently studies with the Mx gene suggest that transgenic chickens expressing Mx would be resistant to avian influenza (Garber et al., 1990).

Although the early chicken embryo is not readily accessible the primordial germ cells themselves present a potential target for gene insertion. On day 1, when the fertilized egg is laid the primordial germ cells are located extra-embryonically at the germinal crescent. Between day 2 and 3, these cells migrate through the vasculature to settle in the gonadal

ridge. It is possible to isolate these cells either by dissection from the germinal crescent or from the blood. Indeed, it has been shown that primordial germ cells from one embryo can be introduced into a surrogate embryo between days 2 - 3 and that these cells populate the gonadal ridge to produce germ-line chimeras (Wentworth, 1989; Simkiss et al., 1989). Clearly, once primordial germ cells can be maintained and passaged in a manner similar to that described for ES cells the establishment of new lines of transgenic poultry will become routine.

Consequences of Imprinting of Transgenes

Transgene inserts are prone to methylation imprinting such that paternally transmitted transgenes are undermethylated whereas maternal transmissions are hypermethylated (Surani et al., 1990). Because DNA methylation can control which genes are expressed, allelic differences in epigenetic modifications can affect expression of the transgenes. In most cases methylation patterns are reversible when transmitted alternately through the male and female germ line; although an example has been reported where transmission through the female line caused irreversible hypermethylation and the gene was only expressed when it was repeatedly transmitted through the paternal germ line (Hadchouel et al., 1987).

It is curious that there is a higher incidence of imprinting of transgenes (ca. 20%) than would be anticipated if one considered random integration into the mouse genome where only about 10% is subject to imprinting (Surani et al., 1988; Cattanach, 1986). There is evidence to suggest that transgenes can be imprinted even when they integrate outside the imprinted domains defined by genetic studies. It is possible that transgenes act as insertional mutations which perturb chromatin structure during development; similar perturbations might also occur in DNA deletion experiments (Surani et al., 1990). Thus a priori it is difficult to predict a specific phenotype even when a gene of known function is modified in a controlled manner.

Observations have been made in mice showing that the expression of transgenes can also be affected by strain differences. These differences are thought to be regulated by strain-specific modifier genes involved in DNA methylation. Cumulative DNA methylation differences have also been observed from one generation to the next (Surani et al., 1990). How these observations might extrapolate to transgenic livestock is unknown. However, imprinting is an important factor to be considered, particularly in situations where one wishes to maintain a stable phenotype.

Discussion

Although ultimately the power of controlled genetic engineering of livestock will revolutionize the industry there remain a number of barriers to overcome. We do not have a sufficient knowledge of the role of specific genes which control performance in domestic farm animals. We also lack understanding of how specific genes are normally regulated. Furthermore, in situations where we would choose to regulate transgene expression

externally, as is apparently the case with GH, we are only beginning to identify inducible promoters having low basal activity *in vivo*.

There are technical problems associated with the reproductive biology of farm animals. The recovery of eggs for microinjection and conditions for survival of pig, cattle and sheep eggs *in vitro* must be optimized. This becomes a complex issue when one considers the genetic diversity of commercially important livestock. The long gestation times and the long gestation intervals of cattle, sheep and pigs, and a relatively small litter size limits the rate at which research can progress.

The efficiency of producing transgenic farm animals is very low, and the costs of maintaining a large animal research facility are enormous. There is also the hurdle of obtaining permission to allow experimental transgenic food animals to enter the food chain. Clearly, economics are also a major problem in promoting transgenic research on large and expensive animals.

With the present techniques of producing transgenic animals, the transgene is incorporated randomly into the genome, or in case of ES cells, directly in one particular stem cell line. The controlled manipulation of genetic traits through ES cell technology can be used to compliment traditional quantitative genetic approaches. However, it is not yet feasible to routinely derive an ES-line for, say, 100 founder breeding animals. In the setting described here that is a serious problem. If with improved techniques several outstanding founder animals can be produced with the transgene at a specific site in the genome, the potential of inclusion in a breeding program improves considerably. The back-crossing procedure is no longer needed then and the creation of two strains producing crossbred stock homozygous for the transgene becomes feasible.

Genetic engineering of livestock is clearly still in its infancy. The most likely outcome of the explosion of knowledge in molecular genetics is that both the traditional and contemporary genetic approaches will complement each other in producing livestock with traits of enhanced growth performance and disease resistance. In particular, the current projects under way to map the pig genome will provide information of enormous value for defining specific traits at the DNA level. It should be possible to extrapolate this information to other species with a high level of confidence. By applying this knowledge it will be possible to modify the genome by transgenic means in a very predictable manner.

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IMMUNOMODULATION OF HORMONES OF THE SOMATOTROPIN AXIS

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Summary

The immunological manipulation of hormones of the somatotropin axis has been described. The activity of growth hormone-inhibiting hormones can be reduced by autoimmunization, leading to the production of polyclonal antibodies which neutralize hormone activity in much the same way that vaccination against protein antigens is used to convey disease resistance. Alternatively, certain monoclonal antibodies to protein hormones actually increase their activity; this phenomenon can be extended to the production of endogenous polyclonal antibodies of restricted specificity which recognize peptide regions of the hormone (equivalent to those for the monoclonal antibody) and result in increased activity of hormones of the growth hormone axis. Lastly, the use of antibodies as hormone (or protein) mimics is described, in which anti-antibodies (termed anti-idiotypes) behave as original hormone.

Keywords: *Meat production, immunomodulation, somatotropin axis.*

Introduction

During recent years, it has become clear that exogenous administration of growth hormone (GH) can improve animal performance. GH will increase milk yield in dairy cows (e.g. Bauman et al., 1989; Phipps et al., 1990) and will stimulate greater lean: fat ratios and also rates of daily gain in meat-producing animals (e.g. Boyd & Bauman, 1989; Campbell et al., 1988; Pell & Bates, 1990; Pell et al., 1990). The reduced fat content of carcasses and the decreased urinary nitrogen output (van Weerden and Verstegen, 1989) of GH-treated animals is of benefit to both the consumer and the environment. However, exogenous treatment with GH involves regular administration of hormone, either as injections or as implants and their effects are relatively short-lived. Whilst this might be a versatile advantage for the strategic use of GH, for example in dairy animals, it is not as suitable for meat-producing animals which are not maintained for reproductive purposes. Immunological modification of an animal's existing hormonal repertoire, producing similar effects to those of exogenous GH, offers an alternative approach. Such immunizations have the additional advantage of requiring only minute quantities of material compared to the considerable amounts needed for simple hormone treatment.

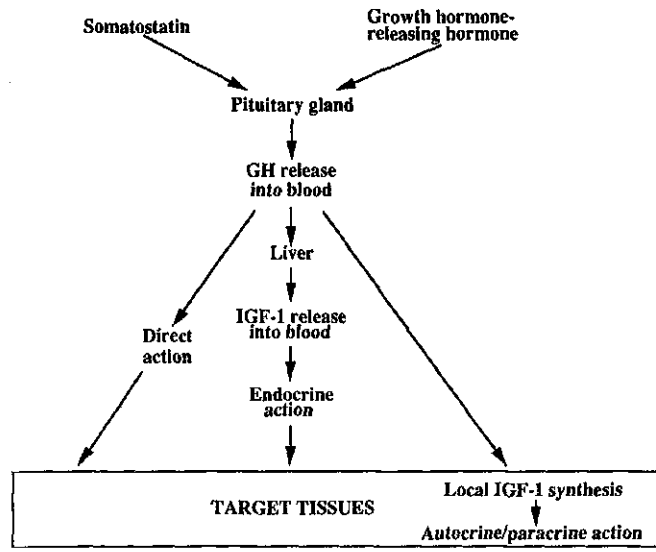

Figure 1. Diagrammatic summary of the somatotropin axis

A schematic summary of the somatotropin axis is presented in Figure 1 and it is clear from this that several sites for potential immunological manipulation exist. Basically, hormones which stimulate GH activity may be amplified or those which inhibit GH action may be suppressed. Therefore, to try and amplify GH action the amount or activity of growth hormone-releasing hormone, GH or IGF-1 (insulin-like growth factor-1) must apparently be increased or those of somatostatin decreased. This simple approach does not take into account negative feedback mechanisms which counterregulate the somatotropin axis and which may confound long term effects.

Alternative approaches for immunomodulation

Neutralization of activity

The simplest modification of hormone activity is to raise polyclonal antibodies against that hormone in the same way that injection of antigen is used to convey disease resistance in animals and man. The mixture of antibodies which is produced will bind to multiple sites on the hormone and inhibit activity, presumably by preventing access of binding sites to hormone receptors and by facilitating hormone destruction via the immune system. This straightforward approach is, of course, well-established in the field of animal health.

Potentiation of activity

Using hypopituitary animal models, it has been shown that certain monoclonal antibodies (MAbs) raised against both human (h) and bovine (b) GH could increase the activity of exogenous homologous GH's; complexes of GH and MAb induced further stimulation of weight gain and sulphate incorporation into cartilage when compared to the increases induced by GH alone (Aston et al., 1987; Holder et al., 1985). The mechanism of action of this phenomenon is not yet fully elucidated (schematically represented in Figure 2) but the specifity of antibody binding to certain epitopes of GH must be critical. However, the molecular topography of sites of binding for these panels of MAb's has, so far, remained undefined, although epitopes have been identified for other panels (Cunningham et al., 1990; Mazza et al., 1990; Roguin et al., 1990). The use of antisera raised against synthetic peptides which cross-react with native GH allows identification of sequence regions of GH which are associated with enhancement of activity. For instance, peptide regions of GH can be selected according to their hydrophilicity and the secondary structure of GH so that peptides with antigenic potential are predicted. A systematic approach for the mapping of topographical sites involved in hormone enhancement can be made using the methods of Geysen et al. (1984) in which hundreds of peptides can be synthesised and binding assays performed on microtitre plates.

The identification of sequence regions of GH which are involved with enhancement of activity is of crucial importance as these peptides can then be used for the development of growth-enhancing vaccines. Thus, animals could be immunized with small amounts of synthetic peptide, inducing the production of endogenous polyclonal antibody of restricted specificity (defined by the peptide design) which would bind to a specific region of GH, enhancing its activity and mimicking the potentiation previously observed using MAb enhancement. It is important to note that MAb's will recognize conformational determinants which can involve discontinuous regions of amino acid sequences whereas potentiation using antisera raised against synthetic peptides involves linear sequences. Thus, it is necessary that the peptide in isolation must be administered so that it retains the three-dimensional structure of the corresponding region of the native GH.

The mechanism of action of MAb- and presumably of peptide antiserum- mediated enhancement remains unresolved; several theories exist and have been reviewed by Aston et al. (1989); the major propositions are considered here. Binding of GH to enhancing antibodies in blood may simply prolong the half-life of GH by acting as a reservoir or slow-release system and protecting GH from degradation. Receptor processing and degradation of GH-receptor complexes may be inhibited in the presence of enhancing antibodies, resulting in decreased receptor turnover and an increased intracellular signal. The binding of antibody may induce conformational changes in GH itself, causing increased affinity of hormone for receptors. Several different receptor subtypes exist for GH (Barnard et al., 1985) and anti-hormone antibodies may inhibit binding to one type but not another (Ivanyi, 1982; Aston et al., 1986; Thomas et al., 1987). Thus enhancement could be due to restriction of GH binding to certain receptor subtypes, therefore increasing availability to others.

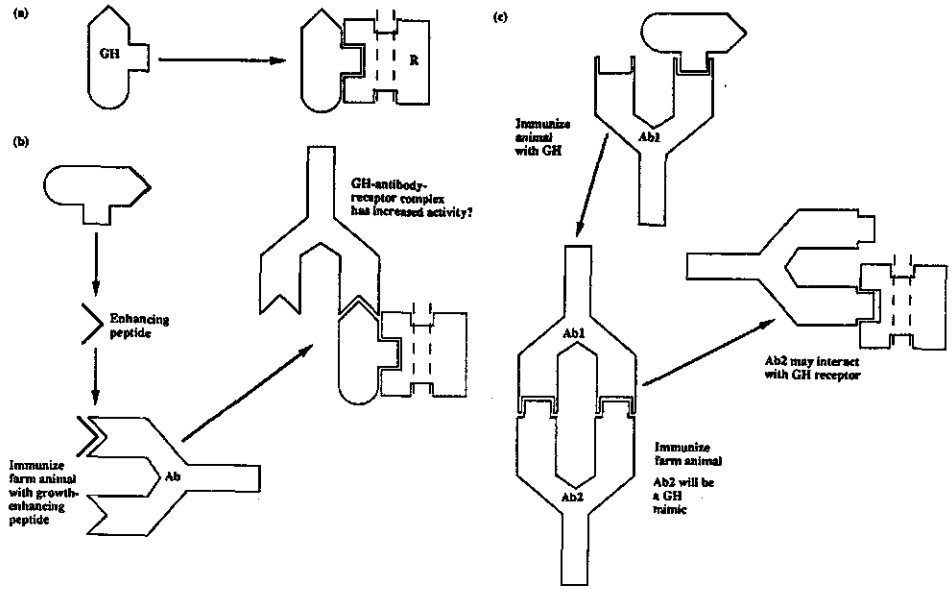

Figure 2. Interaction of (a) GH with receptor (R), (b) GH with MAb and (c) anti-idiotype with GH receptor.

Antibodies as protein mimics

In 1974, Jerne proposed that regulation of the immune system involved a network of interacting antibodies. In this system any new antibody (Ab_1) produced to a novel antigen would itself be novel (and hence 'foreign') to the animal producing it, leading to the production of anti-antibodies (Ab_2). Within these antibody populations there exists a subset of antibodies which are described as the 'internal image' of the original antigen because Ab_2 binds to Ab_1 at the same position as the original antigen. Since Ab_1 is referred to as the idiotypic response, these internal images (Ab_2) are referred to as anti-idiotypes. Anti-idiotypes can be produced in a deliberate fashion using the approach described in Figure 2. Such anti-idiotypes have been produced for a number of hormones, including insulin (Sege and Petersen, 1978), ß-adrenergic compounds (Schreiber et al., 1980), acetylcholine (Wasserman et al., 1982), TSH (Farid et al., 1982) and GH (Gardner et al., 1990). In many cases these antibodies are also capable of inducing the biological response normally attributed to the respective hormone whilst in other cases they may serve as antagonists.

Anti-idiotypes to GH have obvious application to animal production systems as alternative non-hormonal techniques for the manipulation of carcass composition. Identification in monoclonal form of the idiotypes (Ab_1) which induce the formation of hormone mimics (Ab_2) would allow them to be used to immunize animals in order to induce an endogenous production of Ab_2, the GH image. The monoclonal anti-idiotypic antibodies

should mimic single epitopes on the GH molecule and will allow several questions to be addressed: how many epitopes of GH are involved in binding to GH receptors and do mimics of different epitopes on GH bind to specific receptor populations in different tissues? In addition, it is important to discover whether the different subsets of GH receptors bind to different epitopes on the GH molecule and whether they induce different metabolic responses. Studies attempting to resolve these questions have involved the concept of bioactive fragments of GH but anti-idiotypic mimics have a distinct advantage over fragments; they essentially resemble the shape rather than the primary amino acid sequence of the epitope on GH which they mimic. They are thus in the appropriate physical conformation which, as mentioned earlier, is difficult to achieve for short synthetic or cleaved peptides. An additional advantage is that these antibodies may be mimics of epitopes which involve amino acid residues held in close proximity to one other but derived from different parts of the polypeptide chain (discontinuous epitopes). The three-dimensional structure of porcine GH was recently elucidated by using X-ray diffraction (Abdel-Meguid et al., 1987) and it seems likely that such epitopes may well be involved in binding to the GH receptor. The primary amino acid structure of the GH receptor has also been deduced recently using recombinant DNA techniques (Leung et al., 1987) and with eventual detail of its three-dimensional structure, proposed sites of interaction with GH should be possible. Even though this discussion has largely been confined to the consideration of GH mimics, the anti-idiotypic approach to improvement of animal production is versatile as any protein can be mimicked, for example GH receptors, binding proteins or even enhancing antibodies.

Evidence for immunomodulation of the somatotropin axis

Neutralization

Immunoneutralization of the growth hormone inhibiting factor (SRIF), somatostatin, was first shown by Spencer & Williamson (1981) to have a dramatic effect upon the growth rate of St. Kilda lambs. A 76% improvement was observed compared with globulin-immunized controls. There was no alteration in the proportions of muscle, bone or fat suggesting that this improvement was not exerted simply via GH. Despite the sometimes dramatic rise in circulating GH concentrations induced by passive immunizations (infusion of antibodies), there are only marginal changes after active immunizations, even when high titres of anti-SRIF antibodies are detected (Spencer et al., 1983). Other mechanisms have been proposed primarily involving an effect on gut function, possibly mediated by the gastrin family, which include changed rate of passage and improved digestibility of nutrients (Fadlalla et al., 1983; Rodriguez et al., 1988). Since the early encouraging experiments, the positive results have been far less dramatic and are matched by similar numbers of reports of lack of efficacy as well as an erratic pattern of associated changes in IGF-1 concentrations etc. Even in recent reports no clear consensus has emerged with disappointing results in cattle (Trout & Schambacher, 1990) and sheep (Hoskinson et al., 1988) being countered by improvements in a range of parameters observed by Sun et al. (1990a).

The use of severe adjuvanting protocols has been shown to depress growth (Klasing et al., 1987) so the invariant use of Freund's Complete adjuvant in these growth experiments might have led to problems. The difficulty of consistently recording improvement in some ruminant growth parameters by simple administration of GH itself suggests that a more appropriate model is needed, such as lactation in small ruminants or growth in pigs. However, even here contradictory reports exist with both nil effects (Deligeorgis et al., 1988) and positive findings (Sun et al., 1990b) in lactating sheep. Published data from pigs have not yet illustrated the potential of this approach in a single unified protocol.

From the confusion of available data and also the tendency for negative results to remain unreported, the value of SRIF immunization remains, at present, equivocal. In any case, evidence suggests that the somatotropin axis is not the target for effects of SRIF neutralization. No other component of this axis is appropriate for immunoneutralization to improve growth or body composition.

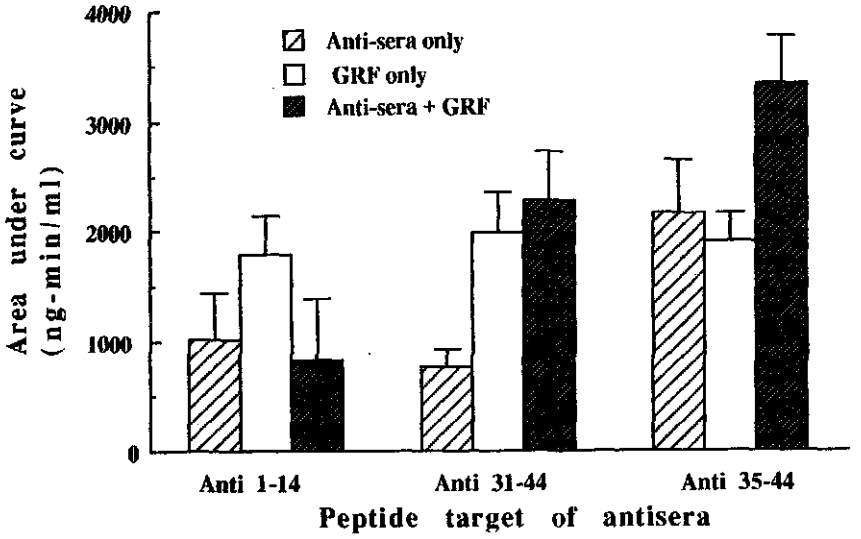

Figure 3. GH release in response to GRF and anti-GRF antisera.

Enhancement

The monoclonal antibody enhancement of GH activity is well established for hypopituitary animals which can, therefore, only be stimulated using exogenous hormone. Of key importance is the demonstration that the activity of endogenous hormone in normal farm animals can be increased and preferably by antibodies produced by the animal itself (active instead of passive immunization). The following describes available information to date.

Growth hormone-releasing factor (called GRF, somatocrinin or GHRF) is a single polypeptide chain of 40 or 44 amino acids and is thus about one-fifth of the size of GH. Using short conjugated polypeptide sequences derived from human GRF, we immunized

sheep using Freund's adjuvant. The anti-hGRF antibodies were purified by ammonium sulphate precipitation and hydroxyapatite chromatography. On the basis of tests *in vitro*, three different antisera were selected for direct infusion into three groups of five sheep. Each sheep received, at different times: antibodies only, hGRF or hGRF complexed to each of the antibodies. Levels of circulating GH were measured 60 min before and 240 min after the treatment. The results are summarised in Figure 3. As there were no significant differences in the pre-treatment GH levels, the area under the plasma GH curve from treatment to 240 min has been treated as a measure of GH release capability. The GRF alone produced similar responses in all three groups. This was significantly reduced in those animals receiving GRF plus anti 1-14 antibodies. These antibodies and those directed against GRF 31-44 when administered alone had no effect on GH concentrations. In contrast, the preparation from anti 35-44 antisera given alone equalled the GH release stimulated by GRF alone. The potency of this particular antiserum was further emphasised by the significant increase in GH levels over antibodies or GRF alone (P and P, respectively) when the complex of antibodies plus GRF was administered. This effect could be seen over the entire 240 min period. Similar additional and significant increases as a result of the 31-44 plus GRF complex could be seen over the 60 min post-treatment (not shown), but these were not sustained. Whether the apparent enhancement effect observed here with antibodies and GRF is the same phemonomon as that with GH remains speculative but does indicate that the principle may have wide application within the management of the growth and development of farm animals. Equally, it may not be confined to hormones of the somatotropin axis.

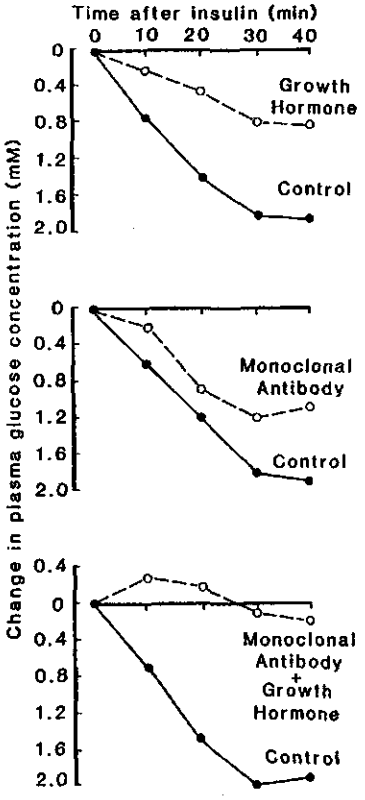

Figure 4. Insulin tolerance test in GH and MAb-treated lambs.

Monoclonal antibody-induced increases in the diabetogenic action of GH were demonstrated for both exogenous and endogenous hormone in lambs (Pell et al., 1989b). Plasma glucose concentrations during insulin tolerance tests are given in Figure 4. After 40 min, insulin induced a decrease in glucose concentrations of 1.6 to 2.0 mmol/l for all groups of lambs during the pre-treatment period. As expected, treatment with GH alone inhibited the insulin-induced fall in glucose concentrations (P). This also occurred in sheep treated with MAb alone (P) implying potentiation of endogenous GH. The fall in glucose concentrations was further inhibited in lambs treated with the MAb-GH complex thus confirming earlier observations of MAb-enhancement in rodents.

Table 1. Lipid metabolism *in vitro* (mol/2h/g wet weight) for samples of subcutaneous fat from lambs passively immunized against a peptide region of bGH.

Treatment group	Lipogenesis	Lipid oxidation	Lipolysis
Control Ig	45.2^{a}	2.69^{a}	5.79
Anti-peptide Ig	$32.3^{a,b}$	1.81^{b}	6.03
GH + control Ig	18.3c	$1.11^{b,c}$	6.93
GH + anti-peptide Ig	$19.7^{b,c}$	1.01^{c}	7.36
S.E. (n=6)	4.7	0.25	0.94
Significance	0.01	0.001	NS

GH activity has also been increased by passive immunization of lambs (Pell et al., 1989a). Antibodies were raised in sheep against a synthetic peptide region equivalent to amino acids 134 to 154 of bGH and these were concentrated by sodium sulphate precipitation. This preparation, when complexed to GH, enhanced sulphate uptake into costal cartilage of Snell dwarf mice by approximately two-fold when compared to stimulation by GH alone. Lambs were treated for 16 days with either control antibody, bGH, anti-peptide antibody or GH pre-complexed to anti-peptide antibody. At slaughter, samples of subcutaneous fat were removed for the determination of rates of lipogenesis, lipolysis and lipid oxidation *in vitro*. As shown in Table 1, both GH and anti-peptide antibody inhibited rates of lipogenesis and lipid oxidation. The animals treated with the GH antibody complex did not exhibit further changes in lipid than those for GH alone but it is possible that the dose of GH used (10 mg per lamb every other day) stimulated maximal changes.

Antibodies to a similar region of bGH potentiated the galactopoietic action of GH (Figure 5). Lactating ewes were treated for 21 days with GH and anti-peptide antibodies using a similar experimental design to that for the lambs. Both exogenous GH and anti-peptide antibody increased milk yield significantly. This, and the previous experiment demonstrate that antibodies raised against specific sequences of bGH can potentiate both exogenous and endogenous GH when the antibodies are administered passively and for short periods of time.

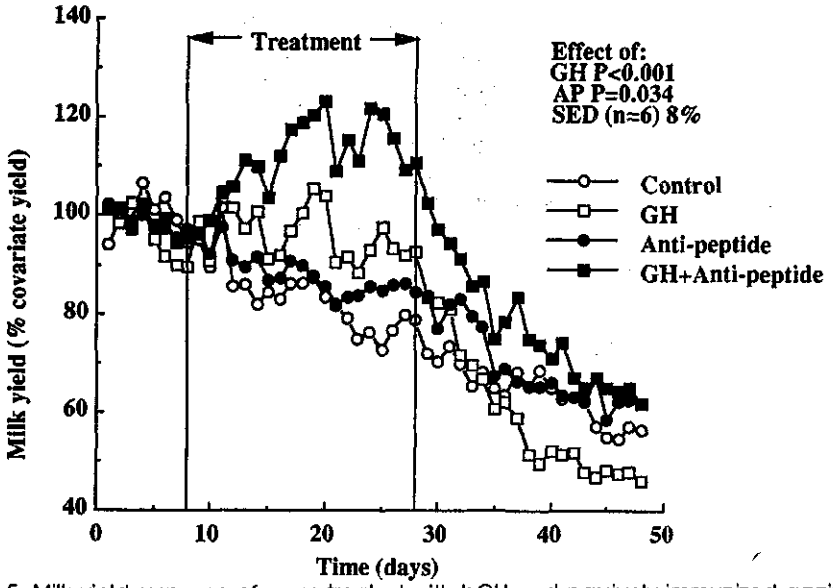

Figure 5. Milk yield response of ewes treated with bGH and passively immunized against a peptide region of bGH.

To further the investigation of the capacity of endogenous antibodies to enhance GH, whilst retaining the sensitivity of a traditional GH bioactivity model, experiments were performed in hypophysectomized rats (James & Cottingham, 1989). Once good levels of anti-hormone antibodies had been detected in response to various porcine (p) GH peptide fragment immunizations, the rats were dosed daily with 50 g recombinant pGH. Resultant growth rates were compared, in the same experiment, to those of hypophysectomized rats which had received adjuvant but no antigen and were similarly dosed with pGH. These latter groups also received a GH-potentiating monoclonal or passive immunizations of anti-peptide antibodies raised in sheep; control rats were treated with pGH in placebo vehicle. As shown in Figure 6 the passive procedures with the monoclonal and the sheep antibodies significantly potentiated GH. In the case of active immunization with pGH fragment 122-138Cys, the endogenous antibodies were able to exert a very effective potentiation of administered pGH. Despite a similar range of titres, the 175-189 fragment was not able to exert a similar effect, though no inhibition was observed either.

Table 2. Carcass composition of lambs actively vaccinated with peptide 133-153 and treated with exogenous GH.

	C	GH	AP	GH+AP	SED	Main effects GH	AP
Weight	23.91	23.68	25.16	24.94	0.85	NS	*
Water	10.67	11.55	12.24	12.35	0.41	0.094	***
Protein	3.39	3.81	3.73	3.88	0.14	**	*
Fat	8.56	6.96	8.33	7.93	0.59	**	NS
Ash	1.16	1.44	1.17	1.29	0.16	0.093	NS

C, control; GH, 0.10 mg/kg/day; AP, active vaccination with peptide; * = P< 0.05; ** = P>0.01; *** = P>0.001

Lambs actively vaccinated with the bGH peptide corresponding to amino acids 133-153 have also provided encouraging data. Lambs were immunized with bGH peptide or ovalbumin and were treated with exogenous GH or vehicle for 10 weeks; carcass weight and composition are given in Table 2. GH alone induced an increase in carcass protein content and tended to increase water and ash accumulation; these increases were offset by a considerable decrease in carcass fat accumulation so that carcass weight was unchanged. Peptide immunized- lambs exhibited a significant increase in carcass weight which consisted of water and protein; little effect was observed on carcass fat content. Actively vaccinated lambs treated with additional GH did not have any further improvement in carcass weight or quality.

These encouraging results indicate that there is potential benefit from endogenously-derived antibodies to potentiate GH activity but this is no substitute for definitive experiments in target species; no such work has been published. However, preliminary positive observations exist. In the course of investigations on the use of different adjuvants, the levels of anti-hormone antibodies raised in response to peptide immunizations were positively and significantly correlated with the growth rate of the animals during the period that the antibody titres were elevated (Figure 7).

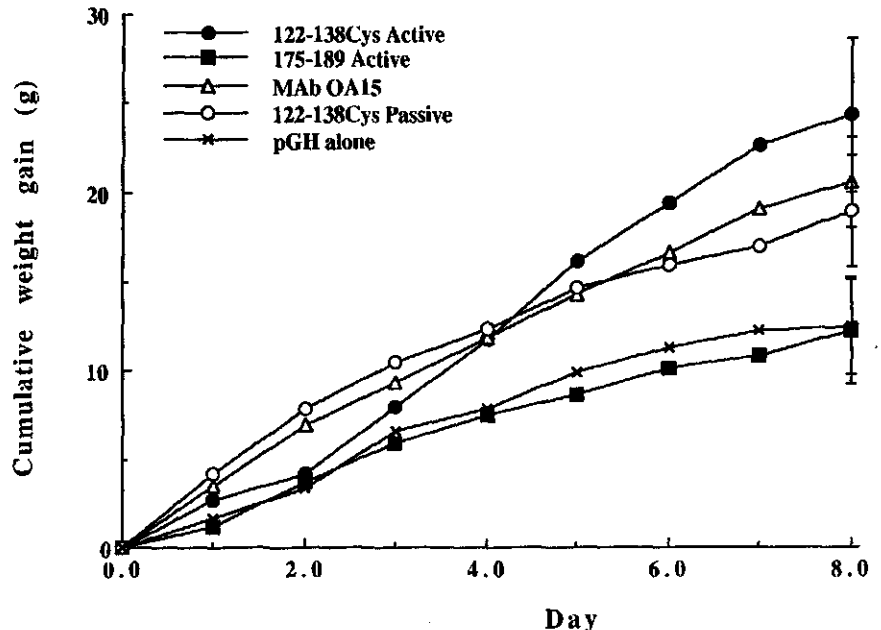

Figure 6. Cumulative weight gain in hypophysectomized rats actively or passively immunized against peptide regions of pGH or treated with MAb, and administered exogenous pGH.

Even though IGF-1 is known to mediate many of the anabolic actions of GH, little research has been published on the immunological manipulation of IGF-1 activity. Several groups have raised MAbs to IGF-1 (Morrell et al., 1989; Cascieri et al., 1990; Tamura et al., 1990). In general, these inhibit the actions of IGF-1 *in vivo*, implying that they bind to epitopes on or near the receptor-binding region. IGF-1 epitopes which recognize both monoclonal and polyclonal antibodies have also been identified recently.

Anti-idiotypes

Anti-idiotypes to GH have been produced and shown to bind to GH receptors in sheep and rat liver and rat adipocytes. They did not however disrupt prolactin binding to the liver (Figure 8), indicating a high degree of specificity for GH receptors; when given to hypophysectomized rats for 3 days, they also increased body weight gain (Figure 9) although somewhat surprisingly, they failed to stimulate serum concentrations of IGF-1 (Gardner et al., 1990). These results were produced using polyclonal antisera and therefore a mixture of antibodies, probably mimicking a number of epitopes on the GH molecule. The production of monoclonal anti-idiotypic antibodies which should mimic single epitopes on the GH molecule would appear to present a much better prospect for producing consistent effects.

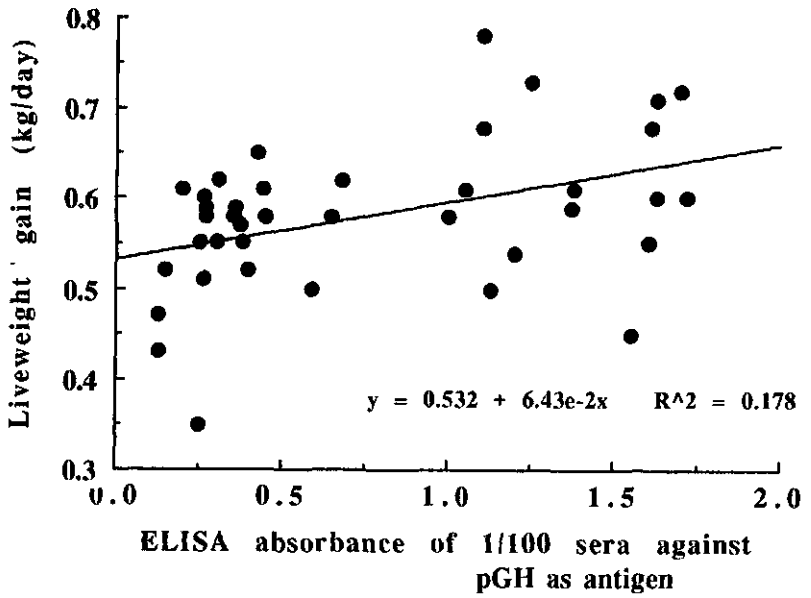

Figure 7. Correlation of growth rate and antibody titre in pigs actively immunized against a peptide region of pGH.

As discussed earlier, the production of antibodies to GH has provided evidence that different forms of GH receptor may exist in different tissues. The studies of Barnard et al. (1985) and Thomas et al. (1987) demonstrated that monoclonal antibodies bound to GH restrict its ability to interact with GH receptors in some tissues but not others. Recent studies by Elbashier et al. (1990) involving a panel of monoclonal anti-idiotypic antibodies to hGH showed divergent effects in different receptor-binding systems. Several of these antibodies inhibited GH binding to rat liver, enhanced binding to the human GH serum-binding protein whilst having no effect on GH binding to rabbit liver. This is possibly the most direct evidence to date to suggest that different epitopes of GH are involved in binding to different receptor populations.

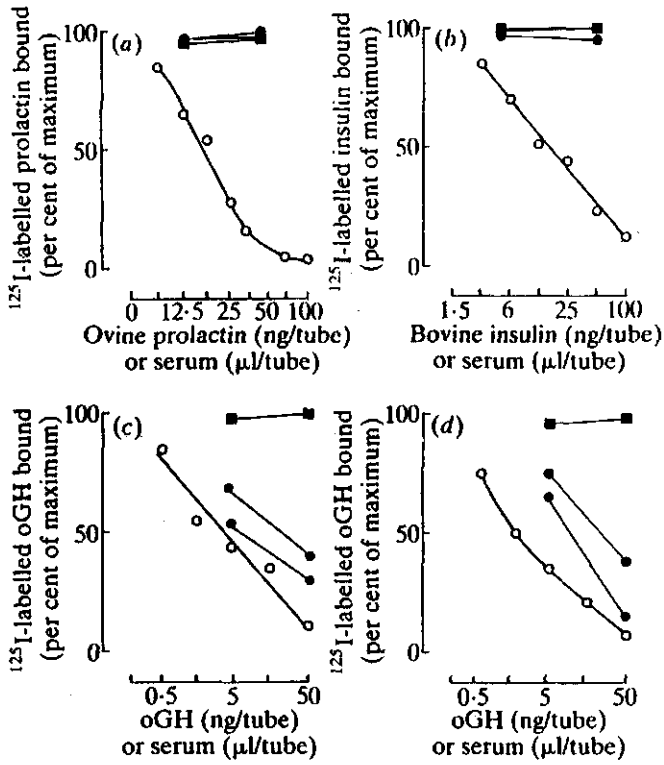

Figure 8. Inhibition of binding of (a) ^{125}I-labelled ovine prolactin to sheep liver membranes, (b) ^{125}I-labelled insulin to sheep liver membranes, (c) ^{125}I-labelled ovine GH (oGH) to isolated rat adipocytes or (d) ^{125}I-labelled oGH to rat liver membranes by the respective unlabelled hormone (open circles), non-immune sheep serum (closed squares) or two sheep anti-idiotypic antisera (closed circles). Values are expressed as a % of the maximum binding of ^{125}I-labelled hormone in the absence of unlabelled hormone.

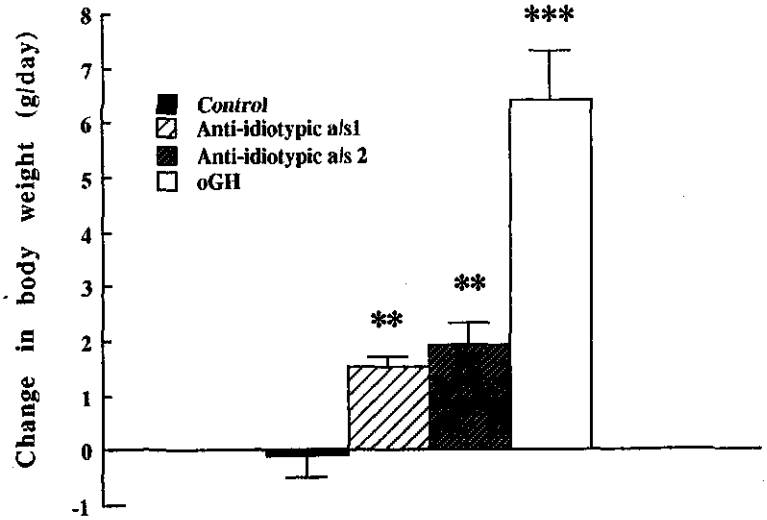

Figure 9. Body weight response of hypophysectomized rats to treatment with oGH and anti-idiotypic antibodies.

Conclusions

The exciting and relatively new field of immunological manipulation of hormone concentration or activity has been reviewed in this article. Several approaches exist and have been described; each has particular disadvantages and merits. Generally, modification of an animal's immune system should produce long-term rather than temporary changes of GH/IGF-1 status and is therefore of benefit where permanent responses are needed, such as for the rapid growth of a lean carcass.

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THE EFFECTS OF EXOGENOUS GROWTH HORMONE-RELEASING FACTOR OR SOMATOTROPIN ADMINISTRATION ON GROWTH PERFORMANCE, CARCASS CHARACTERISTICS, MEAT QUALITY AND REPRODUCTIVE FUNCTION IN POULTRY AND PIGS

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Summary

The present paper reviews the experimental data concerning the effects of exogenous Growth Hormone-Releasing Factor (GRF) or somatotropin (ST) administration in pigs and poultry.

Although somatotropin seems to be more or less involved in the regulation of growth in birds, exogenous administration of GRF or somatotropin has only transient (or, most often, no effect at all) on growth performance and carcass characteristics of chickens.

In ad libitum fed pigs administered porcine somatotropin (pST) during the finishing period, daily feed intake is reduced (2-22%), growth is generally accelerated (up to 47%) and feed efficiency is dramatically improved (3-38%), in connection with a sharp reduction in fat deposition (7-44%). Lean content of the carcass is augmented (2-23%). Due to the increased weight of some organs (liver, heart, etc.), dressing percentage is reduced (1-4%). Administration of GRF or of a GRF analog have qualitatively the same effects as pST.

Main factors of variation of pST effect on performance and carcass characteristics of pigs include: *1) Dose of pST.* Daily feed intake and fat deposition decline linearly with increasing pST doses while the response of feed efficiency, growth rate and lean deposition is quadratic. *2) Form of administration.* Sustained release of pST seems to be less efficient than daily injection. *3) Age and weight.* The effects of pST are similar, both qualitatively and quantitatively, during the growing period or in heavy pigs than during the finishing period. *4) Genotype, sex and castration.* The effects of pST are negatively related to the animal's potential for lean tissue growth.

The effect of pST on the percentage of the various muscle fibre types is unclear. However, an increase in their size is most often noticed. Data indicate pST effects on muscular characteristics may vary widely according to muscles. Physical and sensory properties of meat are generally unaffected or only slightly altered by pST treatment. Besides pST effects on muscle and fat composition, the most consistent changes concern elevated ultimate pH measurements, increased shear force values and decreased tenderness. Consumer acceptance of fresh pork or processed products does not seem to be impaired by pST treatment.

The impact of pST treatment on the onset of puberty is not clear. However, there is convincing evidence that any possible adverse reproductive change associated with chronic administration of pST to prepubertal gilts is transient. Administration of pST during gestation has no effect on litter. The impact of pST treatment on milk production by lactating sows is still controversial.

Keywords: *GRF, GH, poultry, pigs, growth, carcass characteristics.*

Introduction

The aim of the present article is to review the experimental data concerning the effects of exogenous administration of GRF (Growth Hormone-Releasing Factor) or ST (Somatotropin) on performance, carcass characteristics, meat quality and reproductive function in pigs and poultry.

The paper is organised into the following sessions: the effect of exogenous administration of ST or GRF on performance in poultry; the main effects of exogenous porcine somatotropin ((r-)pST) or GRF administration on growth performance and carcass composition in ad libitum fed pigs; the main factors of variation of performance response to rpST administration; meat quality in rpST treated animals; the impact of rpST administration on reproductive function.

The effects of exogenous ST administration on growth performance and carcass characteristics in poultry

As in mammalian species, ST seems to be involved in the regulation of growth in poultry. ST has lipolytic and antilipogenic effects in birds (John et al., 1973 ; Foltzer et al., 1975 ; Foltzer & Miahle, 1976 ; Harvey et al., 1977 ; Campbell & Scanes, 1986). Administration of ST antisera (Scanes et al., 1977) or hypophysectomy (Nalbandov & Card, 1943 ; King, 1969 ; Scanes et al., 1986) results in a reduction of growth rate. However the effects of hypophysectomy are only partially reversed by chicken or mammalian ST administration whereas growth is fully restored by exogenous T3 injection (Marsh et al., 1984 ; Scanes et al., 1986). Moreover, there is no evidence for a positive relationship between growth potential and chicken somatotropin (cST) secretion. Dwarf chicks exhibit higher circulating cST levels than their normal counterparts (Harvey et al., 1984 ; Lilburn et al., 1986 ; Huybrechts et al., 1987). Similarly, blood cST levels are higher in slow growing than in fast growing strains (Burke & Marks, 1982 ; Stewart & Washburn, 1983 ; Lilburn et al., 1986 ; Goddard et al., 1988). However IGF-I levels are higher in normal than in dwarf chickens (Huybrechts et al., 1987), in connection with a higher number of hepatic cST receptors (Leung et al., 1987 ; Kuhn et al., 1989).

Immunoneutralization of somatostatin has been shown to increase growth rate and decrease abdominal fat in chickens (Spencer et al., 1986 ; Buonomo et al., 1987). However, since neither cST nor IGF-I levels were elevated in immunized birds, the benefits gained

from somatostatin immunoneutralization may be exerted through mechanisms unrelated to the somatotropic axis.

Effects of mammalian ST

In early studies, relatively impure preparations of ovine (oST) or bovine (bST) somatotropin did not stimulate growth in chickens (Eaton et al., 1955 ; Libby et al., 1955 ; Glick, 1960). More pure bST or oST preparations or recombinant bST (r-bST) have no effect on growth rate in normal chickens (Tojo et al., 1979 ; Scanes et al., 1975, 1984 ; Marsh et al., 1984). However, increased growth rate has been reported in chickens treated between 6 and 12 weeks of age with a tryptic digest of bST (Myers & Peterson, 1974) or in chick embryos treated with a bST preparation (Hsieh et al., 1952). Administration of r-bST at very high doses (0.5 or 2.5 mg/kg BW per day) in female broiler chicks between 4 and 6 weeks of age increased growth rate and feed intake during the first week of treatment (Buonomo & Baile, 1988). However, r-bST had no effect on performance during the second week, while high antibody titres appeared in blood. No significant effect of r-bST treatment was observed on carcass characteristics at the end of the two week period.

Effects of cST

Purified or semipurified preparations of cST administered for short periods (4-9 days) have a stimulatory effect on growth of young chickens (Tojo et al., 1979 ; Scanes et al., 1986). Leung et al. (1986), observed a transient stimulation of body growth in 4 week old cockerels administered 5, 10 or 50 ug pituitary-derived cST (p-cST) per day for 2 weeks. However, differences between treated and control birds were not significant at the end of treatment. Continuous infusion of p-cST (20 ug/kg BW per day) in 2-5 week old pullets had no effect on feed intake, body weight gain, feed efficiency or carcass composition (Cravener et al., 1989). Above approaches of ST effect on chicken growth may be considered as sub-optimal, since doses and(or) durations of treatment were limited, due to the scarcity of adequate quantities of pure cST. With the availability of recombinant cST (r-cST ; Souza et al., 1983), which exhibits distinct growth promoting activity in the hypophysectomized rat (Souza et al., 1984 ; Burke et al., 1987 ; Peebles et al., 1988), it was possible to investigate the effect of ST administration on performance in chicken over longer periods of treatment. Thrice daily (Burke et al., 1987) or twice daily (Peebles et al., 1988) administration of high doses of r-cST (50, 250 or 1500 ug/kg BW per day) had no stimulatory effect on performance of young chickens. Liou et al. (1986), found that the combination of exogenous r-cST and dietary thyroid hormones depressed growth rate of broiler chickens between 21 and 42 days of age. Protein and ash content of the carcass as well as nitrogen retention were not affected by exogenous r-cST administration (Burke et al., 1987). Dressing percentage has been reported to be lower in p-cST treated birds (Cravener et al., 1989).

Effects of GRF

GRF has been shown to stimulate cST secretion both *in vitro* and *in vivo*, and to potentiate cST response to TRH in chickens (Leung & Taylor, 1983 ; Harvey et al., 1984 ; Leung et al., 1985 ; Harvey & Scanes, 1985) and turkeys (Proudman, 1984). Exogenous administration of GRF doses known to vastly stimulate cST secretion, has transient (Leung et al., 1986) or no effect (Buonomo & Baile, 1984, 1986) on body weight gain and feed efficiency in broiler chickens.

Conclusion

In a recent review, Johnson (1989) discussed the possible reasons for the failure of growth hormone to improve performance in poultry:

- broiler chickens exhibit very rapid early growth at a time when endogenous production of cST is very high (Burke & Marks, 1982 ; Vasilatos-Younken & Leach, 1986 ; Vasilatos-Younken & Zarkower, 1987). Thus, exogenous ST may negate the growth promoting activity of endogenous cST secretion in young chickens,

- broiler chickens have a unique pattern of somatotropin secretion, with a high pulse amplitude and a more rapid pulse frequency than in other species (Johnson et al., 1987 ; Vasilatos-Younken & Zarkower, 1987). Vasilatos-Younken et al., (1988) demonstrated that pulsatile administration of p-cST improved performance of 8-11 week old pullets, whereas continuous infusion did not. Therefore, the pattern of administration of cST may be important in obtaining positive responses to the hormone. However, this experiment should be repeated in younger birds.

The effects of exogenous pST or GRF administration on growth performance and carcass characteristics in swine

Effects of porcine somatotropin (pST)

In the first attempts to investigate the effects of exogenous pST administration on pig growth performance, imperfectly purified pituitary extracts were used (Turman & Andrews, 1955 ; Henricson & Ullberg, 1960 ; Lind et al., 1968 ; Machlin, 1972). During the 1980's, progress in preparative biochemistry provided improved pituitary preparations. At the same time, GRF was discovered and synthesized and recombinant pST became available, having the same biological and zootechnical effects as native pituitary pST (Ivy et al., 1986, Evock et al., 1988).

Table 1. The effects of pST administration on growth performance and carcass characteristics of ad libitum-fed finishing pigs.

Breed	"Sex"	Daily dose	DFI	ADG	FCR	Fat thickness	LEA	DP	Lean	Ref. %
		2 mg*	-10	+17	-23					1
	C&F	2 mg	-14	+9	-21					2
LWxDU	C	30 ug/kg		+11	-19	-11	+21		+26	3
	C&F	3 mg	-22	+5	-25	-38	+11			4
LWxLR	E&F	3 mg							+9	5
	C&F	4 mg	-9	+13	-19	-36	+16		+12	6
		4 mg	-8	+29	-29					7
DU		4 mg**	-4	+4	-7	-21			+7	8
LWxLR		4 mg**	-4	+6	-10	-13			+4	8
PP		4 mg**	-5	+3	-8	-7			+2	8
	C&F	50 ug/kg		-9	-11	-23	-3			9
LWxLR		5 mg	-7		-24				+6	10
HAxLW		5 mg	-13		-24				+9	10
LW		5 mg	-12	-5	-12				+12	11
PP		5 mg	-3	+1	-3				+14	11
	C	60 ug/kg	-2	+19	-20	-37	+7	-3		12
		60 ug/kg		+7	-15					13
	C	70 ug/kg		+11	-20	-37	+25			14
LW	F	70 ug/kg		+18	-22	-19	+6	-3		15
LWxDU	C	70 ug/kg		+14	-17				+19	16
MS	F	6 mg	-10	+43	-38	-41		-4	+33	17
LWxPPxMS	F	6 mg	-17	+18	-29	-44		-2	+11	17
PP	F	6 mg	-7	+31	-31	-36		-1	+3	17
LRxLW	F	100 ug/kg	-10	+47	-41	-31				18

Data expressed as % changes of treated vs control pigs
DFI: Daily Feed Intake ; ADG: Average Daily Gain ; FCR: Feed Conversion Ratio ; LEA: Loin Eye Area ; DP: Dressing Percentage
Breed : DU = Duroc ; HA = Hampshire ; LR = Landrace ; LW = Large-White ; MS = Meishan ; PP = Piétrain
"Sex": E = entire males ; C = castrated males ; F = females
* as an implant ; ** as twice weekly injections of 14 mg
From 1: Knight et al., 1988 ; 2: Azain et al., 1989 ; 3: Etherton et al., 1986 ; 4: Bechtel et al., 1988 ; 5: Baile et al., 1990 ; 6: Skaggs et al., 1989c ; 7: Goodband et al., 1988 ; 8: Kanis et al., 1990 ; 9: Smith et al., 1987 ; 10: Nossaman et al., 1989 ; 11: Fowler & Kanis, 1988 ; 12: Trenkle, 1988 ; 13: Jones et al., 1989 ; 14: Bark et al., 1989 ; 15: Bryan et al., 1989a ; 16: Etherton et al., 1987 ; 17: Bonneau et al., 1990a ; 18: Campbell & Taverner, 1988

Unless otherwise stated, the results presented in this paper were obtained with daily injections of the hormones. Relatively few published data are available concerning the efficacy of prolonged release pST implants (Knight et al., 1988, 1989, 1990 ; Baile et al., 1989 ; Becker et al., 1989).

A selection of results relating to the influence of exogenous pST administration on growth performance and carcass characteristics of finishing ad libitum-fed pigs are presented in Table 1. Despite a significant reduction of daily feed intake, pST treated pigs grow faster with a dramatically improved feed efficiency. Fat percentage in the carcass is sharply reduced with a concomitant increase in muscle proportion. More generally, pST enhances the development of all protein rich tissues (muscle, skin and bone) to the detriment of fat (Bonneau et al., 1989 ; Bark et al., 1990 ; Caperna et al., 1990 ; Thiel et al., 1990b).

Dressing percentage falls 1-4% after pST administration. Part of the decrease is due to the increased size of some organs. The weights of liver, heart and kidney are augmented 4-30%, 2-22% and 15-52%, respectively (Grebner et al., 1987 ; Bechtel et al., 1988 ; Evock et al., 1988 ; Kanis et al., 1988b ; Trenkle, 1988 ; Bonneau et al., 1989 ; Bryan et al., 1989a). Preliminary results (Bidanel et al., unpublished) suggest that increased weight of blood and intestinal content at slaughter may also account for some part of the decline in dressing% in pST-treated animals.

Effects of GRF

Daily or three times daily injection of GRF or GRF analog increases blood pST levels, in a dose related manner, throughout the entire period of administration, with no desensitization of the somatotroph cells (Dubreuil et al., 1990a, 1990b). The effects of exogenous GRF or GRF analog administration are qualitatively similar to those obtained with pST (Table 2).

Table 2. The effects of GRF administration on growth performance and carcass characteristics of ad libitum-fed finishing pigs.

GRF type	Daily dose*	Number inject. per day	DFI	ADG	FCR	Fat thickness	LEA	DP	Lean	Ref. %
GRF1-44	30	1		+6	-9		+13			1
GRF1-44	20	2	-6	+8	-13	-12	+11			2
GRF1-44	40	2	-8	+14	-19	-22	+12			2
GRF1-29	15	2	-2	0	-17	-21	+6	-2		3
analog	5	3	-8	+3	-11	-7	+2	-1	+3	4
analog	10	3	-6	+12	-16	-24	+4	-3	+5	4
analog	20	3	-21	+7	-26	-32	+13	-2	+6	4
analog	10	1	-10	-1	-11	-16	+10	-1	+5	4

Data expressed as % changes of treated vs control pigs
* ug/kg/d
DFI: Daily Feed Intake ; ADG: Average Daily Gain ; FCR: Feed Conversion Ratio ; LEA: Loin Eye Area ; DP: Dressing Percentage From 1: Etherton et al., 1986 ; 2: Johnson et al., 1989 ; 3: Dubreuil et al., 1990c ; 4: Dubreuil et al., 1990b

However, the improvement in performance is significantly lower with GRF than with pST injected at the same dose (Etherton et al., 1986 ; Johnson et al., 1989). As does pST, GRF or GRF analog accelerate the development of some organs (Dubreuil et al., 1990b) and of all protein rich tissues (muscle, skin, bone) to the detriment of fat (Pommier at al., 1990).

Conclusion

Exogenous pST or GRF administrations dramatically improve both rate and efficiency of lean tissue growth to the detriment of fat deposition. The fact that somatotropic hormones are a limiting factor for performance in pigs may be related to the observation that endogenous blood pST has fallen to low levels during the growing and finishing periods, compared to the neonatal period (Klindt & Stone, 1984 ; Scanes et al., 1987 ; Louveau et al., 1990).

Factors of variation of performance response to pST administration

Among the various factors of variation of performance response to pST administration, nutrition certainly plays a key role. However, this will not be developed in the present paper, as the effects of pST administration on nutritional requirements are reviewed elsewhere (Van Vlissingen et al., 1990b). Factors reviewed include those related to pST (dose, form and schedule of administration) and animal (age and weight, genotype, sex and castration). Possible interaction of pST with B-agonist will also be considered.

Dose, form and schedule of administration

The dose of injected pST is either constant (expressed as mg per day) or adapted to the increasing weight of the animal (expressed as ug per kg live weight per day). The dose providing maximum effect is not the same for the various performance criteria (Figure 1). Feed intake declines linearly with increasing doses while feed efficiency is not further improved beyond 80-100 ug/kg per day or 6 mg per day. Therefore, growth rate response to increasing pST doses is quadratic. The dose at which maximum growth rate is obtained may vary according to experimental conditions from 3 mg per day (Darden et al., 1990 ; Fitzner at al., 1990) to 60-70 ug/kg per day or 6 mg per day (Boyd et al., 1986 ; Evock et al., 1988 ; Mc Laren et al., 1987). Carcass fat content is reduced linearly, whereas carcass lean content is increased quadratically with increasing pST doses (Boyd et al., 1986 ; McNamara et al., 1990 ; Yen et al., 1990). However, Thiel et al. (1990b) observed a linear increase in muscle content with pST doses ranging from 50 to 200 ug/kg per day.

Little information is available concerning the comparison of daily injection vs continuous release of pST. However, the preliminary observations of Knight et al. (1988) are consistent with a lower efficacy of continuous release versus daily bolus injection of pST.

Van Vlissingen et al. (1990a) found only minor differences for the effects on performance and carcass quality between three schedules of pST administration: constant (4 mg/d), increasing (from 2 up to 6 mg /d), decreasing (from 6 down to 2 mg /d). As could have been expected, the improvements in growth rate and loin eye muscle area are higher with continuous daily injections than with daily injections during alternate weeks (Bryan et al., 1990b).

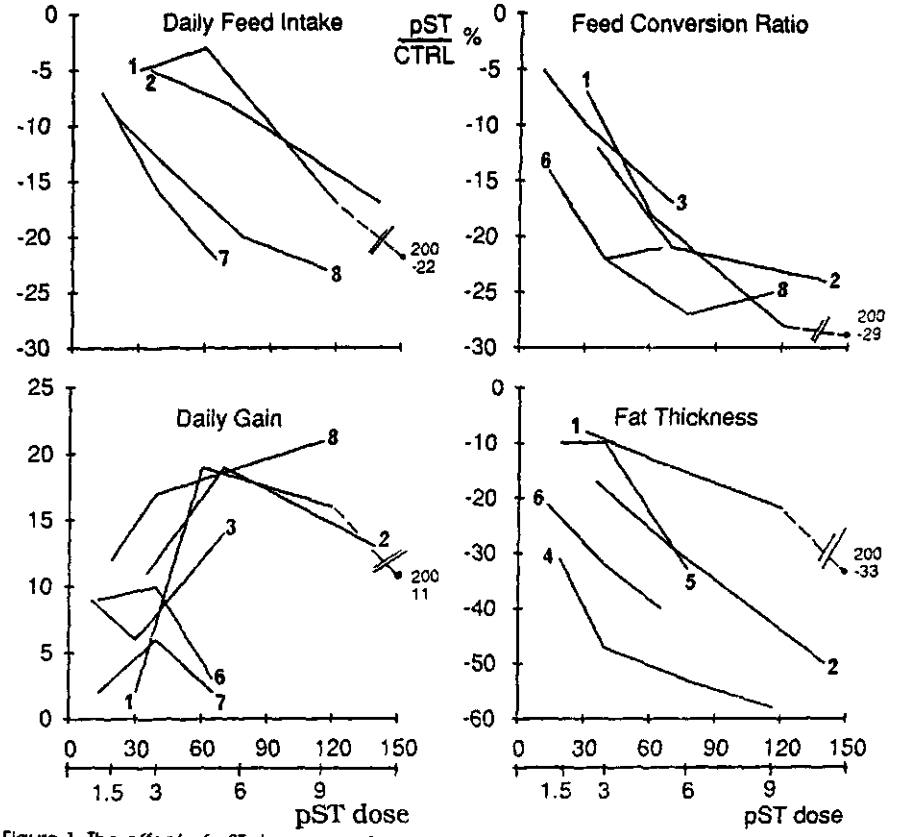

Figure 1. The effect of pST dose on performance and carcass characteristics of pigs (data expressed as % changes of treated vs control pigs. From 1: Boyd et al., 1986 ; 2: Evock et al., 1988 ; 3: Rebhun & Etherton, 1985 ; 4: Mc Laren et al., 1987 and Grebner et al., 1987 ; 5: Demeyer et al., 1988 ; 6: Darden et al., 1990 and Baldwin et al., 1990 ; 7: Fitzner et al., 1990 ; 8: Mc Laren et al., 1990).

Age and weight

The finishing period, during which muscle growth rate is still steady whereas adipose tissue development accelerates, is usually considered as the best time for pST administration to pigs.

However, pST treatment during the growing period (25-30 to 50-60 kg live weight) has similar effects as in older pigs. Daily administration of 100 ug/kg per day enhances protein retention by 35-50% and reduces fat accretion by 26-32% (Campbell et al., 1988a). According to Campbell et al. (1989b), animals treated with pST during the growing period also exhibit improved performance, except for fat accretion, during the finishing period, long after the end of treatment. Such carryover effect of pST is however controversial (Smith et al., 1989).

The repartitioning effect of pST is also observed in animals treated beyond 100 kg live weight. The changes in performance are similar (Jones et al., 1989 ; Crenshaw et al., 1990 ; Shoup et al., 1990) or higher (Kanis et al., 1990) than in pigs treated during the finishing period.

Genotype

In all genotypes of pigs so far studied, performance responds favourably to pST treatment. In genotypes differing only slightly for their growth performance and carcass characteristics, no interaction between pST treatment and genotype is observed (Bark et al., 1990 ; Shoup et al., 1990). The effects of pST on performance are similar in lines of pigs selected for either leanness or fatness (Campbell & Taverner, 1988 ; Bark et al., 1989). Pigs from the 3 halothane sensitivity groups (NN: Normal/Normal ; Ns: Normal/sensitive ; ss: sensitive/sensitive) also respond similarly to pST treatment, although the improvement in feed efficiency is lower in ss than in NN pigs (Skaggs et al., 1989a, 1989b).

On the other hand, genotype x treatment interactions are clearly demonstrated when the effects of pST administration are compared in obese versus lean (Yen et al., 1990), obese versus double-muscled (Bonneau et al., 1990a) or conventional versus double-muscled pigs (Kanis et al., 1990). The improvement in performance is particularly impressive in the slow growing-fat Chinese pigs, as pure breed or crossbred with conventional pigs (Fung & Qi, 1988 ; McLoughlin et al., 1989 ; van der Steen et al., 1989 ; Bonneau et al., 1990a, Prunier et al., 1990). In very lean breeds, such as Pietrain or Belgian Landrace, subcutaneous fat almost disappears while muscle percentage in the carcass is only slightly increased (Demeyer et al., 1988 ; Bonneau et al., 1990a ; Kanis et al., 1990). Overall, it can be considered that the relative improvement in performance due to pST treatment is in inverse proportion to the animal's potential for lean meat growth. However, pST effect is still significant in the leanest breeds (Kanis et al., 1990 ; Bonneau et al., 1990a).

Sex and castration

The repartitioning effect of a high dose of pST (100 ug per kg per day) is more pronounced in castrated males than in females and in females than in entire males (Campbell et al., 1989a), so that differences in performance between "sexes" are narrowed with pST treatment. With lower pST doses (3 or 4 mg per day), castrates also exhibit higher responses to pST, but the superiority of female carcass composition is still apparent in treated animals (Bonneau et al., 1989 ; Kanis et al., 1990).

Interaction with ß-agonists

Provided that nutritional conditions are satisfactory, the repartitioning effects of pST and ß-agonists seem to be additive in swine (Anderson et al., 1989 ; Jones et al., 1989).

Meat quality in pST-treated pigs

The effect of pST on muscle and fat composition will not be discussed in this paper as these aspects are covered elsewhere (Beermann et al., 1990). However, we will consider the effects of pST administration on muscle fibres as well as on physical and sensory characteristics of pork meat.

Muscle fibre types

The effect of pST treatment on the percentage and size of the various fibre types is still controversial. In the *longissimus dorsi* or *semitendinosus* muscles, pST treatment increases the size of fibre types (Beerman et al., 1987 ; Solomon et al., 1988, 1990 ; Lefaucheur et al., unpublished results). However, in the same muscle, Whipple et al. (1989) did not find any difference in fibre size. The percentage of the various fibre types in *longissimus dorsi* may be unaffected (Solomon et al., 1988 ; Lefaucheur et al., unpublished results) or altered towards a higher (Whipple et al., 1989) or lower (Solomon et al., 1990) percentage of white fibres. In another predominantly white muscle (*semimembranosus*), neither fibre percentage nor fibre size are significantly affected by pST treatment (Whipple et al., 1989). In the predominantly red *semi spinalis* muscle, the percentage of type IIB fibres and the size of all fibre types are increased by pST administration ; lactate dehydrogenase activity is augmented while citrate synthase and ß-hydroxy-acyl-CoA-dehydrogenase activities are reduced by pST treatment (Lefaucheur et al., unpublished results). In summary, pST seems to increase fibre size with a still controversial effect on the percentage of the various fibre types in predominantly white muscles. The metabolism of predominantly red muscles is altered towards a reduction of oxidative and an elevation in glycolytic pathways, in association with the increased percentage of the mostly glycolytic type IIB fibres. That pST effects may vary according to muscle type is further demonstrated by the observations of Evock et al. (1990): pST increased RNA content and RNA/DNA ratio in *longissimus dorsi* whereas DNA concentration was increased in *semi membranosus* muscle.

Physical characteristics

Treatment with pST generally has no significant effect on muscle pH fall after slaughter (Bonneau et al., 1989 ; Ender et al., 1989 ; Hagen et al., 1990a ; Lefaucheur et al., unpublished results)). However, elevated pH measurements 45 minutes or 24 hours after slaughter have been reported (Demeyer et al., 1988 ; Skaggs et al., 1989a ; Mourot et al., 1990). Similarly, a tendency for higher pH measurements has been noticed in pigs treated with a GRF analog (Pommier et al., 1990).

Shear force, drip and cooking losses, and reflectance of meat are generally not significantly affected by pST treatment (Beerman et al., 1988 ; Demeyer et al., 1988 ; Kanis et al., 1988c ; Prusa, 1988 ; Ender et al., 1989 ; Gardner et al., 1990 ; Williams et al., 1990 ; Mourot et al., 1990). However, Novakofski (1987) and Williams et al. (1990) observed a greater shear force value in muscles of pST treated pigs. In some cases meat colour has been reported to be negatively (Kanis et al., 1988c) or positively affected (Demeyer et al., 1988).

Sensory properties

Sensory characteristics of pig meat, as assessed by laboratory panels, are generally unaffected by pST treatment (Novakofski, 1987 ; Beerman et al., 1988 ; Demeyer et al., 1988 ; Kanis et al., 1988c ; Prusa, 1988 ; Thiel et al., 1990a ; Hagen et al., 1990a ; Williams et al., 1990). However, significant reductions in tenderness (Evock et al., 1988 ; Beermann et al., 1988 ; Prusa, 1988 ; Boles et al., 1990 ; Thiel et al., 1990a ; Williams et al., 1990), juiciness (Beermann et al., 1988) or flavour (Prusa, 1988) have been reported. The decreased tenderness could be related to the increased collagen deposition (Caperna et al., 1990); however collagen as % of total proteins as well as soluble collagen as % of total collagen are unaffected by pST treatment. Such deleterious effects of pST treatment on sensory quality of meat are mostly observed with high pST doses and often reported as of little practical significance.

Prusa et al. (1990), using a large consumer panel, reported a positive consumer acceptance of meat from pST treated animals. Degree of liking, tenderness, juiciness and flavour were slightly, but significantly, higher in meat from pST treated than from control animals.

Processing characteristics of meat does not seem to be affected by pST treatment as well as sensory quality of frankfurters (Reagan et al., 1990) or cooked hams (Kuecker et al., 1990) manufactured from pST meat.

The effect of pST administration on reproductive function

PST and development of ovarian activity

The dramatic reduction in adipose tissue development as well as endocrine changes triggered by pST treatment may have some consequences on reproductive function (Aherne & Kirkwood, 1985 ; Kirkwood et al., 1989). The normal schedule of cytoplasmic maturation of oocytes is accelerated by pST (Hagen & Graboski, 1990). Progesterone secretion by ovarian follicles is modified (Bryan et al., 1988, 1989a, 1989b), although Spicer et al. (1990) did not find any effect on progesterone content of follicular fluid. Number of hCG binding sites are reduced in granulosa cells (Spicer et al., 1990) and increased in luteal tissue (Kirkwood et al., 1990b). Ovarian response to PMSG/hCG stimulation is altered and the amplitude of estrogen-induced LH peak is reduced (Kirkwood et al., 1989a, 1990a).

The effect of pST treatment on puberty attainment in gilts is not clear. Some authors observe that less treated gilts reach puberty and at an older age than control (Bryan et al., 1989a). On the other hand, others do not obtain any significant effect on age at puberty, or percentage cyclic gilts at the end of treatment, even with high pST doses (Andres et al., 1989 ; Prunier et al., 1990 ; Bidanel et al., 1990 ; Kirkwood et al., 1989b). Genital tract development of prepubertal gilts is mostly unaffected by pST treatment (Bryan et al., 1988, 1989b, 1990b ; Terlouw et al., 1989 ; Prunier et al., 1990). However, Hagen et al. (1990b) and Bryan et al. (1990b) observed a significant increase in uterus weight and length in gilts receiving 5 mg pST per day for 20 or 40 days.

Sexual activity seems to return to normal very rapidly after the end of pST treatment. The response to boar stimulation is similar or even better in pST treated than in control gilts (Day et al., 1988 ; Bryan et al., 1990). Moreover, duration of oestrous cycles, ovulation rate, percentage pregnant females and embryo survival are not significantly affected by pST treatment (Day et al., 1988 ; Andres et al., 1989, 1990 ; Kirkwood et al., 1989b, 1989c). In summary, any possible reproductive change associated with chronic administration of exogenous pST to prepubertal gilts seems to be transient.

Little information is available concerning the effect of exogenous pST administration on male sexual development. Hagen et al. (1990a) observed no effect of pST on the development of the male genital tract.

PST administration to pregnant or lactating sows

Exogenous pST administration to sows during the last 2 or 3 weeks of gestation has no significant effect on birth and weaning weight of piglets or on their survival rate (Kveragas et al., 1986 ; Baile et al., 1989). However, Kveragas et al. (1986) noticed that body glycogen and lipid contents at birth as well as fasting blood glucose profiles were higher in piglets born from pST treated than from control sows.

According to Harkins et al. (1989), exogenous pST administration during lactation induces a large increase in milk production, with no alteration in milk composition. Piglets suckling a pST treated sow weigh 6% more at weaning. The increase in milk production and concomitant decline of daily feed intake are responsible for larger body weight and fat losses in treated sows. Other authors do not confirm the stimulating effect of pST treatment on milk production in sows. However, their experimental conditions were not favourable for the observation of a positive effect, either because of harsh environmental conditions (Cromwell et al., 1989a) or due to infrequent pST injections (Cromwell et al., 1989b, Crenshaw et al., 1989).

Conclusion

Exogenous administration of somatotropic hormones does not seem to have any significant impact on growth performance and carcass characteristics of young broiler chickens whereas it dramatically improves both rate and efficiency of lean deposition and inhibits lipid deposition in swine. Therefore, the use of GRF or recombinant pST could sharply reduce feeding costs and improve carcass quality in pig production. The impact of pST treatment on meat quality seems to be limited. Deleterious effects (if any) on the onset of reproductive function are transient and quickly reversed after the end of treatment. Therefore, provided that proper delivery systems can be developed, exogenous administration of somatotropic hormones to swine seems to be a very promising technique, leading to the production of a cheaper product, better fit to the lean meat consumer demand. However, public perception of the acceptability of meat from such animals might be a limitation to its development.

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INFLUENCE OF EXOGENOUS SOMATOTROPIN ON THE COMPONENTS OF GROWTH IN RUMINANTS

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Summary

Somatotropin treatment of sheep and cattle increases body weight gain by 8-10% and feed conversion by a comparable amount. However, this is often accompanied by an increase in non-carcass components and the carcass weight may not necessarily be significantly increased. Yet, somatotropin still imparts a repartitioning of carcass components to more protein and less fat. The regional sites where repartitioning takes place are predominantly in the hindquarter and the subcutaneous fat depots. The improvements in feed conversion efficiency are driven by the components of gain as opposed to any real change in the biological conversion processes.

Administration of exogenous somatotropin presents a management tool to enhance growth performance and improve carcass composition which is consistent with the desires of the producer and consumer. A key to the successful implementation of this technology will be the identification of a long term delivery system for somatotropin which is efficacious, easily administered and cost effective.

Keywords: *somatotropin, growth, carcass composition, protein turnover*

Introduction

In domestic livestock production, new technologies to dramatically improve lean carcass yield, improve efficiency of feed utilization and increase the rate of daily gain are available. Agents which affect these characteristics, coined repartitioning agents, are exemplified by ß-agonists and somatotropins. Neither of these compounds have yet been cleared for commercial use. Considerable information is available in swine on the anabolic responses to somatotropin administration. However, the data on the influence of somatotropin on growth in ruminants is only now beginning to accumulate.

A number of experiments have been published on the influence of exogenous somatotropin on average daily gain and feed conversion efficiency but very few of these long term studies have reported organ development and carcass composition data. Many short term trials have reported increases in nitrogen retention in response to somatotropin administration (Wheatley et al., 1966; Moseley et al., 1982; Crooker et al., 1990) but these

trials did not define the site of the increased nitrogen and/or protein accretion. By inference, it is often assumed that relatively short term growth trials (three weeks or less) reflect the long term (several months) growth response. However, the location and magnitude of enhanced protein accretion may be drastically altered depending upon the length of somatotropin administration in relation to the animal's age and development. This is particularly important with respect to protein synthesis since skeletal muscle, liver and the intestines can account for 12-32%, 11-25% and 15-33%, respectively, of whole body protein synthesis, depending upon the age of the animal (Reeds, 1989). Therefore, the purpose of this review is to summarise the long term growth trials with sheep and cattle in which exogenous treatment with somatotropin was applied, and to develop a hypothesis as to the action of somatotropin on the components of growth.

Performance trials

The increase in average daily gain (ADG) induced by somatotropin treatment varies considerably across species and sex (Table 1). These differences undoubtedly reflect differences in experimental design, dose of somatotropin, duration of administration, breed of animal and dietary regimen. McShane et al. (1989) found that under controlled intake regimen, higher energy diets induced a greater absolute gain and somatotropin increased ADG by 8-10% over controls, depending upon diet. The largest increases in ADG in response to somatotropin treatment have been reported for very young (one week of age) Holstein bull calves (18%, Groenewegen et al., 1990), for dairy heifers (24%, Grings et al., 1990) and for Belgian White Blue heifers (23.5%, Fabry et al., 1987). On a percentage basis, it appears that in both sheep and cattle, the largest responses in ADG occur in younger animals. This is not surprising given the proposed actions of somatotropin and IGF-1 on muscle protein synthesis and cartilage development (Green et al., 1985) and the capacity for muscle and skeletal development in the young animal. The average increase in ADG for these trials, in cattle and sheep, is approximately 10%, which is somewhat below the response observed for somatotropin treated swine (Chung et al., 1985; Campbell et al., 1988).

Sheep and cattle have tended to respond to treatment with somatotropin by small changes either upward or downward in dry matter intake (DMI). In finishing beef steers, Moseley et al., (1990) reported a linear decrease in feed intake (-6% to -16.7%) with increasing doses of somatotropin. Similarly, Wagner et al. (1988) reported a -7.8% decrease in DMI in finishing beef steers treated with somatotropin. The data in swine shows marked decreases in DMI in response to somatotropin (Etherton, 1989). A hypothesis to explain this depression in DMI, might be that the abundance of nutrients from mobilized fat stores cannot be utilized by the growing tissues at a rate fast enough to reduce circulating nutrient concentrations, therefore, the animal responds by reducing DMI to bring the body to homeorhesis. On the other hand, in young growing cattle and sheep treated with somatotropin, it would be expected that the protein and energy requirements cannot be met by mobilization of energy reserves, therefore DMI may be increased to help support the stimulated metabolic response to somatotropin. An alternative reason for the increase in DMI in young, growing animals is noted by Groenewegen et al. (1990) who reported a significant increase (21%) in DMI with a pelleted starter/grower diet fed to bull calves (one to 14 weeks of age). This response may simply have reflected an increase in digestive tract volume since the reticulorumen, small intestine

and large intestine weights were 24, 28 and 19% larger, respectively, for the somatotropin-treated bull calves. On average, the proportional increase in gut was 3-fold greater than the increase in carcass accretion (Groenewegen et al., 1990). Others have reported significant increases (14.3%) in the weight of the small intestine of somatotropin-treated cattle even under short term treatment conditions (Eisemann et al., 1989b). When expressed on a unit empty body weight basis, small intestine weight was also significantly greater in somatotropin- treated cattle (9.2%) (Eisemann et al., 1989b), again inferring that gut development was disproportionate to whole body growth. However, these observations do not necessarily imply a direct causal relationship for enhanced capacity for intake.

Table 1. Growth response to somatotropin in treated cattle and sheep[a,b]

	ADG	DMI	F/G	Initial Wt. (kg)	Age (mo)	Dur. (wk)	Dose (mg/kg/d)	Reference
Cattle								
steers	15	2	-12	231	8	16	0.08	Early et al., 1990a
steers	10	-7.8	-18	336	--	20	0.20	Wagner et al., 1988
steers	6	3	-4	237	9	22	0.04	Enright et al., 1990
steers	7.9	-6	-11.6	393	--	17	0.033	Moseley et al., 1990
steers	-7.0	-13.1	-6.3	393	--	19	0.10	Moseley et al, 1990
steers	-37.7	-16.7	34.4	393	--	22	0.30	Moseley et al., 1990
heifers	10	--	--	89	2	12	0.11	Brumby, 1959
heifers	9	6	-2	92	4	21	0.60	Sandles and Peel, 1987
heifers	8	--	-8	180	8	16	0.10	Sejrsen et al., 1986
heifers	24.0	--	--	295	--	21	0.14	Grings et al., 1990
heifers	8	--	-8	228	7	21	0.09	McShane et al., 1989
heifers	10	--	-10	229	7	32	0.09	McShane et al., 1989
heifers	23.5	1.5	-20.3	439	--	18	0.05	Fabry et al., 1987
bull calves	18	21	0	45	0.25	13	0.10	Groenewegen et al., 1990
bull calves	7.1	0	-5.3	45	0.75	15	0.08	Maltin et al., 1990
Sheep								
wether	4	-4	-7	28	--	8	0.25	Muir et al., 1983
wether	20	--	-14	40	--	15	0.37	Wagner and Veenhuizen, 1978
wether	12.3	--	-19.6	25.5	--	6	0.20	Wise et al., 1990
ewes & wethers	17	--	-22.4	25.5	--	6-8	0.16	Beerman et al., 1990
ewe	22	6	-14	17	2	12	0.10	Johnsson et al., 1985
ram lambs	1	<1	<1	17	2	4	.1-.2	Rosemberg et al., 1989

[a] Responses in ADG, DMI and F/G are all based upon a percentage response compared to controls.
[b] The values reported do not necessarily imply statistically significant responses.

The most consistent response in both cattle and sheep is that of a statistically significant improvement in the feed/gain (F/G) conversion rate (Table 1). The majority of long term trials under both *ad libitum* and restricted intake regimes showed a 4-22% (=9%) improvement in feed/gain ratio. The observed improvement in (F/G) by 9% coupled with an average increase of 10% in ADG certainly suggests a performance advantage with somatotropin treatment. However, Moseley et al. (1990) reported that steers administered a high dose of somatotropin (300 g rbST/kg/d) responded with a 16.7% reduction in feed intake and a 37.7% slower ADG which resulted in a 34.4% poorer F/G ratio than controls.

Yet the carcass composition characteristics of these steers reflected the repartitioning effects of somatotropin with a reduction in carcass fat and an increase in carcass protein. It is apparent that the location and chemical components of the enhanced tissue accretions to somatotropin treatment need to be assessed before the performance responses are deemed beneficial.

Three studies have examined the interaction of somatotropin with other growth promoting agents. Steers which received somatotropin plus oestradiol via a Compudose implant (Wagner et al., 1988; Enright et al., 1990) and bull calves which received somatotropin plus the ß-agonist Clenbuterol. Maltin et al., (1990) responded with an additive effect for F/G and ADG. An interpretation is that the growth promoting effects of somatotropin operate through mechanisms different than either estradiol or the ß-agonists such that a combination of these agents produced greater responses than either agent alone.

This review focuses on somatotropin and does not cover growth hormone-releasing factor (GRF) (See Enright, 1989). However, two studies with young growing sheep reported that GRF administered either 2 or 4 times daily produced improvements in ADG and F/G similar to that produced by administration of ovine somatotropin (Beermann et al., 1990; Wise et al., 1988). As sources of GRF become more readily available to the research community, the data on GRF as a growth promoting agent will begin to increase. Recent data in pigs substantiates that GRF administered at an appropriate dose and frequency can markedly improve growth rate and efficiency of growth and lean carcass yield (Dubreuil et al., 1990; Pommier et al, 1990). Clearly, GRF represents an alternative to somatotropin as a means to improve growth performance in domestic livestock.

Components of gain

Organ development

The number of published long term growth trials in cattle and sheep using somatotropin treatment in which ADG was increased and full carcass composition was compiled are few in number (Early et al., 1990a; Groenewegen et al., 1990; Sandles and Peel, 1987 and Johnsson et al., 1985). Within these studies, some striking similarities appear, with the exception of the Sandles and Peel (1987) study, which used a bigger dose of somatotropin than the other studies. Carcass weight accretion was increased by 6.2-9.9% whereas non-carcass weight accretion was disproportionately increased (Table 2). The calculations for the Groenewegen et al. (1990) and Johnsson et al. (1985) data would include differences in gut fill but in each case specific organs and other non-carcass tissue components were increased in weight disproportionately to carcass weight accretion. In sheep, Johnsson et al. (1985) reported significant increases in the weight of the skin (minus the fleece; 46%) and pluck (trachea, lung, heart, liver, spleen; 27%) over those of control animals. These values represent a 2.5 to 4-fold increase compared to the relative increase in the carcass component. Similarly, in bull calves, Groenewegen et al. (1990) found a 1.6-fold increase in lungs and liver weight and a 3-fold increase in the gut weight compared to the relative increase in the

carcass component. Early et al. (1990a) also reported large increases in the weight of the liver, kidneys and lungs plus trachea in somatotropin-treated steers.

In another study in sheep, somatotropin or GRF treatments induced significant increases in weight of several non-carcass components such as pelt, liver, head and feet (Wise et al., 1988). Disproportionate increases, due to ST, in liver weight compared to carcass weight is commonly found across trials (Table 3). Liver growth was increased 1.6 to 2.6 fold compared to carcass growth. The organs undergo the greatest growth (liver, kidneys, lungs) represent such a small component of total weight gain that a relatively small decrease in dressing percentage is observed (Table 2). However, the important question is whether alteration of organ growth has influenced organ function. Early et al. (1990a) examined blood chemistry profiles of somatotropin-treated steers and found the majority of compounds examined (Ca, P, Na, K, Cl, total protein, albumin, alkaline-phosphatase, glutamate oxaloacetate transaminase, creatinine kinase and glucose) were unaltered by somatotropin treatment. However, serum urea nitrogen, creatinine, total bilirubin, conjugated bilirubin and glutamate-pyruvate transaminase were lower in somatotropin-treated steers but these values remained within the range of normal physiological concentrations for the cattle (Duncan and Prasse, 1986). The changes in serum urea nitrogen and cholesterol will be discussed in context with carcass component changes. The lower total and conjugated bilirubin concentrations likely reflect the larger liver since the liver is the site of clearance of these break-down products of haemoglobin.

Table 2. Comparison of weight gain responses in long term trials with somatotropin or saline treated ruminants[a]

	Carcass accretion[b]	Non-carcass accretion	Dressing %	Reference[d]
Cattle				
steers	6.2	29.6	-3.7	Early et al., 1990b
steers	6.6	0	+0.6	Enright et al., 1990
heifers1	6.3	11.8	0	Sandles and Peel, 1987
bull calves	7.9	80.5[c]	-3.3	Groenewegen et al. 1990
Sheep				
ewe lambs	11.0	30.0[c]	-5.8	Johnsson et al., 1985
wether lambs	3.7	3.7	0	Muir et al., 1983
ram lambs	0	1.4	-2	Rosemberg et al., 1989

[a] Responses are all based upon a percentage response compared to controls.
[b] The initial carcass weight was calculated assuming the dressing percentage of controls applied to both treatment groups at treatment initiation.
[c] Part of this non-carcass accretion would include differences in gut fill.
[d] Responses do not necessarily imply statistically significant responses.

Data on the influence of somatotropin on kidney function are quite scarce. Wheatley et al. (1966) found reduced water intake and urinary sodium excretion during somatotropin treatment of sheep. Also, Parving et al. (1978) found short term treatment of humans with human somatotropin resulted in increased renal plasma flow and glomerular filtration rate. In two short term studies with humans, somatotropin had no influence on kidney size (Christiansen et al., 1981; Parving et al., 1978). Since somatotropin did not substantially alter blood chemistry profiles of treated steers, it is unlikely that homeostasis was impaired.

Of interest is the influence of somatotropin treatment on immune function of animals. In the study of Groenewegen et al. (1990), the thymus weight of the somatotropin treated calves was almost 2-fold greater than that of controls, which represented 12 times the relative increase induced in the carcass by ST. B.W. McBride, R.J. Early and R.O. Ball (unpublished) also recorded a 2-fold increase in the weight of mesenteric lymph nodes in somatotropin steers (same study as Early et al., 1990a,b,c). Interestingly, similar observations have been made for somatotropin-deficient animals (Berczi, 1986). In monogastric animals, Kelley (1989) reviewed the influence of somatotropin on lymphocytes and macrophages and reported that somatotropin regenerated a number of T-cell dependent immune responses in somatotropin deficient animals. Furthermore, somatotropin has been shown to activate the oxygen free radical burst in macrophages both *in vivo* and *in vitro* (Edwards et al., 1988). Burton et al. (1990a,b) have shown that long term somatotropin treatment of lactating dairy cattle increases peripheral T-lymphocyte proliferative response to mitogen and enhances the concentration of blood IgG_2 levels. This, coupled with observations that somatotropin increases interleukin-1 production by macrophages (I. Politis, X. Zhao, B.W. McBride, and J.H. Burton, unpublished), suggests that somatotropin does not hinder immune function but rather, it may induce characteristics of both cell-mediated and humoral immunity.

Table 3. Liver development in somatotropin versus saline treated ruminants.

	Liver weight (% gain[a])	Fold increase above carcass % gain[b]	Reference
Cattle			
steers	15.4	2.5	Early et al., 1990b
heifers	26[c]	1.6	Sandles and Peel, 1987
bull calves	13	1.6	Groenewegen et al., 1990
Sheep			
wethers	9.6	2.6	Muir et al., 1983

[a]Percentage increase versus control.
[b]An estimate of disproportionate gain compared to the carcass development calculated as the percentage increase in liver weight divided by the percentage increase in carcass gain of rbST treated versus control animals.
[c]Non-significant increase in liver weight in somatotropin-treated heifers. All other reported differences were statistically significant.

Carcass Composition

Table 4 summarises 5 published long-term somatotropin growth trials that conducted full carcass chemical analysis (as opposed to rib section analysis or carcass dissection). The most dramatic effect of somatotropin treatment on carcass composition is a reduction in carcass fat by 10.7-17.5% (=13.1%). The carcass composition parallels the observations that somatotropin treated steers have lower circulating concentrations of cholesterol (Early et al., 1990a) which has been correlated with lower fat containing carcasses (Wheeler et al., 1987). As expected, protein and water content increase to the same degree (+2.3% on average). This agrees with many observations that somatotropin decreases serum urea nitrogen in growing ruminants (Early et al., 1990a; Eisemann et al., 1989a; Davis et al., 1969). Ash content

increases by 6.2% in response to somatotropin treatment. Chemical composition of the 9-10-11th rib section from finishing steers showed significant linear relationships with recombinantly-derived bovine somatotropin (rbST) dose (Moseley et al., 1990). Percent fat was reduced 13.4, 21.2 and 54.4%, percent protein increased 10.6, 13.6 and 39.4% and per cent water increased 10.2, 15.2 and 39.9% in steers receiving 33, 100 and 200 g rbST/kg/d, respectively compared with control steers. As in dairy cattle (Bauman and McCutcheon, 1986), somatotropin acts as a repartitioning agent in beef cattle. Many of the studies report that it took 30-45 days of somatotropin treatment before weight gains began to diverge between treated and control cattle. However, repartitioning of the carcass muscle and fat compartments probably begins immediately upon initiation of somatotropin treatment.

Table 4. Influence of somatotropin treatment on carcass chemical composition of ruminants[a,b]

	% Change				
	protein	fat	ash	water	Reference
Cattle					
steers	1.9	-11.0	7.8	1.9	Early et al., 1990b
heifers	0.5	-17.5	5.6	0.9	Sandles and Peel, 1987
bull calves	1.9	-14.3	2.6	4.7	Groenewegen et al., 1990
Sheep					
wethers	4.5	-12.0		1.8	Muir et al., 1983
ram lambs	2.7	-10.7	8.6	2.2	Rosemberg et al., 1989

[a]Long term trials where values represent percent changes relative to control data.
[b]Values do not necessarily imply statistically significant differences.

The data presented in Tables 5 and 6 depict the geographic sites at which somatotropin acts. Early et al. (1990b) showed that somatotropin treatment of steers induced the greatest proportional effects on dissectible lean and fat in the hip, loin and flank area. Surprisingly, the greatest effect on bone was in the ribs, chuck, brisket, plate and shank (Table 5). In most instances, the lean:fat ratio was increased in somatotropin-treated steers (Early et al., 1990b) again depicting the reciprocal action of somatotropin on protein/lean vs fat components of the carcass.

The geographic sites of action of somatotropin on fat development in the carcass are shown in Table 6. The majority of the difference in fat deposition occurred in the subcutaneous deposits in the hip and loin (-20.4%). Very similar observations by Butler-Hogg and Johnsson (1987) were reported for lamb carcasses where the sites at which somatotropin acts on fat accretion were subcutaneous depots of the hindquarter.
.The mechanisms by which somatotropin affects growth have been extensively covered by Hart and Johnston (1986) and McBride et al. (1988), and the subsequent actions of IGF-1 on growth have been discussed by Steele and Elsasser (1989). Somatotropin, per se, is lipolytic (Hart et al., 1984) and also increases adipose tissue sensitivity to lipolytic agents, such as epinephrine (McCutcheon and Bauman, 1986). Somatotropin also appears to decrease fatty acid synthesis in adipose tissue via an insulin antagonism (Vernon, 1982; Etherton et al., 1987). Some of the cell associated activities mediated by IGF-1, as summarised by Steele and Elsasser (1989), include increased sulfate incorporation, and increased mRNA and DNA

synthesis in chondrocytes. Presumably, those cartilage related events help explain the augmented bone growth in somatotropin-treated animals.

Table 5. Average daily gains of bone, lean and fat from steers treated with rbST[a,b]

	% Change			
	total carcass	hip and loin	flank	ribs, chuck brisket, plate shank
Weight	7.8	3.4	36.8	9.0
Bone	16.7	3.9	--	18.0
Lean	25.0	32.8	200.8	12.0
Total fat	-11.0	-15.4	< 1	-10.2

[a]Adapted from Early, McBride & Ball, 1990b. Values are expressed relative to controls.
[b] Values do not necessarily imply statistically significant responses.

Table 6. Fat distribution in the carcass of steers treated with rbST[a,b]

	% Change		
	total carcass	hip and loin	flank, ribs chuck, brisket plate, shank
Subcutaneous	-14.2	-20.4	-9.0
Intermuscular	-7.9	-7.5	-7.2

[a]Adpated from Early, McBride and Ball, 1990b. Values are expressed relative to controls.
[b] Values do not necessarily imply statistically significant responses.

A total of three studies have been published to date regarding the influence of somatotropin treatment on protein synthesis in cattle and sheep (Table 7). The work of Eisemann et al. (1989) was relatively short term in nature but produced rather similar responses in skeletal muscle to those of Pell and Bates (1987) and Early et al., (1990c). In the semitendinosus muscle, a skeletal muscle that is classified as having primarily white fibres, somatotropin did not significantly alter the fractional rate of protein synthesis in any of the three studies. In contrast, somatotropin increased the fractional rate of protein synthesis in a variety of skeletal muscle groups dominated by red fibres (Pell and Bates, 1987; Eisemann et al., 1989). The numeric increase in each of the three studies was very close. In the organs studied, the fractional rate of protein synthesis was not altered. However, when the absolute rate of protein synthesis and degradation was considered (g/d; Table 8), somatotropin increased both protein synthesis and protein degradation in the liver (Early et al., 1990c). Eisemann et al. (1989) found somatotropin altered the absolute rate (g/d) of protein synthesis in skeletal muscle and the small intestine. The duration of somatotropin treatment and the stage of growth of the steers in each of these trials varied and discussion of each may help to clarify the different responses (Table 8). The fractional rate determinations of Early et al. (1990c) were made at the termination of a 112-day growth trial, during which the rate of growth induced by somatotropin decreased over time. The fractional rate determinations were applied to tissue protein density (at slaughter) to

Table 7. Maximal fractional synthetic rate in somatotropin-treated ruminants[a]

	% Change						
	Skeletal muscle		heart	liver	kidney	Small intestine	Reference
	α white fibres[b]	α red fibres					
Cattle							
steers	2.2	20.1	8.1	-1.4	-0.7	-1.6	Early et al., 1990c
steers	26.7	28.9	--	11.5	--	20.3	Eisemann et al., 1989
Sheep							
wethers	6	30	--	--	--	--	Pell and Bates, 1987

[a] Values are expressed relative to controls and do not necessarily imply statistically significant differences.
[b] Semitendinosus muscle

Table 8. Comparison of maximum protein synthesis rate change (PS) (g/d) and degradation rate (PD)(g/d) of various tissues from control vs. somatotropin-treated steers[a].

		Early et al. 1990c	Eisemann et al. 1989
Skeletal muscle	PS	10.8	27.7
	PD	11.6	--
Heart	PS	11.9	--
	PD	11.0	--
Liver	PS	57.4	19.4
	PD	56.4	--
Kidney	PS	15.6	--
	PD	15.6	--
Small intestine	PS	5.8	46.2
	PD	5.8	--

[a] Values are expressed relative to controls. Responses do not necessarily imply statistically significant responses.

calculate the absolute rate of protein synthesis (g/d). The protein degradation values were determined from the difference of measured accretion (over the whole growth period) and protein synthesis. The underlying assumption under such calculations implies that the fractional protein synthesis value determined at slaughter is representative of protein synthesis throughout growth. This clearly cannot be the case given the differential growth pattern exhibited by these animals. (Early et al., 1990a). The kinetic values more closely depict the conditions at slaughter and suggest that at the termination of growth, in animals aged 11-12 months, somatotropin altered the absolute rate (g/d) of protein synthesis and degradation by approximately the same degree (Early et al., 1990c). The study of Eisemann et al. (1989b) gives a snapshot in time during the early phases of growth with somatotropin treatment. Somatotropin significantly increased the absolute rate of protein synthesis in

skeletal muscle and the small intestine whereas liver growth was probably altered by decreased protein degradation (Eisemann et al., 1989b). The Eisemann et al. (1989b) study also suggests that the augmented protein synthesis exhibited in various tissues likely reflects transcriptional induction as opposed to translational augmentation since protein synthesis per g of both RNA and DNA was unaltered. This would agree with the cell-associated events ascribed to IGF-I as summarised by Steele and Elsasser (1989).

The improvement in the feed:gain ratio exhibited by growing animals treated with somatotropin likely reflects the repartitioning of components of gain, namely, a reduction in fat deposition in conjunction with an increase in protein, water and ash accretion. This agrees with the measurement made by Groenewegen et al. (1990) who found that the efficiency of protein, fat and ash accretion was unaltered by somatotropin treatment. Furthermore, total oxygen consumption (otherwise expressed as heat production; HP) per unit of tissue weight was unaltered in tissues (skeletal muscle, liver, kidney, intestine and brain) of somatotropin-treated steers (Early et al., 1990c). Therefore, the improved efficiency of gain (or retained energy; RE) *per se* must be driven by the components of gain (i.e. ME = HP + RE) which are altered by repartitioning caloric input into proportionally more protein within both the carcass and non-carcass components (Early et al., 1990b).

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SESSION III
SAFETY, WELFARE AND REQUIREMENTS OF THE TARGET ANIMAL

* Animal safety and welfare
* Thermal balance
* Nutrient requirements of pigs
* Disease resistance

SUMMARISED AND ADOPTED CONCLUSIONS FROM PAPERS AND DISCUSSION

ON

SAFETY, WELFARE AND REQUIREMENTS OF THE TARGET ANIMAL

Chairman:

R. Dantzer *Institut National de la Santé et de la Recherche Médicale - France.*

Discussion moderator:

N.C. Steele *United States Department of Agriculture, Livestock and Poultry Science Institute - USA*

- *As pointed out by Dr. Mussmann in his introduction to the session, the use of* ***somatotropin (ST) holds much promise in animal production,*** *including reduction of animal waste. However, it is strongly opposed to by those who favour organic, i.e. natural, farming and claim that administration of ST increases the level of stress farm animals are exposed to in intensive husbandry systems.*

- *The way biotechnology can impact on* ***welfare of farm animals*** *was discussed by Prof. Ingvar Ekesbo. Although biotechnology can have a positive influence on health and welfare, for example when it aims at enhancing resistance to pathogens by genomic manipulations, it has potential risks for the well-being of animals. These risks must not lead to the ban of biotechnology but to a* ***careful and objective assessment*** *of its consequences on health and welfare.*

- *The next three papers addressed whether the use of ST can interfere with* ***health of target animals.*** *Since ST increases heat production and decreases the amount of subcutaneous fat, it has been speculated that ST-treated animal might be more susceptible to thermal stress. This possibility was examined by Ann Becker who reported the results of a series of experiments carried out at the University of Missouri at Columbia on dairy cows and finishing hogs exposed to cold and heat stress. The administration of* ***exogenous ST did not have any detrimental effect on performance or thermal balance of animals exposed*** *to heat or to cold. In addition, the increase in production performance due to ST treatment was maintained in both extreme environments.*

- *Martje Fentener van Vlissingen summarised the evidence pointing to a modification by pST treatment of* ***protein requirements*** *for maximal growth rate and optimal dietary protein utilization. Because of improved protein utilization, it does* ***not appear necessary to drastically revise the animo acid composition of the diet fed*** *to pST-treated animals. However, if the full benefit of the pST treatment is to be obtained, both protein requirements and mineral requirements must be better defined in view of the reduced food intake displayed by pST-treated animals.*

- *Based on a survey of the existing literature, James Roth emphasized the fact that ST treatment at doses anticipated to be used in food producing animals is* **not associated with any important detrimental effect on animal health.** *However, few published studies appear to have been specifically designed to examine the possible negative influence of ST on specific components of health. As far as immune function is concerned, the general opinion is that ST does not impair immune function but, on the contrary, is* **capable of enhancing a wide variety of immune responses.** *He presented data obtained in his own laboratory at Iowa State University suggesting that repeated injections of pST have no negative influence on immunocompetence and overall health.*

- *In the discussion, the chairman, Robert Dantzer, pointed out that* **welfare must be dissociated from production performance** *and physical health, even if its assessment includes these two aspects. The concern for welfare reflects the fact that farm animals have a mental life the quality of which can be altered by the way they are kept. Objective methods have been developed to assess welfare and they need to be used if there is an authentic concern for welfare of farm animals in relation to biotechnology. Norman Steele asked for a clear separation between the issue of animal rights and the issue of animal welfare to clarify the debate about what is acceptable from the viewpoint of the animal. The meaning and generality of the data presented at the session were discussed.*

- *In conclusion, there is an agreement on the fact that the administration of ST at doses anticipated to be used in food producing animals has* **no gross detrimental effects on physical health of the target animal**. *However, safety does not imply that ST has no impact on animal welfare and a fortiori that biotechnology is safe in this respect. The* **public concern for animal welfare still needs to be responded to in an appropriate manner.**

BIOTECHNOLOGY FOR CONTROL OF GROWTH AND PRODUCT QUALITY IN MEAT PRODUCTION. IMPLICATIONS AND ACCEPTABILITY FOR ANIMAL SAFETY, HEALTH AND WELFARE

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Summary

The definition of biotechnology in conjunction with this paper comprises a broad spectrum of manipulations in animals including utilization of phenomena such as immunological tolerance, manipulations of receptors by monoclonal antibodies or other means, or the injections of engineered proteins or peptides produced by recombinant DNA technologies. It does not include manipulations like artificial insemination, egg or embryo transplantations. The paper is restricted to animals kept for farming purposes.

Developments in biotechnology may lead to genetic manipulation of farm animals that would not serve their health and welfare but one may also visualise manipulations that would improve their health and welfare. It is important that basic species-specific biological characteristics will not be changed through chemical or other supplies nor through genetic manipulation so that the single animal or its offspring can be caused suffering.

Animals resulting from manipulated embryos and the offspring of such animals should be carefully monitored with respect to untoward effects of the genetic material that has been introduced before being allowed for farming purposes. Whenever an untoward effect is found, the animal and its offspring must not be allowed for farming purposes.

The animals used at present for farming purposes should be preserved in populations of large enough effective size and otherwise in a way that makes it possible to again start breeding a variety that may not have been bred for several years, should this be judged desirable.

The Council of Europe's Convention for the protection of animals kept for farming purposes is proposed to be completed with rules which increase the protection for such animals by indicating limitations in man's right to manipulate animals kept for farming purposes. Three such rules are proposed.

A clear distinction must be made between experimental animals and animals kept for farming purposes. The proposed rules have reference to animals kept for farming purposes. They do not intend to stop objective, scientific research in the areas where important progress can be made without jeopardising the health or welfare of animals or man. It is of the utmost

importance, however, that financial considerations are not permitted to preclude the application of ethical norms.

Keywords: *Biotechnology, meat animals, safety, health, welfare.*

Introduction

The definition of biotechnology in this connection comprises a broad spectrum of manipulations in animals including utilization of phenomena such as immunological tolerance, manipulations of receptors by monoclonal antibodies or other means, or the injections of engineered proteins or peptides produced by recombinant DNA technologies. It does not include manipulations like artificial insemination, egg or embryo transplantations. The paper is restricted to animals kept for farming purposes.

In principle, DNA could be manipulated in somatic cells, gametes or very early embryos. The consequences for animal welfare would, as far as one can see today, be essentially the same whether gametes or a very early embryo or fertilized egg were manipulated (Berg, 1989).

Introduction of genetic material (genetic manipulation) in somatic cells is of consequence only for the animal or animals that carry the manipulated cells. The genes that may have been introduced will not be present in gametes and therefore not transferred to new generations. Therefore, genetic manipulation of somatic cells, although it may pose risks for the individual animals is of no consequence for other animals.

Genetic manipulation of the fertilized egg or early embryo has more far-reaching consequences and also much greater potential with regard to commercial utilization (Berg, 1989).

General consequences and risks of genetic manipulation of the fertilized egg or early embryo

There are several examples of successful integration of an exogenous gene into the genome of an early embryo, resulting in a transgenic animal (e.g. Pursel et al., 1989; Rexroad et al., 1989; Bondioli et al., 1990). Transmission of the integrated exogenous gene, the transgene, through several generations in a functioning state has been demonstrated for several genes, particularly in the mouse (e.g. Palmiter et al., 1982). This is true for example for genes coding for human haemoglobin chains which are easily distinguishable from mouse haemoglobin (Berg, 1989). Successful genetic manipulation of animals kept for farming purposes is feasible and has been performed, e.g. for pig, cattle, sheep and chicken (Rexroad et al., 1989; Bondioli, 1990; Chen et al., 1990).

When a maximum of success is achieved in attempting to integrate exogenous genes into an early embryo, the foreign gene will be integrated in a stable manner in the genome and be present in most, if not all of the cells of the animals resulting from the manipulated embryo, and transferred to new generations in a stable and functioning state. Thus, a permanent

change has been made in the genetic material that may be transferred to innumerable new generations. The segregation of chromosomes at meiosis and the naturally occurring phenomenon of meiotic recombination will cause the exogenous gene to occur in a vast number of combinations with other genes. The consequences of having the exogenous gene in a countless number of combinations with other genes several generations in the future do not seem to be entirely predictable (Berg, 1989). Therefore, the risk of untoward effects must be carefully evaluated in enough generations (Pursel et al., 1989). Animals who, during such scientific evaluations have exhibited any untoward consequences, or their offspring, must not be allowed to use for farming purposes.

The introduction of an exogenous gene or gene construct into an early embryo may cause integration into an area of the genome where the foreign DNA may lead to untoward consequences (Pinkert, 1987; Rexroad and Pursel, 1988; Pursel et al., 1989). Illegitimate integration of exogenous genetic material is apparently not just a theoretical possibility (Berg, 1989). It makes it necessary to monitor carefully the animals resulting from the manipulated embryos, and their offspring. Such monitoring would be advisable even when methods for safe and legitimate integration into the genome become available.

Such uncertainties and risks seem to be the main reasons why genetic manipulation of the human embryo, even for the purpose of curing recessive disease, is rejected by most medical geneticists and other experts in human medicine. Concern with respect to activation of oncogenes has been voiced also in connection with manipulation of somatic cells and this is probably the main reason why the attitude of several influential research bodies is that therapy in man by genetic manipulation of somatic cells should only be attempted in very serious disorders where no other effective treatment seems available (Berg, 1989).

In view of the particular responsibility that man must have for animals that for thousands of years have been kept for farming purposes, it could be argued that one should be almost as restrictive with respect to genetic manipulation of such animals as one with respect to man. However, there is also argued that animals are farmed because of their usefulness to man and because man has literally been dependant on them for survival (Berg, 1989). There is no realistic possibility for man to stop keeping animals for farming purposes. Accordingly, it seems permissible and reasonable that even some genetic changes may be made to improve the usefulness of these animals. There must, however, be strict animal health and welfare limits to quality and quantity of genetic changes that man may cause in animals kept for farming purposes. Therefore ethical rules are necessary.

Improvement of production efficiency in farm animals by genetic manipulation. Problems and possibilities

Some years ago, great publicity was given to experiments in which several copies of the gene for the human growth hormone had been introduced into mouse embryos (Palmiter et al., 1982). This caused the mice that were later born to develop into "giant mice", showing that animals with greater body mass may be produced by integrating several copies of the gene for growth hormone into animal embryos. The question is if such methods could be used in farm animals for increasing production efficiency.

When considering animals for meat production changes in quantity or quality of muscle tissues may and may not have untoward effects. Such effects could put the animal's welfare in jeopardy. Thus, it may not be taken for granted that a significant increase in body mass and particularly muscle mass will be accompanied by adequate changes in the body's support system, the skeleton. It would be more than just a hypothetical danger that legs and spine will not be adequate to support a greatly increased body weight. This could cause malfunction of the skeleton, give rise to locomotor and other behavioural aberrations resulting in injuries, diseases and suffering to the animal.

In the same way increases in milk production by genetic manipulation could lead to risks for increased udder injuries and diseases. Already now udder injuries and diseases have been increasing parallel with the increase in milk production. Considerable efforts are made to prevent these disease problems by genetic measures for preventing such diseases e.g. by improving udder forms (Lindhé, 1986; Lindhé et al., 1990). Therefore, genetic manipulation in order to increase milk yield must take udder anatomy into consideration. This does not mean that other risks should not be taken into account, e.g. tendency to get mastitis.

Likewise improvement of the yield or quality of wool by genetic manipulation of sheep embryos may include risks. The wish to change wool quantity or quality would have to be weighed against risks for e.g. negative effects on the thermoregulation of the animal.

In all the above cases the danger of illegitime integration into the genome would exist. Therefore it would be necessary to carefully control the manipulated animals and their offspring with respect to incidence of different disorders before such animals will be allowed to be kept for farming purposes.

There are apparently detrimental effects on the health of transgenic animals (Pinkert, 1987; Rexroad and Pursel, 1988; Pursel et al., 1989, 1990). The problems seem to be anatomical as well as physiological. Altered endocrine profiles, metabolism changes, altered thermoregulation and libido, lowered fertility, increased susceptibility against infections, lameness, arthritis are reported (e.g. Pinkert et al., 1990).

Three requisites must be fulfilled before any animal, which is a result of genetic manipulation has to be allowed to be used for farming purposes, i.e. is allowed to leave the limited sphere of research and enter the sphere of animal husbandry. The first is that it must have been fully proved that exact that manipulation, which was intended to be done, really has occurred, is stable and that no integration has occurred into any other area of the genome than where it was meant to be located. The second requisite is that there must be secure and reliable screening methods available which make it possible to find and define each manipulated animal in a population, e.g. in a commercial cattle, swine, sheep or poultry herd. This is necessary for making follow up control investigations on manipulated animals which are released into commercial herds. The third is that it should have been shown that the manipulated genome when introduced in a breeding system which permits recombination of genes does not result in detrimental effects in the next generations.

Attempts to improve the economical yield of keeping animals for farming purposes by genetic manipulation would most likely comprise a very large number of animals, perhaps most animals of a given species in a region. Great gains could result if such experiments were successful and had no untoward effects. It could , however, be economically disastrous if an

unforeseen negative effect or purported negative effect scared people away from using either the meat or the milk from manipulated animals. Even an unfounded rumour that the manipulated animals frequently had virus-induced tumours could cause serious problems (Berg, 1989). Thus, it complicates the issue that not only must the real risks be considered, but also the effect of purported risks and claims made by eloquent groups who want essentially all DNA work to be forbidden.

However, neither the assumed or supposed risks nor the scare without a basis in reality should be permitted to stop objective, scientific research in the areas where important progress can be made without jeopardising the welfare of animals or man. It is of the utmost importance, however, that financial considerations are not permitted to preclude the application of ethical norms.

Need for preserving existing genetic material

We are apparently just in the beginning of a period of intense research and research progress in genetic manipulations. In such a situation it is of great importance that agreements are arrived at that animals used at present for farming purposes should be preserved. And they must be preserved in populations of large enough effective size and otherwise in a way that makes it possible to again start breeding a variety that may not have been bred for several years, should this be judged desirable.

Improvement of the animal health by genetic manipulations

Several diseases in man and in animals have environmental, nutritional as well as genetic components to their etiology. An outstanding example in man is early atherosclerosis where it seems clear that in most cases, unfavourable environmental or nutritional conditions cause disease preferentially in those who are genetically predisposed (Berg, 1989). Another example is malignant hyperthermia, an inherited skeletal muscle disorder characterised by a profoundly accelerated muscle metabolism, contractures, hyperthermia, and tachycardia, and which is one of the main causes of death due to anaesthesia. This disorder is very similar to porcine malignant hyperthermia (Ludvigsen, 1957; MacLennan et al., 1990; McCarthy et al., 1990).

The chromosomal localisation for more and more hereditary diseases may be possible to map (Lalley et al., 1989) Animals may differ genetically with respect to resistance towards negative environmental,infectious or nutritional influences and it would be useful if integration of exogenous genes or gene constructs into the genome of susceptible breeds would improve their health and welfare as well as reducing the need to give animals antibiotics. There are examples of by genetic manipulation obtained enhanced resistance against e.g. infection by Salmonella strains in mice (Edwards et al., 1989) or leucosis virus in poultry (Salter & Crittenden, 1989).

Any genetic manipulation aimed at improving the animals' health would seem highly commendable. However, each time the desired changes might be obtained by traditional

breeding experiments, this procedure would be preferable because it does not carry with it the risks of uncertainties caused by integrating exogenous genes or gene constructs into the genome.

Administration of substances for stimulation of growth or other production traits.

A review of the literature indicates a great variation in responses of farm animals to substances given in order to stimulate growth or other production traits (e.g. Machlin, 1972; Bryan et al., 1987; Eppard et al., 1987; Evock, 1988; Kievits, 1988; Kronfeld, 1988; Kelley, 1989; Evock, 1990; Dau & Bane, 1990) Such substances are engineered proteins or peptides produced by recombinant DNA technologies.

This great biological variation indicates risks if the handling and utilization of these substances are not taking into account all factors in the animal and its environment which may interfere with the substance administered.

However, potential adverse effects of substances like bST, pST etc. and methods to prevent such effects seem to have received much less attention than the efficacy of such substances (Kronfeld, 1988; Sejrsen et al., 1989).

One problem is apparently that there until now have been lack of funds for research regarding the risks. More economical resources have for natural reasons been allocated to investigate the possibilities to utilize such substances. The problem is that the risk research must be mainly supported by public funds whereas the possibility research is mainly commercially supported.

New technique and new methods were introduced in the farm animal environment from the 1950's. At the same time a great increase in the animal production took place (Ekesbo, 1973, 1990). As a not foreseen result there were changes in the disease panoramas for the species concerned. The change was characterised by an increase of what are often called man made diseases, environmentally evoked diseases or production diseases (Ekesbo, 1976). The main reasons for these increases of diseases were changes in relationship between the animal and its environment, it may be mastitis, ketosis or hoof problems in cattle (Ekesbo, 1966; Bakken, 1981), MMA (Bäckström, 1973; Bogner et al., 1978) pleuritis, pneumonia or PSE in pigs (Rülcker, 1968; Lindqvist, 1974), feather, skin or claw damages or salpingitis in egg laying hens (Svedberg, 1976, 1988). In order to prevent these diseases it has been necessary to perform epidemiological studies showing the associations between these diseases and risk factors in the environment, in the management and in the animals (e.g. Ekesbo, 1966; Bakken, 1981; Bendixen et al., 1988a, 1988b). The associations do not explain the causal connections. In order to explain causal connections epidemiological methods must be combined with microbiological, physiological, clinical, ethological and other methods (e.g. Algers 1982a, 1882b; Ekesbo, 1979; Jensen, 1983; Algers et al., 1984; Plym Forshell, 1986; Plym Forshell & Ekesbo, 1990). However, when the causal risk factors are defined, it was and is possible to change the environment and adapt it to the animals (Ekesbo, 1988b). In the meantime, however, much animal suffering and economical losses for farmers have occurred.

In order to prevent such animal health and welfare and economical problems, Sweden and Switzerland have introduced a system for testing new technique from animal health and welfare point of view. The Netherlands are to do the same from 1993 (Steiger, 1990).

It seems even more reasonable to introduce a mandatory testing system from animal health and welfare point of view for substances aiming at stimulation of growth or other production traits. In this connection it is necessary to remind of the fact that quite contrary to what sometimes is claimed (e.g. McClary et al., 1990) production level is no measure of animal health (Ekesbo, 1966, 1988b) but must be taken into consideration when evaluating the effect of different factors on the animals health and welfare (Ekesbo, 1988b).No substance should be allowed to be purchased for use on farm animals before independent scientific research has shown that the substance has no detrimental effects on stress, immune competence, disease resistance, reproductive performance and other for the health and welfare essential biological functions of the species in question. Assessment of the substances could be conducted like it is done in many countries for drugs combined with methods for testing impact on animal health and welfare by environmental factors (Ekesbo, 1984, 1988a, 1988b;). If such precautions will not be taken we might come into principally similar problems as when during the 1950's antibiotics were introduced. In the beginning these substances were used with very little restrictions not only for disease treatment but also for disease prevention and also as so called growth promotors in feed for animals which all created resistance problems. Introduction and use of somatotropin in commercial herds before all health and welfare aspects are fundamentally scientifically investigated and defined could create and cause other problems than the ones mentioned for the antibiotics but not less difficult to solve.

A proposal for ethical rules indicating limitations in man's right to manipulate animals kept for farming purposes

Between 1971 and 1975 a European Convention for the protection of animals kept for farming purposes was elaborated by an ad hoc committee comprising delegations from most of the member states of the Council of Europe. The convention was opened for signature in 1976 and came into force on the 10th September 1978. Until 1990, 17 countries have ratified the convention. They are: Belgium, Cyprus, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, Greece, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom. Also EEC as an overnational organisation has ratified the convention.

According to article 8 - 13 in the convention (Council of Europe, 1976) a Standing Committee in the Council of Europe shall elaborate detailed rules for animal husbandry from animal welfare point of view for each species. This Committee was established in 1979. These rules have to be transformed into binding rules via law or otherwise administrative praxis in those member countries which have ratified the convention within 12 months after the adoption of the committee. EEC must adapt its common rules according to at least the standards of the rules adopted by the Standing Committee. Until now such rules are elaborated and adopted by the Committee for cattle, swine, egg laying hens and fur animals.

In the Standing Committee all nations which have ratified the Convention have full membership, are "contracting parties". Ratification in most countries means a decision by the national parliament. Countries which have not ratified the Convention have status as observers. Several countries have observer status, e.g. Austria, Finland, Turkey, and others. Outside Europe Australia, U.S.A. and Thailand have observer status. The committee also have delegations with status as "experts". To this group belongs the European Confederation of Agriculture, the World Society for the protection of Animals, The Society for Veterinary Ethology and The Federation of Veterinarians of the EEC.

The convention comprises 18 articles. In its first article it says "This Convention shall apply to the keeping, care and housing of animals, and in particular to animals in modern intensive stock-farming system. For the purposes of this Convention "animals" shall mean animals bred or kept for the production of food, wool, skin or fur or for other farming purposes..". Article 3 says "Animals shall be housed and provided with food, water and care in a manner which - having regard to their species and to their degree of development, adaption and domestication - is appropriate to their physiological and ethological needs in accordance with established experience and scientific knowledge."

There are different opinions among experts in law if the convention is covering the current situation of biotechnology in animal husbandry. It seems therefore advisable to include in the convention some basic rules that indicate limitations in man's right to manipulate animals kept for farming purposes. Such rules shall not limit the possibility to do research in biotechnology.

The rules regarding biotechnology could be formulated according to the following:

* Animals produced as a result of genetic manipulation procedures shall not be kept for farming purposes unless it through scientific evidence is shown that their health and welfare will not suffer.

* No substance shall be administered to an animal kept for farming purposes unless it has been demonstrated by scientific studies of animal welfare that the ultimate effect of the substances is not detrimental to the health and welfare of the animal.

* The animals used at present for farming purposes should be preserved in a way that makes it possible to again start breeding a variety that may not have been bred for several years, should this be judged desirable.

Final comments

Man has always had ethical rules, written or unwritten, for animal husbandry. In our time with rapid scientific achievements international agreement on ethical rules are necessary for the protection of the animals, the farmers and the society.

Besides the references given this paper is partly based on discussions which during the latest years have taken place in The Council of Europe's Standing Committee for Farm Animal Welfare.

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EFFECT OF EXOGENOUS SOMATOTROPINS ON THERMAL BALANCE AND CONSEQUENCES IN THERMALLY STRESSFUL ENVIRONMENTS

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Summary

Recombinantly-produced somatotropins, both bovine and porcine, have been shown to alter energy metabolism and body composition. Such alterations have been hypothesized to make the animals more vulnerable to environmental extremes. A series of experiments has been conducted with lactating dairy cows and finishing hogs under simulated cycling hot and cold environmental conditions at the Samuel Brody Climatology Laboratory to test this hypothesis. In both lactating dairy cows and finishing hogs treated with somatotropin, changes in heat production were demonstrated; however, the animals were able to cope with such changes and no thermal imbalance occurred. Physiological changes occurred due to both environment and hormone treatments, yet no interaction between these two effects interfered with the benefits of somatotropin treatment obtained in performance in both species under hot and cold conditions.

Keywords: *somatotropin, lactating cows, finishing hogs, thermal environment, thermal balance, performance*

Introduction

Various researchers have hypothesized that when exposed to thermally stressful environments animals treated with somatotropin would not be able to maintain enhanced performance found under thermoneutral conditions (Curtis, 1989; Verstegen et al., 1989). Further, it was projected that the physiological alterations associated with somatotropin supplementations would override the thermoregulatory mechanisms associated with additional thermal load, and that the effects of thermal stress would be detrimental to performance. Accompanying this effect on performance would be a reduction in quantity and quality of product and efficiency of energy utilization. To test this hypothesis, a series of studies was conducted to determine the effect of somatotropins, both bovine and porcine, on the performance, physiology and thermal balance of lactating dairy cows and finishing hogs in hot and cold environments.

Studies conducted at the Samuel Brody Climatology Laboratory

In a series of experiments conducted at the Samuel Brody Climatology Laboratory located in the Animal Science Research Center at the University of Missouri, Columbia, MO, USA, lactating dairy cows and finishing hogs were exposed to various cold and hot environmental conditions that typify extreme winter and summer conditions in Missouri (Table 1). In the cold experiment for lactating dairy cows, an addition of wind and water spray was applied during the light cycle of the photoperiod to increase the effective cold temperature.

Table 1. Environmental conditions simulating extreme summer and winter weather in Missouri.

Animals	Condition	Temperature (C)	Relative humidity (%)
Dairy	Hot	24 to 35	55 to 65
	Cold	-5 to 5	50 to 55
	TN[1]	18 to 22	50 to 64
Swine	Hot	27 to 35	40 to 70
	Cold	5 to 15	50 to 70
	TN[1]	18 to 25	50 to 55

[1]TN = thermoneutral

Lactating dairy cows in hot and cold environments

Two groups of 12 lactating Holstein cows, 90 to 150 days postpartum with milk production of 25 kg/d or greater, were used in each of the hot and cold studies. Half were injected i.m. daily with 25 mg of bovine somatotropin (rbST; methionyl bovine somatotropin, Monsanto Company, St. Louis, MO) while the remaining cows were injected with a control vehicle of sodium bicarbonate. Cows were maintained in respective environments for 10 days. Cows were milked twice daily, and milk yield and milk composition were determined. Diet available ad libitum consisted of corn silage and alfalfa hay. To assess thermal balance, heat production and evaporative heat loss were measured by indirect calorimetry and capsule method, respectively. Gross energy intake and milk energy secretion were also measured. Rectal temperatures and respiratory rates were measured and used as indicators of thermal balance.

Finishing hogs in a hot environment

Forty crossbred finishing hogs (20 barrows and 20 gilts) averaging 77 kg were used in the first heat study. Hogs were individually penned and fed an 18% corn soybean ration ad libitum. Six percent soy oil was added to increase the energy content to 3.6 Mcal/kg. Half of the hogs were administered a single 100 mg porcine somatotropin (rpST) prolonged release implant (Monsanto Company, St. Louis, MO, USA) on day 0, while the remaining hogs (control) received a placebo implant. Body weights and feed consumption were determined weekly. Rectal temperatures and respiratory rates were taken to assess thermal status. When

final weight was reached, hogs were slaughtered and carcass measurements and quality were determined.

A second study was conducted in a hot environment using 24 barrows. Protocol, diet and rpST administration were similar to the first study. In addition, heat production was determined by indirect calorimetry. When hogs were slaughtered, one-half of the carcass and empty viscera was processed for body composition determination by chemical proximate analyses. Heat production was calculated from the metabolizable energy intake and the energy retained in the fat and protein of the carcass.

Finishing hogs in a cold environment

Twenty-four finishing hogs were exposed to a cold environment using similar protocol and implant procedure as in the previous two studies. Besides difference in environment, the only other change in protocol was the diet. Hogs were fed a 12% crude protein corn-soybean meal diet with energy content of 3.28 Mcal/kg.

Performance of animals supplemented with somatotropins in hot environments

Lactating dairy cows and finishing hogs under hot environments responded to the administration of somatotropins with enhanced performances over the nontreated animals (Table 2). For lactating dairy cows, milk yield increased 31 and 35% over the yields of nontreated cows in the thermoneutral and hot environments, respectively. The response to somatotropin treatment was slightly greater in the hot environment than in the thermoneutral environment. Milk fat increased due to rbST, but rbST or environment did not affect milk protein. Cows treated with rbST had greater feed intake and efficiency regardless of environment.

Table 2. Performance of lactating dairy cows and finishing hogs in hot environments.

	TN		Hot		
Parameter	Control	bST/pST	Control	bST/pST	Effect[1]
Dairy cows					
Feed intake (kg/d)	30.8	36.6	24.1	28.8	B,H
Milk yield (kg/d)	24.9	32.6	20.9	28.3	B,H
Milk fat (%)	2.6	2.9	2.6	3.0	B
Milk protein (%)	2.9	3.0	2.8	3.0	
Hogs					
Gain (kg/d)	1.0	1.0	.8	.8	H
Feed intake (kg/d)	3.4	3.0	2.7	2.4	P,H
Feed/gain ratio	3.4	2.9	3.5	3.0	P
Final weight (kg)	106.5	107.9	101.3	102.3	H

[1]B or P = significant effects of bST or pST (P<.01)
[1]H = significant effects of the hot environment (P<.01)

Somatotropin treatment increased the efficiency of energy utilization for milk production such that milk energy secreted required less energy (5.7, 4.6, 5.2, and 4.1 Mcal feed/Mcal milk for TN-control, TN-rbST, H-control, and H-rbST, respectively). No significant change in body weights was found due to rbST treatment.

Finishing hogs in the hot environment gained at a slower rate than those in the thermoneutral environment. Both rpST-treated and control hogs gained at similar rates in respective environments. However, rpST-treated hogs ate 13% less feed than the control hogs in both environments, resulting in 15% greater feed efficiency.

Finishing hogs in the hot environment had 4% lower final body weight; however, no differences in hot carcass weight or dressing percentage were found due to environment or rpST. Hogs in the hot environment treated with rpST had reduced 10th rib backfat and leaf fat, with the interaction of environment and hormone having a further significant reduction only on leaf fat (P<.02). Loin muscle size and scoring for muscle, colour, marbling and firmness were not affected either by environment or rpST.

Performance of animals supplemented with somatotropins in cold environments

Lactating dairy cows and finishing hogs responded to the administration of somatotropins while in cold environments (Table 3). Overall milk yield was higher in rbST-treated cows in both thermoneutral and cold environments. Cows treated with rbST produced 16.3 and 17.4% more milk than the control cows in thermoneutral and cold conditions, respectively. These increases were considerably less than those found in the heat study. Milk fat was not affected by environment or rbST, while milk protein was slightly increased by the cold environment.

Table 3. Milk yield and composition of lactating dairy cows and performance of finishing hogs in cold environments.

	TN		Cold		
Parameter	Control	bST/pST	Control	bST/pST	Effect[1]
Dairy cows					
Feed intake	36.2	39.1	36.1	38.4	
Milk yield (kg/d)	28.8	33.5	31.0	36.4	B,C
Milk fat (%)	3.7	3.7	3.5	3.4	
Milk protein (%)	3.0	3.1	3.4	3.5	C
Hogs					
Gain (kg/d)	.8	1.0	.7	.7	C
Feed intake (kg/d)	3.6	3.5	3.9	3.4	
Feed/gain ratio	4.2	3.5	5.3	4.6	P,C
Final weight (kg)	113.1	115.7	108.2	111.0	C

[1]B or P = significant effects of bST or pST (P<.01)
[1]C = significant effects of the cold environments (P<.01)

Finishing hogs in the cold environment gained at a slower rate than those in the thermoneutral environment, and this rate was not affected by rpST. Control and rpST-treated hogs overall had similar feed intakes; however, rpST-treated hogs had lower feed intake during the first several weeks. Feed intake was lower in rpST hogs in the cold, but again, the differences tended to diminish in the last weeks of the study. Despite the increased feed intakes in the rpST hogs toward the end of the study, feed/gain ratios were 16 and 13% greater than those in control hogs in thermoneutral and cold conditions, respectively.

Finishing hogs in the cold environment had a 5% lower final body weight and tended to have lower hot carcass weights than those in thermoneutral environments. There were no differences in dressing percentage, 10th rib back fat, loin muscle size, leaf fat and muscle scoring due to either rpST or cold conditions.

Assessment of thermal balance of animals supplemented with somatotropins in hot environments

Based on rectal temperatures and respiratory rates, which are indices of thermal stress, lactating cows and finishing hogs treated with somatotropins did not experience significant thermal imbalance. In the hot environments, rectal temperatures and respiratory rates were significantly increased; however, no significant increase in these parameters was due to either rbST or rpST. Lactating cows treated with rbST had greater energy intake than controls; this increase occurred in hot environments where energy intake decreased in all cows (Table 4). Energy output in the milk, accompanying the increase in milk yield, was greater in rbST-treated cows in both thermoneutral and hot conditions, although overall milk energy was less in the hot environment. Cows treated with rbST had higher heat production but also had a higher evaporative heat loss. This higher evaporative heat

Table 4. Assessment of thermal balance of lactating dairy cows in a hot environment.

	TN		Hot		
Parameter	Control	bST/pST	Control	bST/pST	Effect[1]
Rectal temperature (C)	38.2	38.5	39.7	39.9	H
Respiratory rate (/min)	43.2	51.2	86.3	91.4	H
Energy intake (Mcal/d)	83.9	94.6	65.0	76.1	B,H
Heat production (Mcal/d)	30.6	36.4	30.3	38.0	B
Milk energy (Mcal/d)	15.0	21.0	12.7	18.8	B,H
TEVHL[2] (Mcal/d)	9.2	12.4	13.7	17.1	B,H

[1]B = significant effects of bST (P<.01)
[1]H = significant effects of hot environment (P<.01)
[2]TEVHL = total evaporative skin and respiratory heat loss

loss explains how the rbST-treated cows, despite higher heat production, can maintain thermal balance regardless of environment and sustain efficient milk production.

Heat production of finishing hogs treated with rpST was similar when measured by indirect calorimetry during the peak of the cycled temperatures (data not shown), and when estimated from proximate analysis of the carcass in both thermoneutral and hot environments (Table 5). In contrast to the dairy cow, energy intake in the finishing hog was significantly reduced by rpST. When heat production was compared to metabolized energy intake, the rpST-treated hogs had a higher percentage of metabolizable energy being converted to heat in both environments. Energy retained was a combination protein and fat deposition. Protein deposition rates were increased significantly, but fat deposition rates were decreased even more dramatically. As a result, total energy retained was less in the rpST-treated hog (Figure 1).

Table 5. Assessment of thermal balance of finishing hogs in a hot environment.

	TN		Hot		
Parameter	Control	bST/pST	Control	bST/pST	Effect[1]
Rectal temperature (C)	39.3	39.5	39.6	39.7	H
Respiratory rate (/min)	36.9	39.7	69.1	77.3	H
MetabolizableT9450 energy intake (kcal/d)	8365	7875	5950		P,H
Energy retained as protein (kcal/d)	331	599	385	481	P
Energy retained as fat (kcal/d)	4425	3175	3015	1249	P,H
Heat production (kcal/d)	4693	4591	4474	4220	
Moisture in carcass (g/d)	145	322	169	301	P

[1]P = significant effects of pST (P<.01)
[1]H = significant effects of hot environment (P<.01)

Despite the increased percentage of metabolizable energy converted to heat production, there were no significant differences in rectal temperatures and respiratory rates due to rpST. The rpST-treated hogs contained significantly greater amounts of moisture, which acts as a "heat sink" that could greatly enhance the ability of rpST-treated hogs to tolerate the additional heat load. The mechanism by which that much water was retained in rpST-treated hogs is not known, but we are pursuing the hypothesis that sodium retention may increase in rpST-treated hogs.

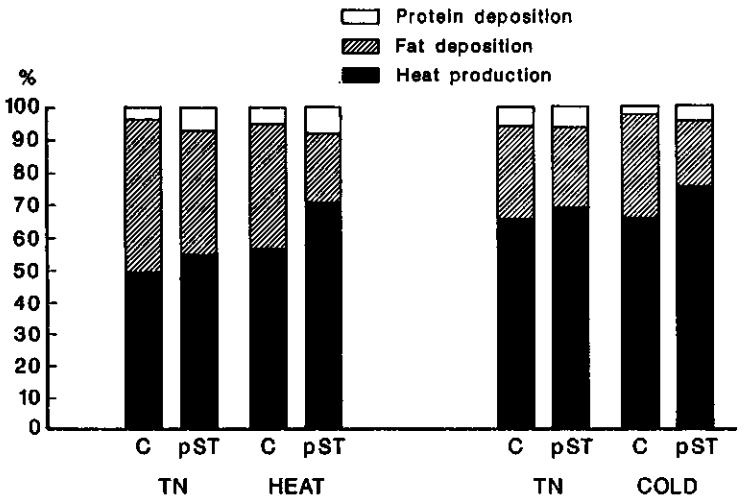

Figure 1. Assessment of heat production and fat and protein deposition relative to metabolizable energy intake in pST-treated finishing hogs under hot and cold environmental conditions.

A clearer assessment of thermal balance based on percent of metabolizable energy intake is shown in Figure 1 and suggests that rpST-treated hogs partition energy differently than the control hogs. These data support the concept that rpST is a "partitioning agent" as demonstrated by nutritional and physiological data.

Assessment of thermal balance of animals supplemented with somatotropins in cold environments

As in the hot environments, lactating cows treated with somatotropins did not have significantly different rectal temperatures and respiratory rates from the control cows in either the thermoneutral or cold environment. Finishing hogs treated with rpST had slightly higher rectal temperatures in both thermoneutral and cold environments; however, no significant differences in respiratory rates were found. Neither of the species treated with somatotropins demonstrated greater susceptibility to cold than the nontreated animals. In both species in the cold environments, rectal temperatures and respiratory rates were lower (Tables 6 and 7). Energy intake in the lactating dairy cows was slightly, but not significantly, higher than in the hot study. Energy output in the milk and heat production were higher in the rbST-treated cows than in the control cows in both thermoneutral and cold environments (Table 6). Total evaporative heat loss was higher in the rbST-treated cows in thermoneutral but lower than the control cows in the cold. Overall, cold reduced total evaporative heat loss by over 50% and appears to be a major method of heat conservation by dairy cows in cold environments.

Table 6. Assessment of thermal balance in lactating dairy cows in a cold environment.

	TN		Cold		
Parameter	Control	bST/pST	Control	bST/pST	Effect[1]
Rectal temperature (C)	38.5	38.6	38.3	38.3	C
Respiratory rate (/min)	52.7	57.4	27.3	24.9	C
Energy intake (Mcal/d)	96.8	104.6	100.5	105.3	
Heat production (Mcal/d)	31.9	37.6	32.1	35.2	B
Milk energy (Mcal/d)	21.0	23.9	20.3	25.4	B
TEVHL2 (Mcal/d)	11.7	12.5	5.1	4.8	B,C

[1]B = significant effects of bST (P<.01)
[1]C = significant effects of cold environment (P<.01)
2TEVHL = total evaporative skin and respiratory heat loss

Finishing hogs treated with rpST in the cold environment had higher net heat production than hogs in thermoneutral (10.3 versus 7.2 kcal/kg.75/hr) when measured by indirect calorimetry at the end of the trough of the cycle. Net heat production as estimated by proximate analyses was not different (Table 7). The higher heat production at the trough of the cold cycle in the live animal suggests that, in the cold, hogs may let heat production and rectal temperature rise and fall with the daily temperature-humidity cycle while maintaining a constant overall heat production. In contrast to the studies in the hot environment, feed intake, regardless of treatment or environment, was not significantly different. If heat production and energy retained were evaluated as a percentage of metabolizable energy intake, heat production was only slightly higher in the rpST-treated hog in either environment (Figure 1); however, energy retained as protein was greater in rpST-treated hogs but to a lesser degree in hogs in the cold environment. Energy retained as fat was less in the rpST-treated hog than in the control but was similar among the treated hogs in each environment. This lower fat content was hypothesized to make the rpST-treated hog more vulnerable to cold stress (Curtis, 1989); however, the slight increase in heat production appeared to enable the rpST-treated hog in a cold environment to maintain homeothermy. Rectal temperatures were slightly higher (P<.04) in treated than in control hogs in both thermoneutral and cold environments. As was observed in rpST-treated hogs in the hot environment, rpST-treated hogs in the cold environment had significantly higher moisture content; however, this amount was reduced in the cold animal. The implication of this in cold tolerance is not understood.

Table 7. Assessment of thermal balance of finishing hogs in a cold environment.

	TN		Cold		
Parameter	Control	bST/pST	Control	bST/pST	Effect[1]
Rectal temperature (C)	39.3	39.6	39.1	39.2	P,C
Respiratory rate (/min)	36.6	37.0	27.9	25.9	C
Metabolizable energy intake (kcal/d)	11775	11546	12890	11086	
Energy retained as protein (kcal/d)	671	759	361	520	P,C
Energy retained as fat (kcal/d)	3335	2779	4020	2200	P
Heat production (kcal/d)	7769	8007	8509	8366	
Moisture in carcass	362	476	187	331	P,C

[1]P = significant effects of pST (P<.01)
[1]C = significant effect due to cold environment (P<.01)

Conclusion

The administration of exogenous somatotropins does not have a detrimental effect on performance or thermal balance in lactating dairy cows and finishing hogs in hot or cold environments. Somatotropins increased the efficiency of production in both species; and this efficiency was maintained, although not always to as great an extent, in hot and cold environments. Energy utilization appeared to be different in animals treated with somatotropins, but this difference was not detrimental to thermal balance. In both hot and cold environments, somatotropin-treated animals maintained homeothermy, with no costly loss in performance and production.

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EFFECTS OF pST ON NUTRIENT REQUIREMENTS OF PIGS

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Summary

Growth rate and composition are modified when pST is administered to growing pigs. The accretion rate of protein and minerals is enhanced, and heat production is increased. Nutrient requirements cannot be simply predicted by the application of factorial models, as derived from nutrient requirement estimations in normal, untreated animals. Utilization of nutrients appears to be more efficient in pST-treated pigs. In addition, protein accretion seems to depend less on dietary energy supply, leading to an enhanced protein accretion rate combined with a low fat accretion rate. Since feed intake is commonly reduced by pST-administration, diet composition needs to be adapted in order to provide the required daily nutrient supply. It is concluded that the effect of pST is expressed in combination with all practical feeds or feeding strategies. If the full benefit of the pST-effect is to be obtained, dietary nutrients must meet animal requirements. Animal wastes, and thus environmental pollution by excess of animal wastes, can be reduced if the diet is carefully balanced and if supply of individual amino acids and minerals is not excessive.

Keywords: *pST, nutrient requirements, pigs.*

Introduction

When pST (either pituitary-derived or produced by recombinant-DNA technology, Evock et al., 1988) is administered to growing pigs, nutrient utilisation is influenced in various ways. Protein metabolism is enhanced, resulting in an increased net protein accretion rate. The growth of body adipose tissues, as this occurs normally, is diminished distinctly. Energy retention is decreased and heat production is enhanced. Retention of dietary minerals is increased. Voluntary feed intake is decreased, so that under ad libitum feeding conditions composition of growth is influenced rather than average daily gain, which is clearly enhanced under restricted feeding conditions. Most effects of pST-administration are clearly dose-dependent, but expression of pST-effects is also related to genotype, age and gender of the animal. Since practical application of pST will probably concentrate on finishing pigs (50 - 100 kg, possibly extended to a slaughter weight of 140 kg) the assessment of nutrient requirements during this growth period should receive most attention. The effects of pST are generally expressed on any practical feed and feeding schedule. Nutrient requirements, defined as nutrient supply corresponding to maximal production or efficiency, do not necessarily correspond to an economic optimum, when the cost of feed is considered.

Although endocrine mechanisms and target tissue effects are being progressively elucidated, these will not be covered in this paper.

Requirements of dietary protein and amino acids

The estimation of protein/amino acid requirements provides specific difficulties. Many of the published studies were not designed to estimate requirements of protein or specific amino acids. Maximum response can be truncated because other essential nutrients are limiting the growth and protein accretion. A positive control group, exceeding requirements, should be included in order to define the maximum response level in each study. Specifically this second issue imposes problems in the interpretation of data on pST-treated pigs, because the maximum response level to increasing of dietary protein supply has not been fully established, yet. Several authors have explored the dose-response relationship between dietary protein and protein accretion in pST-treated pigs. Campbell et al. (1989b, 1990) fed increasing levels of dietary protein (8.3 - 23.8%) at a fixed feeding level of 1.85 kg/animal/day to fast growing boars (30 to 60 kg). Protein deposition in terms of maximum protein accretion plateau at 173 g/d in pST-treated animals and was obtained with 383 g of dietary protein per day. Protein accretion in placebo-treated control animals was 144 g/d as a maximum, that was reached when feeding 326 g of dietary protein per day. At low dietary protein levels, the expression of pST-effect was inhibited, as was also reported by Caperna et al. (1989b), Beermann et al. (1990), Darden et al. (1990), and Smith et al. (1989).

The required dietary content of lysine (the first limiting essential amino acid in practical diets) was estimated to be 1.00 - 1.16 % by Andres & Cline (1989) (Table 1). Higher inclusion levels were compensated for by decreased voluntary feed intake by the animals tested (crossbred barrows, 55 - 82 kg). Boyd et al. (1989), using a factorial approach and adopted normal efficiency parameters, calculated a lysine requirement of 35.8 g/d in pST-treated pigs with a protein accretion of 260-280 g/d. Untreated pigs, retaining 130 g of protein per day, would need 20.5 g of lysine per day. Campbell et al. (1989d) also reported on lysine requirements in pST-treated pigs growing from 60 to 90 kg. For control animals, 20.1 g of lysine per day (0.88 % of the diet) resulted in a maximal protein accretion of 118 g protein, whereas pST-treated animals required 28.4 g of lysine (1.31 % of the diet) for a maximal daily protein accretion rate of 216 g. Goodband et al. (1990), testing dietary lysine contents of 0.6 - 1.4 % in a 17.8 % crude protein diet, observed optimalisation of daily gain at 1.19 % lysine and minimal feed conversion efficiency at 0.98 % lysine in the diet of finishing swine. Krick et al. (1990) estimated requirement of dietary lysine to be 23 to 24 g/d in pST-treated growing pigs (20 - 60 kg). Krick et al. (1990a) considered lysine requirements for pST-treated genetically fast-growing pigs (55 - 100 kg) to be marginally increased by 4.5 g/d over placebo-treated controls (requiring 31 g of lysine per day).

Table 1. Summary of dietary lysine requirements in pST-treated finishing pigs.

		estimated lysine req.		
growth phase (kg-kg)	control/ treated	% of diet	g/d	reference
55 - 82	T	1.00 - 1.16	23.3 - 31.7	Andres & Cline 1989
50 - 100	C		20.5 35.8 *	Boyd, 1989
60 - 90	C T	0.88 1.31	20.1 28.4	Campbell, 1989d
60 - 100	T	1.00 - 1.20	25 - 30	Goodband, 1990
55 - 100	C T		31.0 35.5	Krick, 1990a

* calculated with standard efficiency coefficient

Dietary lysine also affects bone mineralization and conformation in pST-treated animals (Goodband et al., 1989). When dietary lysine concentration was stepwise increased from 0.8 to 1.4 % of lysine, bone ash decreased linearly, while bone wall thickness increased.

The required balance between dietary amino acids is probably not changed essentially by pST-treatment. Caperna et al. (1990) studied collagen accretion in barrows, treated with rpST during 42 days from 30 kg live weight onwards. They found the increase in collagen deposition to be proportional to the increase in protein deposition. Modification of the composition of protein accretion might influence the pattern of amino acids required, but so far no indications were found for such a shift to occur.

Contrary to untreated animals, protein deposition in pST-treated animals hardly responds to increased energy content of the diet (Campbell et al., 1988, Verstegen & Van der Hel, 1989; Van Weerden & Verstegen, 1989; Van Weerden et al., 1989). Protein and energy requirements seem to be dissociated in pST-treated finishing pigs, if dietary protein is not rather low, as was the case in the study by Azain et al. (1989). Young pigs, treated with pST, however, seem to respond to increase of dietary energy intake by increasing protein accretion (Campbell et al., 1988, 1989b).

According to the referred studies, protein accretion was enhanced more than dietary requirements in pST-treated animals, indicating enhanced dietary protein utilization (Table 2.). The explanation for improved dietary protein utilization in pST-treated pigs can be related to digestibility of dietary protein or by modification of amino acid/protein metabolism. Various N balance studies in pST-treated animals did not reveal any changes in protein digestibility, as estimated from faecal excretion of nitrogen (Verstegen & Van der Hel, 1989; Verstegen et al., 1990; Van Weerden & Verstegen, 1989; Van Weerden et al., 1990). Gonzales & Easter (1990), however, detected inconsistent, but statistically significant changes in apparent ileal (prececal) digestibility of some amino acids in two out of four feedstuffs tested in pST-treated pigs, as compared to placebo-treated controls.

Tabel 2. Utilization of dietary lysine by finishing pigs, as deduced from an N balance study in pigs with an initial weight of 70 kg and fed diets with different protein contents (Van Weerden, unpublished results).
Abbreviations: CP = dietary crude protein content (%); T = total; ID = ileal digestible; Plac = placebo-treated, pST = pST-treated.

CP	DAILY LYSINE INTAKE (g)		DAILY LYSINE ACCRETION (g)		LYSINE ACCRETION EFFIC. (%)			
					TOTAL		ILEAL DIGEST.	
	T	ID	Plac	pST	Plac	pST	Plac	pST
16	18.4	14.7	9.5	11.8	52	64	65	80
18	20.7	16.6	10.5	13.2	49	64	61	80
20	22.5	18.0	10.8	14.3	48	64	60	80

Data on improved dietary protein/amino acid utilisation, blood urea nitrogen and urinary nitrogen excretion provide evidence that the effect of pST is mediated by dramatic improvement of efficiency of utilisation (Andres & Cline, 1989; Boyd et al., 1989; Campbell et al., 1989b; Caperna et al., 1989b; Etherton et al., 1986; Krick et al., 1990b; Verstegen & Van der Hel, 1989; Verstegen et al., 1990; Van Weerden, 1989). Protein requirements for maintenance (inevitable metabolic losses due to skin wear, hair loss, enzyme secretion, etc.) are estimated to be approximately 1 $g/kg^{0.75}$, or 10 % of an appropriate diet. There are no studies that demonstrate modification of maintenance requirements for protein by pST-treatment, but even a substantial change in maintenance requirements would be minor in comparison to other changes in protein metabolism (Figure 1.). The utilisation of dietary protein for growth is greatly modified: control animals use about 60% of the ileal digestible protein for protein accretion. From data such as those presented in Table 2 it is deduced that pST-treated animals utilise at least 75% of the ileal digestible protein for protein accretion (Figure 1.).

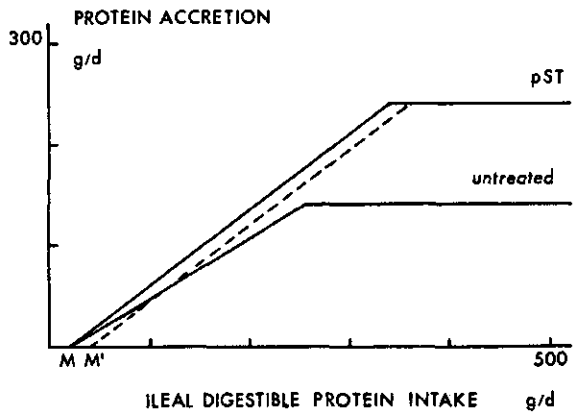

Figure 1. Modelled relationship between ileal digestible protein intake (g/d) and protein accretion rate (g/d) in pST-treated 60 kg pigs as compared to untreated animals. The slope of each curve represents efficiency of dietary protein utilization for protein accretion (0.75 and 0.60, respectively). The horizontal maximum of each curve represents the maximum protein accretion rate for each type of animal. Maintenance requirement for dietary protein (M = 1 g of protein per kg of metabolic weight) is the intersection with the horizontal axis. M' represents a putative enhanced (doubled) maintenance requirement in pST-treated animals.

Heat production and dietary energy requirements

According to Van der Hel et al. (1990), Noblet & Dubois (1990), Verstegen & Van der Hel (1989) and Verstegen et al. (1990), heat production is increased by approximately 10 % in pST-treated animals, when environmental temperatures are within the thermoneutral zone. This increased heat production is not due to changes in activity of the animals, but to modification of basal metabolic rate. The thermoneutral zone may be narrowed, when pST is administered. Knight et al. (1990) did not detect such an increase in heat production in pigs, implanted with a pST prolonged release implant, but the reduction of backfat was marginal as well. When subjected to heat stress, pST-implanted animals reduced voluntary feed intake, but maintained their improved feed conversion efficiency (Knight et al., 1989 & 1990). Stoner et al. (1989) reported feed/gain to be unchanged in heat-stressed pST-treated animals, whereas control animals had a higher feed/gain ratio at high environmental temperatures.

Dietary energy retention is reduced by pST administration, but positively correlated with dietary energy intake (Campbell et al., 1988, 1989a, 1989b, 1990). The enhanced heat production seems to have an impact on dietary energy requirements. Efficiency of energy deposition is reduced, due to increased maintenance requirement and/or altered coefficients for partial efficiency of dietary energy for protein or fat deposition, respectively (Verstegen & Van der Hel, 1989).

Control of the fat content of the animal product may be a matter of concern, because product appreciation may be negatively influenced if the pork is too lean. Intramuscular and intermuscular fat of the carcass can hardly be manipulated by energy content of the diet. It may be controlled by adapting pST-dosage (Etherton,et al. 1987; McLaren et al., 1990), by increasing slaughter weight (Kanis et al., 1990a), or the withdrawal period after pST-treatment (Campbell et al., 1989c). Adaptation of feed intake by pST-treated animals partially compensates for higher dietary energy level (Kanis et al., 1990b). When pST-treated pigs are force-fed, the excess feed intake is deposited as an increased carcass fat percentage (Newcomb et al., 1990).

Requirement for minerals and trace elements

Mineral deposition is influenced by pST-administration as a result of increasing skeletal weight rather than mineral content of the bone tissue (Bark et al., 1990; Caperna et al., 1989a; Evock et al., 1988; Goodband et al., 1989). This is reflected by increased calcium and phosphate balance (Van Weerden & Verstegen, 1988). This increase of bone mass, or increased mineral retention may be as much as 20 % (Table 3.). According to Goodband et al. (1989) pST treatment may alter biomechanical properties of some bones that become more flexible. Absorption of dietary minerals may be enhanced by pST-treatment, as is suggested by the study of Goff et al. (1988).

Table 3. Change in skeletal mass or Calcium/phosphorus retention resulting from pST administration to pigs.

LIVE WEIGHT	PARAMETER ASSESSED	pST-TREATED (% over control)	SOURCE
55 kg	weight of femur without marrow	5 - 12	Caperna 1989
115 kg	carcass bone	19	Bark 1990
90 kg	Ca balance	19	Van Weerden
	P balance	18	1989

In several studies, using rather high dosages of pST, mobility problems were encountered (Bryan et al., 1987; Evock et al., 1988; Fentener van Vlissingen et al., 1990, data not shown). McLaren et al. (1990) detected no differences in mean soundness score, but gave no frequency distribution of classes of locomotion problems. Evock et al. (1988) identified the problems as disturbed (epiphysial) growth plate development, or osteochondrosis. It seems, that these problems cannot be simply related to pST, because they were not reported in all papers presenting experiments with rather high doses of pST (exceeding 4 mg/animal/day). Housing conditions and dietary mineral supply may play a role.

Dietary mineral utilization is enhanced, due to the pST-induced increased mineral deposition. Dietary calcium and phosphorus requirements may be increased proportionally. This increase may be less than proportional, if economy of mineral utilisation is improved concomitantly. Caperna et al. (1989a) found Zn-metabolism to be unchanged in pST-treated pigs. Hepatic Fe and Cu concentrations, but not total contents, were diminished by pST-treatment. Serum Fe concentration and haematocrit were less than in placebo-treated controls. Summarizing these findings, dietary Ca, P and Fe may require special attention when formulating diets for pST-treated pigs.

Feed intake and feed composition

Voluntary feed intake is clearly diminished by pST administration and has been compensated for by various feeding strategies in different trials. This phenomenon is a serious problem in designing proper experiments to estimate dietary requirements. Daily intake of nutrients, for the assessment of utilization, can be estimated afterwards.

When feed is restricted, somatotropin has a marked influence on growth rate, whereas the effect is more marked on the composition of gain in ad libitum-fed animals (Fentener van Vlissingen et al., 1990). Voluntary feed intake by pST-treated pigs is clearly influenced by dietary protein and energy contents (Andres & Cline, 1989; Azain et al., 1989; Jewell & Knight, 1990;) and heat stress as well (Knight et al., 1990).

Because voluntary feed intake is reduced by pST-treatment the composition of the feed should be adapted to provide the daily absolute intake of essential nutrients, such as essential amino acids and minerals.

It is remarkable, that genetic improvement for growth rate and feed efficiency is reflected in both elevated basal plasma growth hormone concentrations (Arbona et al., 1988) and reduction of feed intake (Kanis, 1990). Kanis recommends to incorporate feed intake capacity in index selection. When pST-treated pigs were kept to reach a slaughter weight of 140 kg, a paradoxical effect occurred: voluntary feed intake was enhanced by pST in animals growing from 100 to 140 kg (Kanis et al., 1990a). This was accompanied by continued enhanced growth rate, feed conversion efficiency, and lean parts percentage.

The use of pST and breeding strategies

Breeds of pigs respond differentially to pST-treatment. In general, it can be stated that slow growing, rather fat breeds respond more strongly that fast growing, lean breeds (Bark et al., 1989, 1990; Kanis et al., 1990a; McLaughlin et al., 1989; Noblet & Dubois, 1990; Yen et al., 1990).

When the breeding strategies are aimed to increase lean tissue accretion to a high rate, the dissociation between energy and protein requirements, as observed in pST-treated animals, may not occur. Also, it will, most likely, not be possible to limit the expression of high growth rate to the category of slaughter pigs. Animal reproduction may become less productive concomitantly.

PST-treated animals could provide good models for the determination of nutrient requirements of future breeds and hybrids, provided that appropriate partial coefficients of nutrient utilization for protein, fat and mineral accretion can be applied. At the moment, nutrition research tends to lag behind the genetic improvement of commercial slaughter pigs. This frequently results in studies, where the positive control animals do not reach their maximal attainable growth rate. Nutrient requirements research is also very elaborate, resulting in a time lag between the experimental work and the publication of nutrients requirement recommendations. PST, as an experimental tool, may help to overcome these limitations by providing adapted models for nutrient requirements calculations.

Conclusions and definition of priorities in nutrition research in pST-treated pigs

Protein requirements for maximal growth rate and optimal dietary protein utilization are modified by pST-treatment. Protein accretion rate seems to be enhanced more than dietary protein requirements, due to improved dietary protein utilization. It is not anticipated that the dietary amino acid composition needs to be drastically adapted for pST-treated animals.

Although heat production is enhanced by pST, dietary energy supply is not limiting for growth, as is the case in untreated animals. Efficiency of utilization of dietary energy for protein and/or fat accretion may be reduced.

Mineral requirements may be increased by pST-treatment.

Voluntary feed intake is reduced by pST-treatment, and diet composition needs to be adapted accordingly, in order to provide the required absolute daily intake of nutrients.

Breeding programs will not result in future breeds and hybrids, that mimic pST-treated animals. PST-treated animals may, however, be used to anticipate nutrient requirements of modern slaughter pigs.

For optimalisation of the diet for pST-treated pigs, both protein requirements and mineral requirements must be better defined. If pST is considered a powerful tool to minimize the potential of environmental pollution by animal wastes, amino acid supply and mineral supply should be meeting, but not exceeding, animal requirements, and feed composition should be carefully balanced.

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INFLUENCE OF SOMATOTROPIN ON DISEASE RESISTANCE IN FOOD PRODUCING ANIMALS

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Summary

An important part of ensuring target animal safety is examining the influence of somatotropin on immune function and disease resistance. The consensus from several field trials and production studies has been that somatotropin treatment, at doses anticipated to be used in food-producing animals, is not associated with detrimental effects on animal health. Higher dosages used experimentally have had detrimental effects on the health of treated animals. Few studies have been specifically designed to examine the influence of somatotropin on variables of immune function in food-producing animals. Extensive studies on immune function have been conducted in laboratory rodents, and more limited studies have examined humans, dogs, dairy cattle and pigs. From these data it appears that somatotropin treatment, at doses anticipated to be used in food-producing animals, is not associated with clinically relevant detrimental effects on immune function. In fact, several lines of evidence, reviewed in this paper, indicate an immuno-enhancing effect of somatotropin. Other investigators have suggested that animals treated with somatotropin have physiological demands and health effects similar to untreated, high-producing animals. In summary, with attention to management considerations (including diet and environment) it appears that somatotropin treatment will probably not impact target animal safety in a detrimental manner.

Keywords: *disease resistance, growth hormone, immune function, immunotoxicology, somatotropin*

Introduction

Biotechnological advances in the control of growth and product quality, especially the use of somatotropin, present unprecedented potentials for enhancing meat and milk production. The effect of somatotropin on production variables, metabolism, and nutritional requirements are well documented, and have been discussed in detail by previous speakers in this session. This paper addresses the influence of somatotropin on immune function and disease resistance in food-producing animals. This topic is of interest because of concerns for animal welfare and because demonstration of target animal safety is required for approval of new animal drugs.

Summary of the literature

The literature regarding the use of somatotropin in food-producing animals dates back to the 1940's (review: Peel & Bauman, 1987). A summary of these studies is complicated by many variables including species examined, breed, gender, the formulation and purity of somatotropin used, as well as the dosage administered, duration of treatment, and other differences in experimental design (Etherton, 1989).

Few studies have been specifically designed to evaluate the influence of somatotropin on immune function and disease resistance in food-producing animals (Holden, 1990). Much data on this topic is available from studies performed *in vitro* and *in vivo* in humans, laboratory rodents, and non-food-producing domestic animals (such as dogs). In addition, there are several reports of the use of somatotropin to improve production in cattle and swine in which no adverse health effects were noted. By considering the data available from these studies, along with limited data from immunologic studies, we are able to reach some consensus on the overall effect of somatotropin on immune function and disease resistance.

Observations on the influence of somatotropin on animal health from studies designed to evaluate somatotropin influence on production

Most studies of somatotropin in food-producing animals address production and efficacy questions. Generalized health assessments are mentioned in some reports, but often the methods used for these assessments are not described. While these studies do not address specific effects on immune function, it has been suggested that the productivity of animals treated with somatotropin may be the best indication of adverse effects on animal health (McClary et al., 1990). Several reports specifically state that somatotropin treatment at dosages used to improve production is not associated with any adverse health effects (Table 1).

Data reflecting a negative impact on animal health have been reported only from studies where relatively high doses of somatotropin were administered, or where transgenic animals producing high levels of somatotropin were studied. Machlin (1972) reported liver and kidney degeneration, haemorrhage of the stomach, edema, arthritis, and increased mortality in pigs receiving 0.22 or 1.10 mg/kg/day of pituitary derived porcine somatotropin (but not those receiving 0.13 mg/kg/day). Evock et al. (1988) noted mobility problems in pigs treated with 140 ug/kg/day (but not those given 35 or 70 ug/kg/day) of pituitary derived porcine somatotropin. Transgenic pigs producing bovine (Pursel et al., 1989) or rat (Ebert et al., 1988) somatotropin at up to 50 times the normal serum concentration showed a variety of detrimental health effects including gastric ulcers, arthritis/joint pathology, cardiomegaly, dermatitis, renal disease, and testicular atrophy. Reviews of the literature on the use of bovine somatotropin (bST) in cattle note similar relationships between relatively high doses of bST (up to five times the anticipated recommended dose) and health

Table 1. Reports stating that somatotropin treatment at dosages anticipated to be used in food-producing animals is not associated with adverse health effects.

Type of growth hormone		Reference
porcine	pST*	Chung et al., 1985 Evock et al., 1988 Machlin, 1972
	rpST**	Meisinger, 1987
bovine	bST+	Fronk et al., 1983
	rbST++	Bauman et al., 1985 Eppard et al., 1987 McClary et al., 1990 Nytes et al., 1990 Oldenbroek & Garssen, 1990 Whitaker et al., 1988

* native (pituitary derived) porcine somatotropin
** recombinant porcine somatotropin
\+ native (pituitary derived) bovine somatotropin
\++ recombinant bovine somatotropin

effects such as increased incidence of mastitis, digestive disorders, and lameness (Gibbons, 1990; McClary et al., 1990).

Studies designed to evaluate somatotropin influence on immune function and disease resistance

Somatotropin has been shown to affect several variables of immune function including: increasing the size of the thymus gland and enhancing the secretion of the thymic hormone thymulin (facteur thymique serique) in aging animals and humans; enhancing the number and function of lymphoid cells (lymphocytes and natural killer cells); and enhancing the respiratory burst of macrophages and neutrophils (reviews: Kelley & Edwards, 1989; Kelley, 1989; Dau & Bane, 1990). These observations were mostly in non-food-producing animals (i.e. laboratory rodents, dogs, humans).

More recent data, from experiments performed in food-producing animals, support the hypothesis of somatotropin as an immuno-enhancer. In agreement with previous reports in other species, phagocyte respiratory burst function is enhanced after somatotropin treatment in pigs and cows. Native porcine somatotropin (pST) applied to granulocytes at supraphysiologic concentrations (100 ng/ml) *in vitro* was associated with enhanced superoxide anion production (Fu et al., 1990). Such an *in vitro* effect was not observed with bovine neutrophils (Heyneman & Burvenich, 1989). However, *in vivo* treatment with rbST was associated with enhanced superoxide production by bovine neutrophils when administered in one dose of 500 mg (Massart-Leen et al., 1990b) and by day 5 of a 10 day treatment period at 40 mg/day (Heyneman & Burvenich, 1989). Bovine somatotropin treatment of dairy cows (10.3 or 20.6 mg rbST/day for 34 weeks) was associated with an increased response to the mitogen concanavalin A, detectable 6 weeks after the initiation of treatment (Burton et al., 1990; Burton et al., 1991). The basal rate of proliferation was not affected by bST, indicating that it is not itself mitogenic in this assay (Burton et al., 1991).

Treatment with bovine somatotropin resulted in an increase in the total white blood cell count with associated increase in neutrophil and lymphocyte numbers (one dose of 500 mg: Massart-Leen et al., 1990a).

Not all reports note immuno-enhancement associated with somatotropin treatment. Treatment with bovine somatotropin (25 mg/d for 28 d) was not associated with significant changes in lymphocyte blastogenic response to phytohemagglutinin or pokeweed mitogen, interleukin-2 production, or neutrophil ingestion of *Staphylococcus aureus* (Estrada et al., 1990). Bovine somatotropin treatment of heat-stressed dairy cows (25 mg/day for 29 days, heat stress from day 10 to 24 of bST treatment) was not associated with any significant change in total blood leukocyte count or percentages of B lymphocytes or CD2, CD4, or CD8 positive cells (Elvinger et al., 1990).

Early reports speculated that somatotropin may cause increased production of glucocorticoids. This could result in suppression of immune function and predisposition to infectious disease. Bryan et al., (1989) noted enlargement of adrenal glands in pigs treated with somatotropin, and suggested that this could be associated with an increase in the production and secretion of glucocorticoids, although they did not assay those hormones. Sillence & Etherton (1989) found that even though adrenal size increased after somatotropin treatment, no increase was detected in serum cortisol or in cortisol output from adrenal tissue *in vitro*.

From the literature it is clear that somatotropin has an effect on immune function and that this effect, in general, appears to be immuno-enhancing (Kelley & Edwards, 1989; Dau & Bane, 1990). However, as Kelley concluded in his presentation at this meeting two years ago, "it is not yet known whether the kinds of cells that are affected or whether the magnitude of effects that are caused by growth-promoting compounds are sufficient to modify animal health in either a positive or negative manner" (Kelley & Edwards, 1989). It is difficult to design studies to definitively answer questions regarding the effect of somatotropin on disease resistance. Challenge studies with infectious agents are a useful model, but often are not reliable or easily replicated. In addition, different infectious agents may be controlled by different host defense mechanisms. Therefore, results obtained with one infectious agent may not apply to other infectious agents.

Bacterial challenge studies have been conducted in rats treated with pST. When challenged with an infectious dose of *Salmonella typhimurium*, rats treated with pST (500 ug/d) had enhanced survival rates over a 14 day period, as compared to controls (Edwards et al., 1989). Somatotropin (pST) treatment of alveolar macrophages *in vitro*, or those from rats treated *in vivo* with pST, had an enhanced ability to kill *Pasteurella multocida* (Edwards et al., 1990).

There are several reports of studies on somatotropin treatment of dairy cows in which the incidence and severity of clinical mastitis was monitored. Recent reviews of the literature note that most research has shown no effect of bST treatment on clinical mastitis. A few studies have shown an increase in the incidence of clinical mastitis, although only at relatively high doses or in groups where pretreatment disease incidence was higher (Eppard et al., 1989; Dau & Bane, 1990). Similarly, subclinical mastitis (as evaluated by somatic cell count in the milk) was reported by some to be unaffected, and by others to be increased or

even decreased by bST treatment. The duration of clinical infections was not affected (Eppard et al., 1989).

Treatment with 40 mg/d of bovine somatotropin for 10 days was associated with a 14 to 27% decrease in production losses in cows challenged with *E. coli* by intramammary infusion (Burvenich et al., 1989). These authors also reported that somatotropin had a beneficial effect on restoring the blood-milk barrier, which is damaged during acute coliform mastitis, with complete restoration of milk composition occurring in the infected glands of bST treated cows only (Burvenich et al., 1989).

Some liken the physiological status of the cow treated with somatotropin to that of an untreated cow that is genetically a high milk producer. Dietary adjustments must be made for such genetically superior cows, and they often are observed to have an increased incidence of clinical mastitis.

Collectively, these data indicate that somatotropin generally is immuno-enhancing and that there are no obvious health effects of somatotropin treatment in the field. Results of immunotoxicology studies should provide more information on how somatotropin affects a wide range of immune function variables. However, such studies, required by the Food and Drug Administration in the United States as part of the investigation into the effect of somatotropin on target animal safety, have yet to be published in their entirety (Gibbons, 1990).

An immunotoxicology study was performed under Good Laboratory Practice (GLP) conditions in our laboratory at Iowa State University, in collaboration with Pitman-Moore, Inc. (Goff et al., 1991). The study was designed to determine the effect of recombinant porcine somatotropin (rpST) on a variety of immune function variables including neutrophil and lymphocyte function, antibody response, haematological variables, and antibody titre to common pathogens in finishing pigs. Investigating a range of variables involved in both native and acquired immunity improved the chances of detecting any potential negative effects on immune function, which could potentially affect the incidence or severity of disease in pST-treated pigs.

The 25 gilts and 25 barrows used in this study were of mixed breed and weighed 35 to 50 kg at the beginning of the 14 day acclimation period. No prophylactic antibiotic treatment was administered during the test period. The animals were fed *ad libitum* a pig growing ration containing 16% crude protein, which met or exceeded the NRC nutritional requirements for finishing pigs.

The five experimental groups included: a) 5 mg rpST in 1 ml of vehicle (1x), b) 15 mg rpST in 3 ml of vehicle (3x), c) 25 mg rpST in 5 ml of vehicle (5x), d) 3 ml of vehicle, and e) 3 ml of 0.01 M phosphate buffered saline, pH 7.2 (PBS). The treatment period lasted for 57 days.

There was no consistent significant (P 0.05) effect of rpST treatment on the gross pathology of the pigs, histopathology of the immune system organs, total and differential white blood cell counts, lymphocyte blastogenic response to mitogens, or the neutrophil functions of chemotaxis, bacterial ingestion, reduction of cytochrome C, iodination, and antibody-dependent cell-mediated cytotoxicity. There was no observed gender by treatment

interaction, and no effect of the vehicle alone. Those variables that were significantly affected by rpST treatment included a decreased haemoglobin and packed red blood cell volume (at all three rpST dosages), a decrease in plasma protein level (at 25 mg dose), an increase in neutrophil random migration (at all three rpST dosages), and a decrease in IgG antibody response to tetanus toxoid at 15 days (but not 21 or 28 days) post-immunization (in a dose dependent manner). Additionally, rpST treatment was associated with a decreased rate of body weight gain (at 15 mg dose), increased spleen weight (at 5 mg dose), increased liver and kidney weights (at all three dosage levels), and an increased incidence of renal tubular cytoplasmic vacuolation. There were no observed differences in the overall health of the pigs due to rpST treatment, based on clinical observations as well as determination of antibody titre to, and isolation of, common swine pathogens. Therefore, there was no evidence that the observed influence of rpST treatment on immune function was clinically relevant.

Management considerations

Many factors related to diet (protein, calorie, vitamin, and mineral content, as well as level of nutrition) and environment (temperature, crowding, and other various stressors) have been shown to affect immune function (reviews: Kelley, 1985; Dantzer & Kelley, 1989; Roth & Kaeberle, 1982). Immunosuppression appears to play an important role in the pathogenesis of many of the economically important diseases associated with intensive animal production (review: Roth & Goff, 1989). Although it appears that somatotropin treatment does not have detrimental effects on animal health, pigs and cattle treated with somatotropin may have altered dietary and environmental (temperature) requirements (Elvinger et al., 1990 ; Bos, 1989; Zoa-Mboe et al., 1989). Management practices will need to be optimized in conjunction with somatotropin treatment to ensure the health and welfare of the treated animals, and to enable maximum benefit of the growth enhancer effect. Some authors feel that somatotropin use is adaptable within current management systems (Bos, 1989). Peel & Bauman (1987) note that management of cows receiving bST need not differ much from that of cows producing high quantities of milk due to genetic superiority.

Conclusion

The examination of the influence of somatotropin on immune function and disease resistance is an important part of ensuring target animal safety. Few studies have specifically examined the influence of somatotropin on variables of immune function in food-producing animals. However, the results of extensive studies in laboratory rodents, and more limited studies in humans, dogs, dairy cattle and pigs indicate that, at anticipated recommended dosages, somatotropin is not associated with clinically relevant detrimental effects on immune function. The results of several field trials and production studies concur with this conclusion. Somatotropin treated animals may have altered physiological demands and health effects, which are similar to those of untreated, high producing animals. With attention to management considerations, including diet and environment, somatotropin treatment will probably not impact target animal safety in a detrimental manner.

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SESSION IV
HUMAN SAFETY

* Residues in edible tissues
* Safety of biologically active substances
* Change in composition of edible tissues
* Repercussions for human health

SUMMARISED AND ADOPTED CONCLUSIONS FROM PAPERS AND DISCUSSION

ON

HUMAN SAFETY

Chairman:

B. Hoffmann, *Ambulatorische und Geburtshilfliche Veterinärklinik der Justus-Liebig-Universität - Germany*

Discussion moderator:

G. Hermus, *Netherlands Organization for Applied Scientific Research, TNO Tocicology and Nutrition Institute - The Netherlands*

Discussion panel:

D. Arnold, *Bundesgesundheitsamt, Institut für Veterinär Medizin - Germany*

J. Boisseau, *Laboratoire National du Medicament Veterinaire - France*

G. Guest, *Food and Drug Administration, Center for Veterinary Medicine - USA*

D. Espeseth, *USDA Animal and Plant Health Inspection Service - USA*

- *The **pharmacokinetic profile** of endogenously produced and exogenously applied growth hormone (rbST and rpST respectively) has been **clearly established**. Endogenous growth hormone is secreted in an episodic manner and concentrations in blood following treatment stay within the range marked by the episodic pulses. The few data on tissue levels of bST conform with the pharmacokinetic characteristics of this compound; they are significantly below blood levels and no differences between treated and control animals were observed. In the case of rbST and the doses recommended at present, residues could not be measured in milk.*

- ***Growth hormone** at least in part exerts its activity through insulin-like growth factor I (IGF I). **IGF I levels in blood** increase following treatment. Absolute levels, however, hardly exceed the physiological range, though the total output - as determined by the AUC - may be significantly increased. This is also reflected by the concentrations measurable in tissues and, to a lesser extent, the concentrations measurable in milk.*

- *The development of animal (veterinary)* ***drugs containing proteins*** *as the active ingredient has forced* ***regulatory agencies*** *to develop* ***new concepts*** *along their licensing procedures. As opposed to other chemical entities, the chemical nature, biological activity, and potential for harmful residues are better understood for protein products; important points to be considered are the oral activity, the stability of the product in relation to the various food-processing procedures, e.g. pasteurization, and the likelihood of absorption of the intact molecule or peptidic fragments from the intestinal tract.*

- *Though still under development, the present stage of procedural achievements allowed the* ***United States FDA*** *to develop a final opinion on the human safety aspects of rbST; in reference to the respective article in Science (Science* ***249****, 875-884, 1990) it was clearly stated that the use of rbST in cattle must be considered "safe". Based on similar evaluational procedures also the* ***CVMP of the EEC*** *concluded that the use of* ***bST*** *is* ***safe in respect to human health****. As became obvious during the discussion, the same assumptions must be made for rpST. In a wider sense the question of human safety also relates to the quality of the resulting product and likely direct or indirect effects of treatment on the environment.*

- *High levels of* ***saturated fatty acids in human diet*** *and elevated blood cholesterol levels as a consequence have been viewed as a prime nutrition related problem. However, it must be realized that consumption of fat only in part influences blood-cholesterol levels (effect 20 - 30%), obesity aggregates this effect. Furthermore, also the saturated fatty acids stearic-acid has now be shown to belong to the group of non-cholesterol enhancers. On the other hand the trans-form of oleic-acid is now considered as a cholesterol enhancer.*

  rpST-treated pigs have significantly ***reduced body stores of fat****, also intramuscular fat-content, is decreased. However* ***cholesterol*** *concentrations are* ***not changed****. In fatty tissue itself lipid concentrations are decreased.*

- *Thus the* ***nutritional value of muscular tissue from rpST-treated pigs is improved****, though the overall effect on human nutrition is certainly* ***relative*** *in view of the food array available and the number of factors influencing blood cholesterol levels in the human.*

- *However the reduction of the body stores of fat (reduced trimming!) not only improves carcass quality and pig production but also* ***decreases animal waste*** *and hence nitrogen output. Similarly beneficial effects in respect to* ***reducing the environmental burden*** *from animal production are seen following the use of rbST.*

HORMONES OF THE SOMATOTROPIN AXIS : OCCURRENCE OF RESIDUES IN EDIBLE TISSUES

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Summary

From a pharmacokinetic point of view, residue levels of growth hormone (bST, pST) and/or insulin-like growth factors (IGF-I mainly), are not significantly different in treated and untreated animals (i.e.ranging from 1 to 10 ng/ml in milk, from 2 to 10 ng/g in muscle and from 10 to 30 ng/g in liver). Though most of the data has been obtained with rbST, similar results appear with rpST. Administration of rbst does not induce any significant change in IGF concentrations in milk (about 5 to 20 ng/ml), in muscle (about 75 to 450 ng/g) or in liver (about 75 to 200 ng/g). From a pharmacodynamic point of view, rbST or rpST are devoid of any biological activity in humans. From a toxicological point of view, toxicological data leads to estimation of a large margin of safety after consumption of these residues in edible tissues, so that a zero withdrawal time can be supported.

***Keywords**: somatotropin, insulin-like growth factors, residues, human safety.*

Introduction

The use of growth hormone in animal production has caused a large concern also with respect to the occurrence of residues in edible tissues. It should be noted that recombinant bovine somatotropin (rbST) may soon be marketed to enhance milk production, and in the near future porcine somatotropin (rpST) to enhance pig production. As with any other drug, residues of these hormones can occur in edible tissues; therefore one must be assure that the product quality and the safety are not affected. Already, before its marketing, growth hormone has caused controversy among consumers. The reason being that, although hormones of the somatotropin axis are quite different from the sexual steroids or anabolics, the negative connotation of the word "hormone" may carry over to the somatotropins. From a safety point of view, scientific answers can be given about the residues of growth hormone,disproving this emotional reaction.

The residues of hormones of the somatotropin axis have to be dealt with in three different ways, according to their pharmacokinetic, pharmacodynamic and toxicological profile.

Nature of residues

As with any other compound, following treatment with growth hormone, residues are composed of the parent drug or the somatotropin, and its metabolites. In addition, growth hormone induces secretion of endogenous components or somatomedins (or insulin-like growth factors, IGF-I and IGF-2). Therefore, these latter compounds must also be dealt with as residues.

Growth hormone or somatotropin is naturally produced by the pituitary gland. This is a protein and its genetically coded amino acid sequence differs among animal species. Therefore, there is no one unique somatotropin but different types such as bovine somatotropin (bST), porcine somatotropin (pST), etc... For example, the amino acid sequence between bovine somatotropin and human somatotropin differs by approximately 35 % (Table 2) (Birmingham et al., 1988, Santome et al., 1976).

Table 1. Homology (%) of somatotropins of different species (Santome et al., 1976).

Animal species	Homology (% /bovine)
bovine	100,0
ovine	99,5
equine	90,5
porcine	90,0
rat	86,9
human	65,1

Moreover, in the same species, somatotropin appears to be a family of several proteins, the major one being a 22 kDa form consisting of 191 amino acids. Thus, pituitary bST exists as four variants comprised of 190 or 191 amino acids. Their variations lie in the amino acid terminus (phe or ala) and at position 127 in the molecule (val or leu) (Table 2) (Santome et al., 1976). pST, on the other hand, has only one natural variant.

The recombinant somatotropins (rST) are very similar to pituitary natural forms. At present, recombinant bovine somatotropins are produced by four different companies, Monsanto, American Cyanamid, Elanco and Upjohn, and the products are either exactly the same or differ from each other only by virtue of the number of amino acids added at the amino terminus of the molecule (range one to nine) (Juskevich et al., 1990). rpST produced by Pitman Moore is identical to the natural pST. On the whole, they have the same biological properties and profiles as the endogenous ones. For instance, no statistical significant differences concerning distribution half-lives, terminal distribution half-lives, total body clearances or volumes of distribution has been established between the recombinant bovine somatotropin rMet-bST and a recombinant naturally occurring variant, rAla-Val-bST (Birmingham et al., 1988).

Table 2. Differences in the sequence of amino-acids of the natural variants of bST (Santome et al., 1976).

1	2	3	127	191
ALA	PHE	PRO	.....LEU	..... PHE
ALA	PHE	PRO	.....VAL	..... PHE
	PHE	PRO	.....LEU	..... PHE
	PHE	PRO	.....VAL	..... PHE

Pharmacokinetic profile

Pharmacokinetic profile in non-treated animals

Somatotropins, or growth hormones (GH) are natural substances and their endogenous secretion induces plasma and tissue concentrations even in non-treated animals.

Somatotropin concentrations in plasma

The secretion of GH is episodic. This has been clearly shown in blood plasma of cattle, either in a 9 week old calf or in a 10 month old Fleckvieh bull (Figure 1) (Schams et al., 1989). Endogenous bST blood levels widely vary between 0 and 100 ng/ml plasma. The average value is approximately 0.4 ng/ml.

Schams et al. (1989) also measured blood somatotropin levels in growing Brown Swiss cattle up until 6 months of age with more frequent samplings during brief periods (once every 15 minutes during a 6 hour period). Such a protocol displayed the amplitude and the frequency of episodic secretions (Table 3) (Schams et al., 1989).

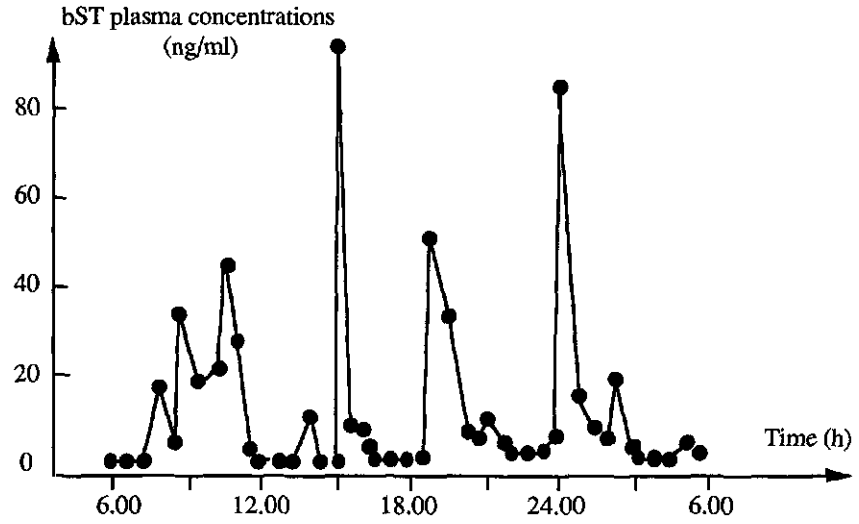

Figure 1. Episodic secretion of bST in a 10 month old Fleckvieh bull (Schams et al., 1989).

Table 3. bST levels in plasma of growing Brown Swiss cattle (Schams et al., 1989).

Age	overall mean		basal concentrations		amplitude		frequency of episodes	
(mnth)	male	female	male	female	male	female	male	female
1	14.7	11.6	10.6	8.8	20.5	15.0	9.1	8.7
2	4.4	4.1	3.7	2.9	7.6	5.8	10.0	10.0
3	7.8	5.0	5.2	3.7	11.1	4.6	10.3	9.0
4	11.2	3.9	6.8	3.1	16.7	5.7	9.4	8.7
5	22.4	3.3	12.2	2.8	35.1	3.9	8.3	6.7
6	22.8	8.7	15.8	5.2	37.5	10.7	5.2	14.5
7	15.2	19.0	7.0	6.2	29.3	48.3	8.6	6.3
8	19.9	11.1	7.3	6.4	34.5	16.6	9.3	6.5
9	26.4	8.7	8.3	4.8	48.9	12.0	8.3	7.0
10	20.5	6.9	8.3	4.4	33.4	8.4	7.2	5.3
11	17.8	7.1	7.0	4.6	29.1	9.7	7.8	7.0
12	15.1	6.3	7.5	4.9	23.5	5.3	6.5	6.0
13	12.6	7.1	5.1	5.5	17.8	7.3	8.3	4.5
14		6.2		5.7		4.3		2.0

Milk residues

Endogenous bST is hardly detectable in bovine milk and most authors could not measure bST in milk. In general, levels were found to be below 0.3 or 0.5 ng/ml, depending on the method used. In a recent paper, levels between 0.5 and 1.5 ng/ml milk were reported (Figure 2) (Ketelslegers et al., 1990, Schams, 1990) ; also, these concentrations are very close to the limit of detection of the analytical method.

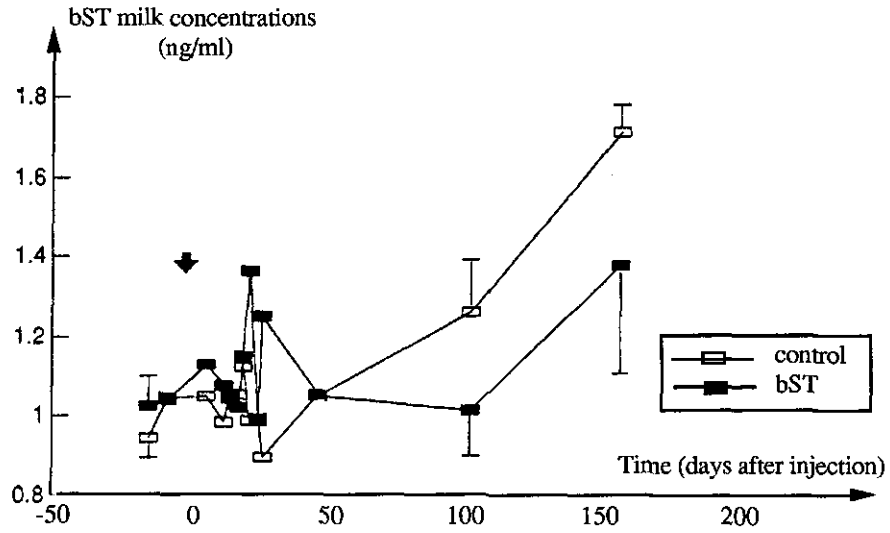

Figure 2. bST concentrations in milk of rbST-treated and non-treated cows (Ketelslegers et al., 1990).

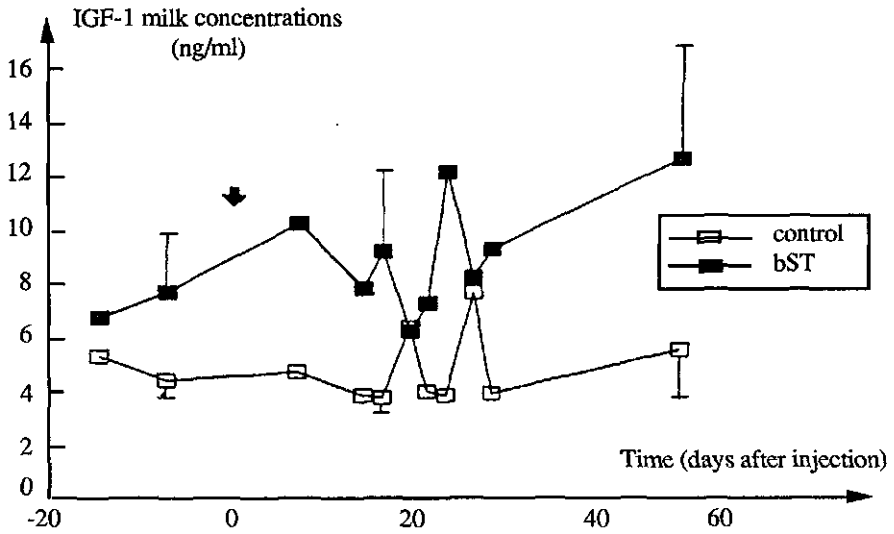

Figure 3. IGF-I concentrations in milk of rbST-treated and non-treated cows (Ketelslegers et al., 1990).

IGF-I is also secreted into milk of non-treated cows and were shown to vary between 0 and 30 ng/ml, depending on the age and stage of lactation of the cow (Figure 3) (Ketelslegers et al., 1990, Schams, 1990, Torkelson et al., 1988). During the second half of lactation, the IGF-I concentrations (mean s.e.m.) in milk from control cows were 24.2 2.8 ng/ml (n=17) (17). On the other hand, higher IGF-I levels have been found in bovine colostrum, up to 150 ng/g (Malven, 1977, Ronge et al., 1988).

Pharmacokinetic profile in treated animals

In treated animals, most of the pharmacokinetic studies have been performed in cattle with one recombinant rbST variant (sometribove), a prolonged release formulation intended for marketing. Pharmacokinetic studies with rpST are limited, as the final pharmaceutical formulation does not seem to be established as yet.

Somatotropin concentrations in plasma

After subcutaneous (sc) application of 500 mg sometribove every 14 days, which is approximately equivalent to a daily exposure of 36 mg/cow/day, plasma concentrations within an animal increased by average from 2 to 10 (Figure 4) (personal communication, 1989) ; they return to basal values 11 or 12 days after injection. During such a treatment cycle, plasma concentrations were from 5 to 20 times higher than in control animals, depending on the time of measurement (personal communication, 1989).

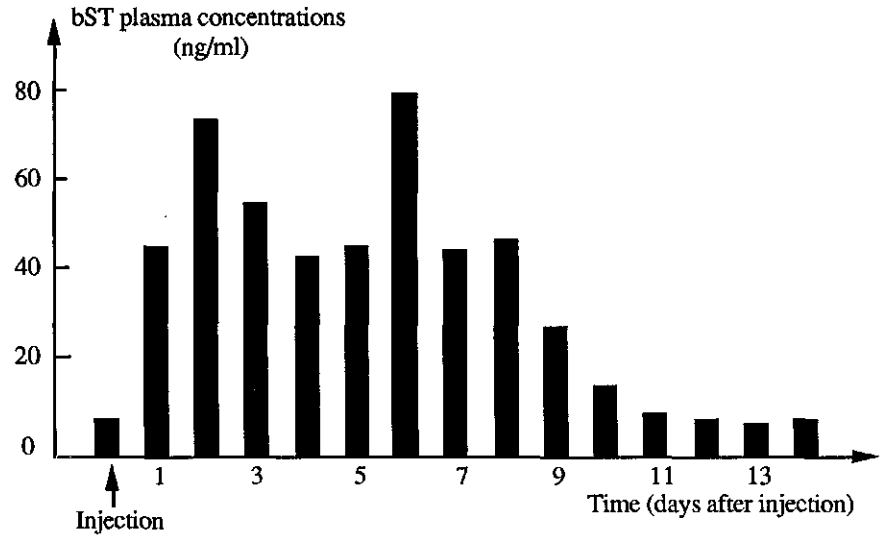

Figure 4. Immunoreactive bST (bGH) in the plasma of 6 Simmental (DFV) and 6 German Black and White (DSB) cows following s.c. administration of 500 mg sometribove (personal communication, 1989).

Another study revealed a 4 to 6 fold increase in bST blood concentrations (Ketelslegers et al., 1990). However, on the whole, these plasma concentration variations, though elevated, stay within the physiological range (Figure 1).

In pigs, 1 hour after intramuscular injection of rpST (14 mg as an aqueous solution twice a week), starting at 60 kg live weight until four and a half days before slaughter, a dramatic increase of pST concentrations in blood was seen beyond 300 ng/g. However, these high levels decreased to basal values 26-27 hours later (Table 4) (Schams et al., 1989).

With respect to IGF-I, in pigs, the values were approximately 2-fold higher than the basal values 1 hour after injection and back to basal values 26-27 hours later (Table 4) (Schams et al., 1989).

Table 4. Blood concentrations of pST and IGF-I (ng/g) in non-treated pigs and rpST-treated pigs within 1 h and 26-27 h after the last injection (mean ± s.d.) (Schams et al., 1989).

			Blood concentrations (ng/ml) 1h post treatment		26-27 h post-treatment	
		n	pST	IGF-I	pST	IGF-I
F1	control	6	2.0 ± 1.6	437 ± 110	2.1 ± 0.5	231 ± 37
	rpST	5	240 ± 113	749 ± 346	3.1 ± 3.2	793 ± 89
Duroc	control	6	2.0 ± 1.7	391 ± 73	2.9 ± 0.5	398 ± 58
	rpST	6	321 ± 84	531 ± 172	14.9 ± 32 1.7 ± 0.3 (n=5)	1310 ± 217
Pietrain	control	6	2.0 ± 0.6	193 ± 81	2.7 ± 0.9	183 ± 45
	rpST	6	266 ± 46	373 ± 158	2.1 ± 0.5	720 ± 296

14 mg i.m. twice a week from 60 kg (b.w.) up until 120 kg (18 injections) blood collection 1 h or 26-27 h after last injection-assay sensitivity=0.25 ng/ml

Another study revealed a 4 to 6 fold increase in bST blood concentrations (Ketelslegers et al., 1990). However, on the whole, these plasma concentration variations, though elevated, stay within the physiological range (Figure 1).

Table 5 .Blood concentrations of pST and IGF-I (ng/g) in non-treated pigs and rpST-treated pigs 4.5 days after the last injection (mean ± s.d.) (Schams et al., 1989).

	Blood concentrations (ng/ml)				
	Control		Treatment		
	n	pST	IGF-I	n	pST	IGF-I
F_1	14	1.8 ± 0.7	299 ± 130	16	1.F ± 50.8	369 ± 149
Duroc	17	3.7 ± 3.1	417 ± 136	15	1.6 ± 0.8	432 ± 217
Pietrain	16	2.3 ± 0.9	264 ± 138	16	1.6 ± 0.5	276 ± 127

14 mg i.m. twice a week from 60 kg (b.w.) up until to 100-140 kg. Blood collection 1 h or 26-27 h after last injection-assay sensitivity=0.25 ng/ml

Milk residues

Exogenous administration of rbST to dairy cows (500 mg sometribove every 14 days) have not been reported to increase the endogenous levels of bST in milk (Hart et al., 1985, Mohammed et al., 1985, Schams, 1988, Torkelson, 1988).

Ketelslegers et al. (1990) observed no significant increase of bST over the control values after application of 500 mg sometribove to dairy cows every 14 days (Figure 2). At the same time, these bST levels in milk were 3 to 5 times lower than basal plasma concentrations.

rbST application in similar conditions during 10 cycles did not induce any significant increase in milk IGF-I levels (Figure 3) (Ketelslegers et al., 1990) and no increase in milk IGF-II levels. Schams (1990) did not find any significant difference in IGF-I levels in milk between control and treated animals (about 5 to 20 nanograms per millilitre), even after the 15th s.c. injection of 500 mg bST (sometribove) every 14 days (Figure 5). Once again, these slight increases, if ever shown, lay within the range of the physiological variations observed during lactation.

This data clearly indicates that treatment of cows with a slow release formulation (sometribove) does not increase the physiological bST or IGF-I concentrations in milk.

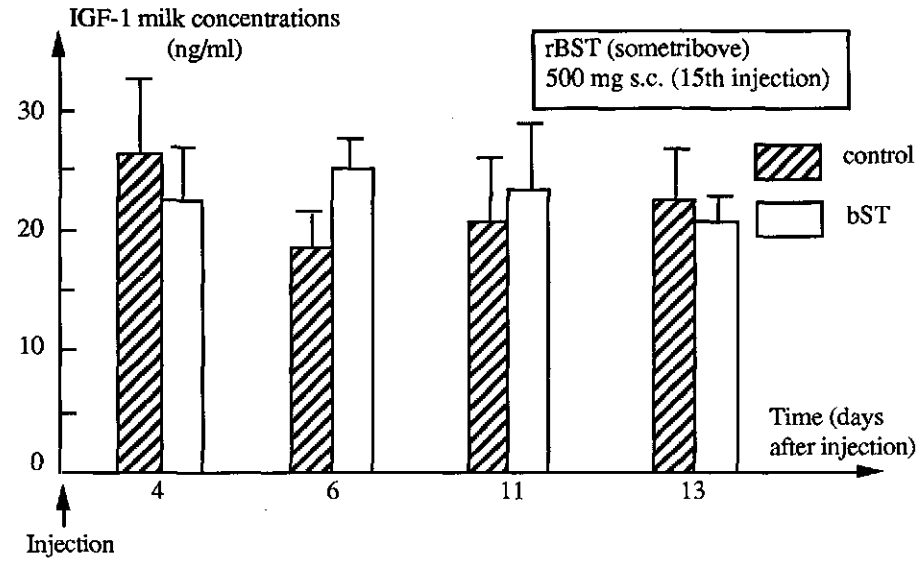

Figure 5. Concentrations (mean ± s.d.) of IGF-I in milk of controls (n=6) and bST treated cows (n=6) on days 4, 6, 11 and 13 after the 15th injection (Schams, 1990).

Muscle and liver residues

In dairy cows, rbST administration (500 mg s.c. every 14 days during 3 injection cycles) did not significantly increase bST levels in muscles compared with control values. The highest bST levels indicated a 2-fold increase in muscle and liver when the blood concentrations are the greatest in the mid point of the injection cycle (Figure 6) (Hammond et al., 1990). The muscle concentrations range from 2 to 6 ng/g, those in liver from 10 to 30 ng/g (Figure 7) (Hammond et al., 1990).

No significant differences in IGF-I concentrations in muscle (from 75 to 450 ng/g) (Figure 6) or liver (from 75 to 200 ng/g) (Figure 7) could be detected after application of 500 mg sometribove to dairy cows every 14 days during 3 injection cycles (Hammond et al., 1990). This data clearly indicates that IGF-I milk concentrations are much lower than those in other edible tissues.

Though most of the data has been obtained for bST, results are similar for pST. In pigs, after intramuscular injection of rpST (14 mg as an aqueous solution twice a week) starting at 60 kg live weight until four and a half days before slaughter, pST concentrations in muscle were quite similar to control values 26-27 hours after the last injection or 4.5 days as well, that is to say below 5 ng/g wet tissue (Schams, et al., 1989).

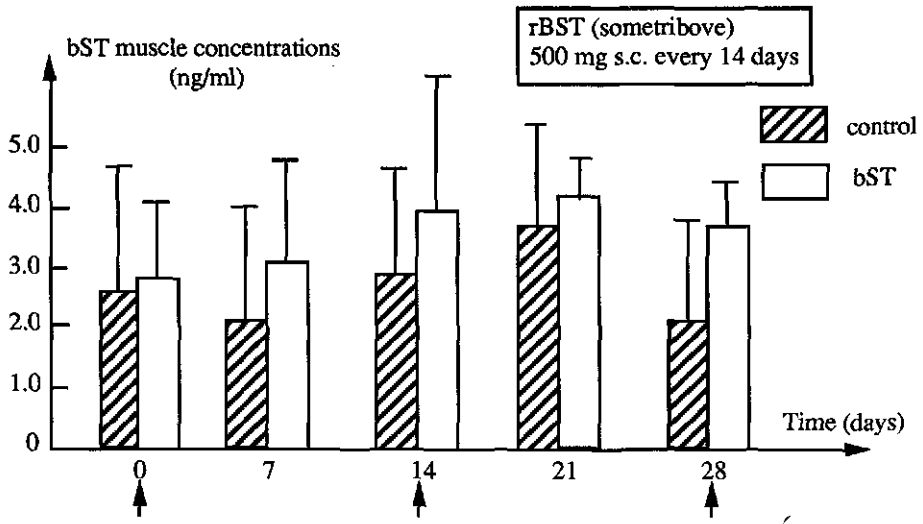

Figure 6. bST concentrations (mean ± s.d.) in muscle of control cows (n=5) and cows administered sometribove for three injection cycles (n=5), on days 0, 14 and 28 (Hammond et al., 1990).

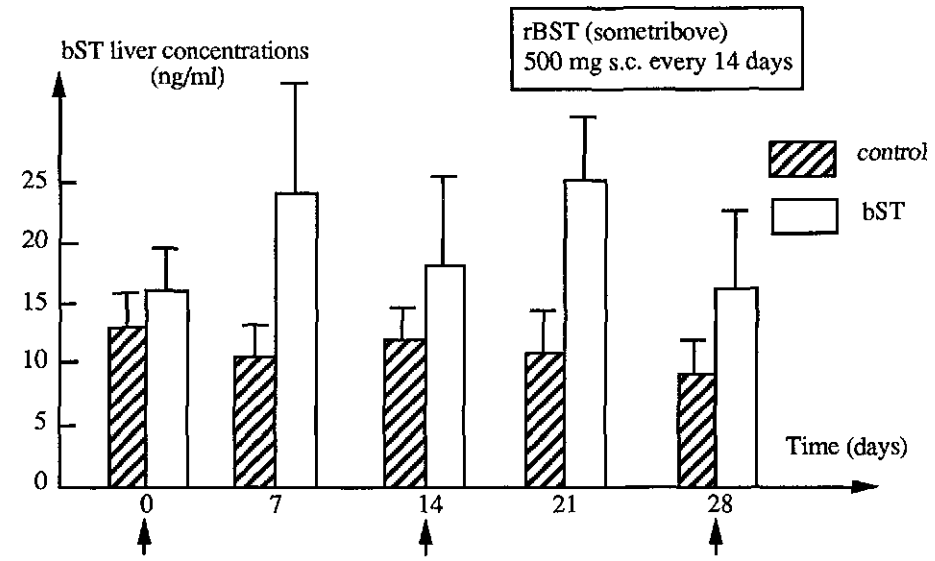

Figure 7. bST concentrations (mean ± s.d.) in liver of control cows (n=5) and cows administered sometribove for three injection cycles (n=5), on days 0, 14 and 28 (Hammond et al., 1990).

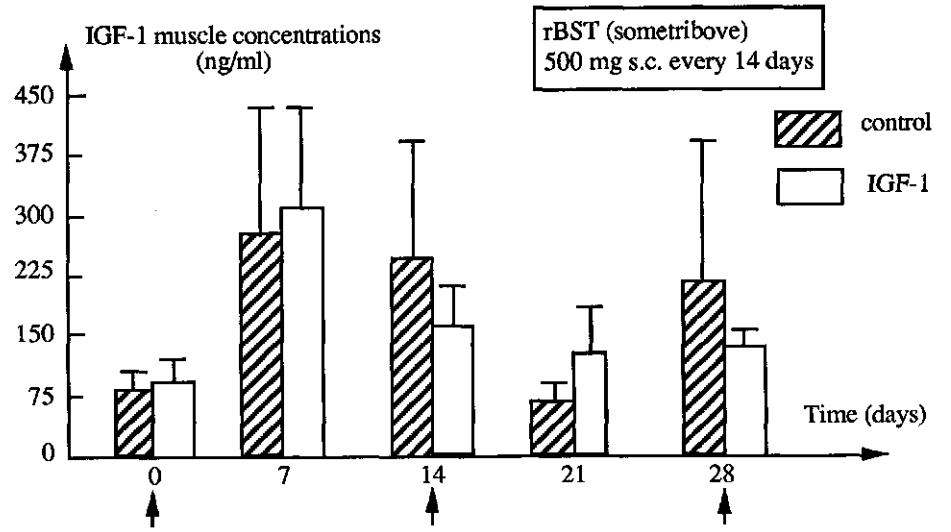

Figure 8. IGF-I concentrations (mean ± s.d.) in muscle of control cows (n=5) and cows administered sometribove for three injection cycles (n=5), on days 0, 14 and 28 (Hammond et al., 1990).

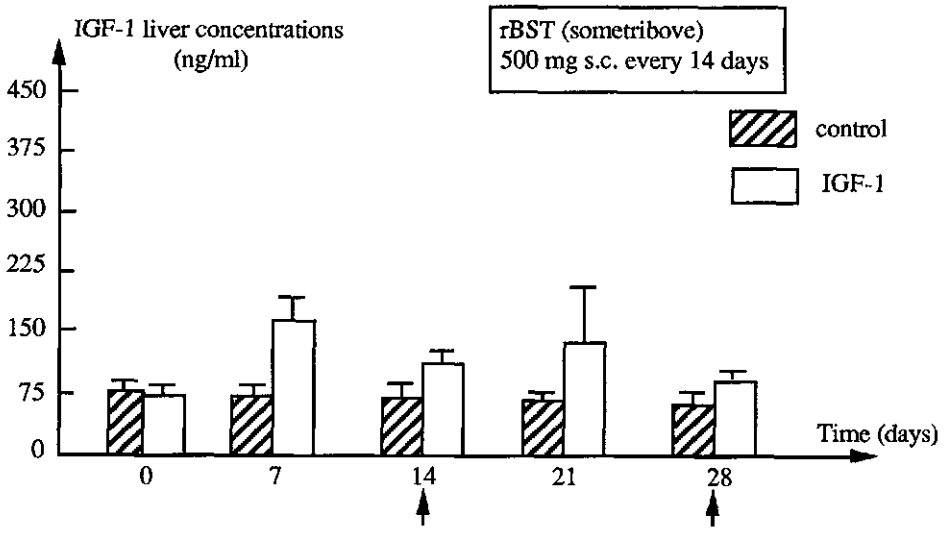

Figure 9. IGF-I concentrations (mean ± s.d.) in liver of control cows (n=5) and cows administered sometribove for three injection cycles (n=5), on days 0, 14 and 28 (Hammond et al., 1990).

Thus, in summary, it can be concluded that bST or IGF-I residues in muscle or liver are not different in non-treated cows from cows administered 500 mg s.c. sometribove. Similar results have been reported in pigs after pST treatment. In fact, these residue concentrations vary according to pharmaceutical formulation (solution, prolonged release formulation), dose and route of injection. Although the bST concentrations immediately after treatment are usually higher than those obtained in control animals, they generally remain inside the large physiological range.

Pharmacodynamic profile

There are several reasons why bST and pST are inactive in humans. From a pharmacodynamic point of view, somatotropins are rather species-specific, bovine (bST) or porcine (pST) somatotropins have no pharmacological or toxicological activity in humans. It has been shown that bST and pST have no affinity for human somatotropin receptors. This explains why the parenteral administration of bovine somatotropin extracted from cattle pituitaries totally failed in the dwarfism treatment in man in the fifties.

Insulin-like growth factors, however, are not specific to animal species : human and bovine IGF-I are identical (Honegger et al., 1986) and, hence, they exert the same pharmacodynamic profile (Daughaday et al., 1990).

Toxicological profile

Whether bound or not to receptors, the somatotropins and IGF-I, as any dietary proteins, are strongly broken down into peptidic fragments in the digestive tract by the combined action of gastric acids and enzymes. These fragments are almost completely devoid of any biological activity. Only limited tryptic digestion retained some activity of the unbroken bST and peptidic fragments have been shown getting 10 % of the bST activity (Hara et al., 1978). Similarly IGF-I is not biologically active following ingestion (Hammond et al., 1990). This explains why oral use of insulin in diabetes mellitus is not possible and why insulin has to be injected. However, in human neonates, the digestive enzymatic activity is limited, ranging from 10 to 100 % of adult enzymatic capacities and intact proteins may be absorbed to a small extent, 1 : 10,000 to 1 : 50,000 (Levinsky, 1985). In fact, both bST and IGF-I have molecular weights of approximately 22,000 and 7,800 daltons respectively. The large size of these molecules prevents any significant oral activity.

Several toxicological studies have been carried out to ascertain this lack of oral activity either with somatotropin or with IGF-I. rbST has been administered to normal or hypophysectomized rats by gavage or subcutaneous injection at up to 100 times or more of the daily dose proposed in dairy cattle, and as long as 90 days. In any case, these toxicological studies on laboratory animals have proven that rbST administered orally up to 50,000 µg/kg/day produced no growth response or deleterious effect (Juskevich, 1990).

Similar tests have been performed with IGF-I on laboratory animals, either orally or by subcutaneous injection. After s.c. application, IGF-I has been shown to enhance growth but there is no evidence of any biological or toxicological effect after oral administration of IGF-I. In addition there is clear evidence that heat treatment by cooking denatures most of the IGF-I residues in meat (Miller et al., 1989).

Estimation of safety factors

As shown above, residues of bST or pST and IGF-I do not present any risk for the consumer ; thus the calculation of a safety factor, as with any other drug, might be considered

obsolete. Nevertheless, such safety factors have been estimated for consumption of bST and IGF-I residues in edible tissues from treated cows after application of sometribove in normal conditions. With respect to pST, safety factors will be appropriate only when the final commercial formulation is available

Safety factors in milk

Assuming that a 10 kg child drinks one litre of milk containing 10 ng/ml a day, he would be exposed to 1 µg/kg/day, in other words 50,000 times less than the no-effect level. The safety factor is therefore 50,000 (Hammond et al., 1989).

The same calculation applied to IGF-I gives a safety factor in the range of 200 to 2,000 (Hammond et al., 1989).

Safety factors in meat

Assuming that every day a 60 kg adult person eats 500 g of uncooked meat containing 3.1 ng/g sometribove, they would be exposed to 0.025 µg/kg/day sometribove. If compared to the no hormonal effect level of 50,000 µg/kg/day, this daily exposure results in a safety margin of 2 000 000 (Hammond et al., 1989).

The same calculation applied to IGF-I with uncooked meat assumed to contain 3 ng/g results in a daily exposure of 1.3 µg/kg/day. Taking into account 200 or 2,000 µg/kg/day doses as a no effect level, the safety factor ranges from 150 to 1,500 (Hammond et al., 1989).

Finally, all the data supports the authorization of a zero withdrawal time for human consumption of milk or meat from bST (sometribove)-treated cows.

Conclusion

There is clear evidence that residue levels of the hormones of the somatotropin axis in edible tissues, somatotropins and insulin-like growth factors (IGF-I mainly), are not significantly different in somatotropin treated animals from the untreated animals (i.e. approximately 1 to 10 ng/ml in milk - from 2 to 10 ng/g in muscle - and from 10 to 30 ng/g in liver). Though most of the data has been obtained for bST, similar results appear for pST.

Furthermore, administration of bST does not induce any significant change in IGF concentrations in milk (about 5 to 20 ng/ml), in muscle (about 75 to 450 ng/g) or in liver (about 75 to 200 ng/g).

Moreover, somatotropins are largely species-specific. Somatotropins and IGF-I are broken down to a large extent in the digestive tract into inactive peptidic fragments. Finally, toxicological tests suggest a large margin of safety after consumption of their residues in edible tissues, so that a zero withdrawal time can be supported.

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SAFETY ASPECTS OF BIOLOGICALLY ACTIVE SUBSTANCES

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Summary

With the advent of recombinant DNA techniques, the investigation of protein products for a variety of uses in food animals has increased dramatically. As opposed to new chemical entities that are generally developed for use in food animals, the chemical nature, biological activity, and potential for harmful residues are better understood for protein products. Because of these considerations, the U.S. Food and Drug Administration (FDA) decided that the testing requirements generally applied to determine the human food safety of compounds used in food-producing animals were not appropriate for protein products. Therefore, new procedures were proposed for both toxicological and residue chemistry testing. This paper presents the basis for FDA's decision regarding the alternative testing requirements, reviews the studies required under the proposed procedures, and describes how these testing requirements were applied in determining the human food safety of recombinant bovine somatotropin for use in lactating dairy cattle.

Keywords: *human food safety, protein products, somatotropin*

Introduction

The introduction of recombinant DNA techniques provided a means for producing protein hormones in quantities not easily obtained by extracting the proteins from animal tissues. The animal drug industry has therefore been able to investigate the potential use of protein hormones in animal production. The increase in the number of protein products considered for use in food-producing animals prompted the FDA to review the testing requirements established for determining the human food safety of these animal drugs because it was apparent that the chemical nature, biological activity, and potential for harmful residues are better understood for protein products, as compared to non-protein drugs.

The scientific literature generally provides a good background for understanding the biological effects of these products, because many of the protein hormones have been studied extensively in both animal models and humans. Due to information available concerning the digestion of proteins in the human gastrointestinal tract and because the consumer will be exposed to residues of these proteins by the oral route, there is reduced concern for potential harmful residues of protein products.

With the information available in the scientific literature taken into consideration, the FDA decided that alternatives to the testing requirements outlined in their "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals"

(FDA, 1987), were more appropriate for determining the human food safety of protein products. A new set of guidelines for protein products is under development and basic testing requirements, including both toxicology and residue chemistry studies, have been proposed. This paper will examine the information available in the scientific literature that was used as a basis for establishing the proposed testing requirements, outline the proposed procedures, and describe how the testing requirements were used to determine the implications of recombinant bovine somatotropin (rbST) use on the safety of food products intended for human consumption.

New Animal Drug Regulation

The FDA has the responsibility of enforcing the Federal Food, Drug, and Cosmetic Act, and the enforcement authority for animal drugs is delegated to its Center for Veterinary Medicine. Before a new animal drug can be approved for use in food-producing animals, several requirements must be met as outlined in the Code of Federal Regulations (1989). One of the requirements is that the pharmaceutical company demonstrate that food products from treated animals are safe for human consumption. The FDA established guidelines (FDA, 1987), for toxicological testing and residue chemistry studies, that would ensure the edible tissues from treated animals are safe for consumers. The testing requirements provided in these guidelines are discussed briefly below.

Toxicology Studies

The toxicology studies that are generally required include a battery of toxicity tests to demonstrate whether the compound produces bacterial gene mutations, mammalian cell gene mutations, or induces DNA repair; two 90-day feeding studies, one in a rodent species and one in a non-rodent species; and a 2-generation reproduction study with a teratology component. These studies are considered the basic toxicology studies required for any compound submitted for approval for use in food-producing animals. The results of these studies, along with knowledge of the particular activity of a compound, dictate whether additional toxicity testing is required.

Additional studies that may be required include: chronic bioassays for carcinogenicity in each of two rodent species if the compound has tested positive in any of the genotoxicity assays or if the results of the subchronic studies raise the suspicion of carcinogenicity; one-year feeding studies in a rodent and non-rodent species when the exposure of people to residues of a compound exceeds 25 μ Dg/kg b.w./day or when there is evidence to indicate that the residues bioaccumulate in the tissues of target animals; and a teratology study in a second species when the compound is structurally related to a known teratogen, when the compound has hormonal activity that may affect the fetus, or when the results of the reproduction/teratology study indicate that the compound may be a teratogen.

Other specialized testing is required when necessary to adequately define the biological effect of the compound. Examples of specialized testing include testing for neurotoxicity, immunotoxicity, hormonal activity, or toxicity following *in utero* exposure.

When data has been obtained from all of the required toxicity tests, a safe concentration for residues in the edible tissues is determined for non-carcinogenic compounds, using the appropriate toxicity study. For carcinogenic compounds, the concentration of residue giving no significant risk of cancer is calculated from the tumour data using a statistical extrapolation procedure (Gaylor & Kodell, 1980; Farmer et al., 1982), using a permitted lifetime risk to the test animal of 1 in 1 million.

Residue Chemistry Studies

In addition to the toxicity studies, the determination of human food safety of a particular product requires information regarding the residue of the compound in edible tissues. The first study generally required is a total residue study, which provides information on the concentration of total residue (parent compound plus metabolites) found in various edible tissues.

In addition to the total residue study, metabolism studies must be conducted in the target species. A metabolic profile is established and structural identification may be required for major metabolites. FDA may also require a determination of the persistence of metabolites in edible tissues and a determination of the amount of residue that is covalently bound. Metabolism studies are also required in one species of laboratory animals that was used for toxicological testing. This ensures that at least one of the toxicity test species was exposed to all of the metabolites found in the target species.

If the total residues at zero withdrawal are above the safe concentration, then additional studies will be required to determine a withdrawal period that ensures that residues will be below the safe level when animals go to slaughter. The withdrawal period, or milk discard time, is established from a residue depletion study in the proposed target population under market conditions of use.

Regulation of Protein Products

Because human exposure to the residues of protein products is by the oral route, the general toxicological concerns are rather limited. However, several points must be taken into consideration: 1) whether the protein has the potential to be active orally; 2) the potential for absorption of the intact protein; 3) the possibility that there may be active fragments of the protein that may be formed in the gastrointestinal tract and more easily absorbed as compared to the parent protein; 4) whether the protein being administered to the food-producing animal is an endogenous protein or an analogue of the endogenous protein, and 5) potential local effects of the protein on the gastrointestinal tract.

Protein Digestion and Absorption

There is an extensive amount of information in the scientific literature regarding the digestion of protein in the human gastrointestinal tract (Gray & Cooper, 1971; Horrobin,

1968; Matthews, 1975; McNeish, 1984; Nixon & Mawer, 1970), both in adults and neonates, which addresses the issues of potential oral activity of proteins and the extent of absorption of intact proteins.

The digestion of protein is generally rapid and protein digestion products usually enter the blood almost entirely as free amino acids. There is general agreement that neonates, and even preterm infants, have the complement of enzymes necessary to digest protein efficiently, although reduced activities of some of the digestive enzymes compared to adults limit the capacity for protein digestion (Lebenthal et al., 1983; Lebenthal & Leung, 1987; McNeish, 1984).

The time of closure of gut permeability to proteins (gut closure) in the newborn has not been definitively determined. The results of some studies indicate that gut closure may occur before birth (Roberton et al., 1982), but other studies indicate that it may take place as long as 3 months after birth (Eastham et al., 1978; Reinhardt, 1984). The gut of the newly born infant is impermeable to a large variety of antibodies administered in colostrum or milk (Leissring et al., 1962), however, absorption of foreign proteins must take place to a limited extent as evidenced by the appearance of specific antibodies against proteins (Eastham et al., 1978). Studies performed in other species cannot easily be extrapolated to humans, since the time of gut closure appears to be quite variable among species (Lecce, 1979; Morris, 1968; Warshaw et al., 1974).

The conflicting results of studies done with human neonates to determine the extent of intact protein absorption points out the complexity of the system being studied. A variety of factors may be involved including the type protein, gestational age of the neonate, and perhaps feeding regimen. Studies indicate that the fullterm neonate absorbs similar amounts to non-atopic adults given equivalent antigen loads according to body weight, however, preterm neonates may absorb more antigenically intact protein as compared to fullterm neonates (Levinsky, 1985).

Based on the information available in the scientific literature, one would expect that most protein and polypeptide drugs would have minimal, if any, activity when administered orally because of digestion in the gastrointestinal tract. However, it would be inappropriate to assume that a compound does not have oral activity simply because it is a protein.

For example, some of the releasing factors appear to be orally active in animals and/or humans. This is due, in general, both to their low molecular weight and their high specific activity. Synthetic thyrotropin releasing factor, a tripeptide has limited oral activity in humans (Kaupilla & Ylikorkala, 1982). It has also been shown that synthetic gonadotropin releasing hormone (GnRH), a decapeptide, and its analogues can cause a significant increase in luteinizing hormone when administered by the oral route (Amoss et al., 1972; de la Cruz et al., 1975; Gonzalez-Barcena et al., 1975; Humphrey et al., 1973; Nishi et al., 1975; Yamazaki et al., 1977). Because GnRH is susceptible to proteolytic enzyme degradation, the oral activity is most likely accounted for by its high specific activity (active parenterally in picogram doses) and its relatively rapid diffusion across the gastric mucosa.

However, without a low molecular weight, high specific activity, and/or absorption directly from the stomach, it is highly unlikely that a protein hormone could be absorbed intact in high enough concentrations to produce any biological effects.

Other Considerations

The potential production of biologically active fragments of a protein and subsequent absorption of the fragment needs to be taken into consideration in designing human food safety studies for protein products. In some cases, information may be available in the scientific literature regarding whether these fragments are likely to be produced in the gastrointestinal tract. For example, although fragments of bovine somatotropin (bST) can be produced ***in vitro*** that are active when administered parenterally to test animals (Sonenberg et al., 1972; Yamasaki et al., 1970) and possibly to humans (Nadler et al., 1967; Sonenberg et al, 1965 & 1972), there is a progressive loss of growth-promoting activity in the rat with the increase in the number of peptide bonds hydrolysed and a substantial reduction in activity when the number of bonds split is greater than three (Sonenberg et al., 1968). The mild hydrolysis conditions necessary to obtain active fragments of bST will not be present in the human gastrointestinal tract. Coupled with the large doses necessary to obtain parenteral activity in humans, it appears extremely unlikely that the production of active fragments of bST will be of any human food safety concern.

Analogues of proteins can be synthesized that have a greater potency or longer duration of action than the endogenous protein (for examples see, Brewster & Rance, 1980; de la Cruz et al., 1980; Pless et al., 1986; Velicelebi et al., 1986). Therefore, the chemistry of any protein analogue must be considered in light of the fact that changes in amino acid sequence may increase the oral potency of the protein by conferring an increased resistance to hydrolysis in the gastrointestinal tract. This would appear to be of greatest concern for polypeptide hormones rather than large proteins.

Finally, while most proteins may not be absorbed intact in concentrations necessary to produce biological effects, the potential local effects on the gastrointestinal tract may need to be taken into consideration. This would be done on a case-by-case basis, depending on the biological activity of the protein and the amount of protein that would be consumed.

Proposed Testing Requirements for Protein Products

The first obvious data to require is a determination of the potential for oral activity of the protein drug in test animals, which would address oral activity ***per se***, absorption of intact protein, and absorption of biologically active fragments. In addition, safety of residue in milk needs to be addressed because of the use of cow's milk in infant formulas, as well as the safety of residues at the injection site for products using a sustained-release formulation, which may increase the exposure of consumers to residues of the product originating from the injection site.

It was decided that residue chemistry studies would not generally be required for protein products, unless certain conditions were in effect. First, if the product was for use in lactating dairy animals residue chemistry studies would be required because of the possibility that neonates might absorb more intact protein than adults. Second, if the protein is found to be orally active in test animals then a safe concentration may be required for the product and residues studies would need to be conducted to determine an appropriate withdrawal time.

Lastly, if no biological endpoint can be determined for toxicity testing, it may be necessary to conduct residue studies to determine the potential exposure of humans to the protein.

Proposed Toxicity Tests

An initial study is conducted to determine the potential for oral activity of the protein. The FDA decided that a 2-week oral feeding study would be adequate for this purpose, as studies conducted with proteins demonstrate that their biological effects can be observed in less than 2 weeks.

The design of the study consists of groups of rats treated with 1X, 10X, and 100X the dosage administered to the target species on a mg/kg basis. Two other groups are also included, a vehicle control group and a positive control group (i.e. a group of rats treated with the protein parenterally). A specific biological endpoint is monitored depending on the biological activity of the protein. For example, for rbST growth indices were determined including body weight, weight gain, tibia length, and tibial epiphyseal width. In addition to the specific biological endpoint, standard toxicological profiles are measured including clinical signs, body weight and food consumption, haematology and clinical chemistry parameters, organ weights, and microscopic examination of organs if necessary. The FDA also decided that a determination of the concentration of the protein in the serum by radioimmunoassay would provide valuable information on the potential absorption of the intact protein. The protein is determined in the serum of animals from the positive control group and animals treated with the protein orally.

If this initial study indicates that the protein is orally active, then additional studies may be required to determine a no-observed-effect level. The design of these studies is of a longer duration and is based on the biological activity of the protein. Therefore, the study design will vary from one protein to the next.

In order to determine the safety of residues in milk, the 2-week oral feeding study just outlined may not provide sufficient information because of the possible differences in protein absorption between neonates and older animals. However, additional information is needed only if the protein is biologically active in humans. If the protein is not biologically active in humans then any potential increase in intact absorption of the protein will have no biological effect.

The first study suggested is a demonstration that the protein does not retain biological activity under the conditions commonly used for processing milk for infant use or after pasteurization. If, however, the protein is heat stable, then additional information may be required. Alternatives to the heat lability study may include data to determine to what extent the product is absorbed intact in neonatal animals, or data to demonstrate that the product is not active in neonates when administered orally.

To determine the safety of residues at the injection site, another oral feeding study is suggested, either as a separate study or incorporated into the previously described 2-week oral feeding study. This study contains two groups of animals, a vehicle control group and a group treated with 2X the total protein administered divided by 60. This provides for a 2-fold

safety factor if a 60-kg person were to consume the entire injection site just after the product was administered. Because it is highly unlikely that a person would consume an injection site or that the entire dose of drug would be found at the injection site at the time of slaughter of the animal, the 2-fold safety factor should be sufficient.

Proposed Residue Chemistry Studies

Residue chemistry studies may not always be required for protein products. If the product will be used in lactating dairy animals, no residue studies are required if the protein has adequately been shown to be biologically inactive in humans. However, if it is biologically active in humans, which is usually the case, the residue concentration in milk must be determined. These data are used in conjunction with the results of the oral feeding study and the heat lability study, or a demonstration that residues are not increased over endogenous concentrations, to determine whether residues in milk are safe. It should be pointed out that a recombinant product is considered biologically equivalent to the endogenous protein unless changes in amino acid sequence affect the potency as compared to the endogenous protein.

If the protein was found to be orally active and a safe concentration is necessary then the following residue chemistry studies would be needed: 1) For products that are administered as a single injection and not as a sustained-release formulation, the firm must conduct a residue depletion study to determine when the residues deplete below the safe concentration or to baseline levels in the case of an endogenous compound; 2) For products that are administered as an implant or sustained-release formulation the concentration of residues must be determined to demonstrate that residue levels are below the safe concentration at zero withdrawal. It should be pointed out that for all residue chemistry studies a validated method would need to be submitted along with the results of the studies to ensure that the method is capable of adequately measuring the protein in question.

If no biological endpoint can be measured for the protein product, it is difficult to determine what type of testing will be necessary to demonstrate the human food safety of that product. If the protein product is an endogenous compound, then safety may be demonstrated by determining when residue levels deplete to baseline levels. However, if the product is an analogue of an endogenous protein, then it will be more difficult to demonstrate safety by conducting a residue study. In this case FDA would ask for a determination of the residue levels, but this information must be combined with other information regarding the protein to determine safety. Because of a lack of a definite endpoint it would not be possible to conduct toxicology studies as discussed previously. The types of additional studies that will be necessary have not been determined in general, but would most likely need to be discussed on a case-by-case basis.

Additional Testing

In addition to the studies just outlined, there are cases where additional testing will be necessary to determine the human food safety of a protein product. Additional toxicology and/or residue studies may be required for secondary proteins when it is known that the

effects of the protein product administered to the target animal are mediated through the increase in a separate protein. An example of this is rbST whose effects are mediated through an increase in the insulin-like growth factors.

It may also be necessary to demonstrate that additional amino acids present due to the recombinant process, or any changes in amino acid sequence, do not affect the binding of the protein to the endogenous receptors or the potency of the protein as compared to the endogenous protein. In particular, changes in amino acid sequence which could affect the absorption or degradation of the protein will be taken into consideration. These studies are used to determine the biological equivalency of recombinant proteins with the endogenous protein so that a distinction need not necessarily be made between the two.

Human Food Safety of Bovine Somatotropin

These proposed testing requirements were applied to determine the human food safety of rbST. To begin with, there was substantial information in the scientific literature regarding bST, which provided a basis for determining the types of studies that would be necessary to demonstrate human food safety.

It was well known from studies conducted in the 1950's that bST is not biologically active in humans; there is a well-established biological endpoint that could be used to determine the oral activity of rbST; the amino acid sequence of bST and each rbST is known; information is available in the scientific literature that demonstrates the biological equivalence of bST and rbST; a substantial amount of information is available in the scientific literature regarding active fragments of bST and the hydrolysis conditions necessary to obtain active fragments; and it is known that the effects are mediated through insulin-like growth factors.

Based on the information already available regarding bST, a 2-week oral feeding study in rats was requested for the human food safety section of the approval of rbST. No milk residue data was required because bST is not biologically active in humans.

The FDA had concluded that an increase in growth factors secondary to rbST treatment was unlikely to present any human food safety concerns, based on the mechanism of action of insulin-like growth factors, the concentration of IGF-I found in human milk, preliminary information on the concentration of IGF-I in milk of rbST-treated cows, the way in which milk is processed for infant formula, and our knowledge of protein absorption and digestion in adults and neonates. Nonetheless, the FDA felt it was important to establish the range of concentrations of growth factors after rbST treatment and the potential for oral activity because of the widespread use of milk-based infant formulas. IGF-I was chosen as the growth factor for study because it is the major factor that mediates the effects of somatotropin. While not critical for ascertaining the human food safety of bST, FDA requested the following studies with IGF-I: a 2-week oral feeding study in rats, a determination of IGF-I residues in milk, and a heat lability study with IGF-I under the conditions used for processing infant formula.

Results of Studies with Recombinant Bovine Somatotropin

The results of all of these studies confirmed that the use of rbST in dairy cattle would present no increased health risk to consumers (Juskevich & Guyer, 1990).

Five oral feeding studies were conducted with rbST. Negative results were obtained with oral administration of rbST in all studies. The length of the studies conducted varied from 14 days to 90 days. The high dose of rbST administered in these studies varied according to the pharmaceutical companies' proposed dosage for treatment of dairy cattle and ranged from 5 to 50 mg/kg/day.

Two oral feeding studies were conducted with IGF-I. Negative results were obtained with oral adminstration of IGF-I in both studies. The duration of both studies was 14 days and the high dose administered was 1 and 2 mg/kg/day.

Although a determination of milk residues of bST were not required, several milk residues studies were conducted. The results of these studies demonstrated that there was no increase in bST in the milk of dairy cows treated with rbST at the proposed dosage.

Studies were requested to determine the increase in IGF-I in the milk of dairy cows treated with rbST. Survey studies were conducted to determine the concentration of IGF-I in milk of untreated cows. The baseline concentration is quite variable, ranging from less than 0.7 to 8.2 ng/ml in 95% of the cows, with a maximum of 30.5 ng/ml. The concentration depended on parity and stage of lactation of the cow. Several studies were conducted to determine the increase in IGF-I concentrations in milk after treatment with the proposed dosages of rbST. Results of the studies showed that, in some cases, there were minor increases after rbST treatment, and some of the increases were statistically significant. However, the concentrations were in the physiological range found in human breast milk.

Heat lability studies demonstrated that 90% of bST activity is destroyed during pasteurization. The heat lability studies requested for IGF-I demonstrated that pasteurization did not alter the concentration of IGF-I in milk, but processing conditions used for preparing infant formula decreased IGF-I activity. Prior to heat treatment, raw milk and pasteurized milk contained 5.6 and 8.2 ng/ml, respectively. After heat treatment of these samples, less than 0.5 ng/ml was detected. Approximately 0.7 ng/ml was found in a commercial infant formula.

Conclusions

In summary, the FDA is developing an alternative set of guidelines for the determination of the human food safety of protein products, taking into consideration that the chemical nature, biological activity, and potential for harmful residues are better understood for protein products. While these alternative testing requirements present a different series of studies than those generally required, the approach is scientifically well-founded and the studies supply the information necessary to determine the human food safety of protein products. These proposed guidelines are continuing to be revised as new protein products are presented and further experience is obtained with the regulation of protein drugs.

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DOSE-RESPONSE EFFECTS OF PORCINE SOMATOTROPIN ON YIELD, DISTRIBUTION AND NUTRITIONAL COMPOSITION OF EDIBLE CARCASS TISSUES

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Summary

Daily administration of a wide range of porcine somatotropin (0, 50, 100, 150 and 200 μg rpST/kg live weight) increases total skeletal muscle mass 28 to 38% and reduces separable adipose tissue mass 35 to 74% in carcasses of market barrows. Bone mass is increased 10 to 17% and skin mass is increased 14 to 38%. Similar changes in tissue distribution are observed among the four wholesale lean cuts, and greater reductions in percentage fat are observed in the fat cuts. Distribution of primal cut weights is altered toward decreased percentage of carcass weight in the fat cuts (belly and jowl), and increased percentage of carcass weight in lean cuts (ham, loin, butt and picnic). Muscle weight distribution within the ham is not changed. Proximate composition of skeletal muscle exhibits a dose-dependent decrease in lipid concentration and a small, but significant increase in protein concentration. Longissimus cholesterol concentration is not altered, and only minor increases in percentage of polyunsaturated fatty acids are observed in subcutaneous or intramuscular fat in rpST treated animals. Adipose tissue of rpST treated pigs contains 14% to 50% lower lipid concentrations, and 50% to 150% higher water and protein concentrations. Despite these changes in proximate and nutritional composition, sensory characteristics of fresh pork are only influenced at very high doses of rpST, and these changes are small. Consumer acceptance of fresh pork from rpST treated pigs is equal or greater than for pork from untreated animals.

Keywords: *somatotropin, tissue distribution, nutritional composition.*

Introduction

As the relationships between human health and over-consumption of cholesterol and total calories, calories from fat or saturated fat became better understood, dietary guidelines were developed and promoted. These include the recommendations that we limit consumption of calories from fat to less than 30% of total calories consumed, that we reduce intake of calories of both saturated and unsaturated fatty acids to less than 10% of total calories, and that we reduce cholesterol intake to 100 mg or less per 1000 calories consumed per day (National Research Council, 1988). Because red meat and animal fats contribute over 37% of the total fat and over 30% of all cholesterol consumed per capita in the U.S., implications

for reduced consumption of these foods is clear, unless nutrient composition of fresh meat and processed meat products is improved.

The potential for improving efficiency of pork, beef and lamb production through commercial application of biotechnology products like somatotropin (ST) and somatotropin releasing factor (SRF) is greater than has been demonstrated by genetic selection or any other management strategy currently available (see summaries by Campbell et al., 1988; Enright et al., 1989; Beermann and DeVol, 1990; Bonneau and McBride and Moseley, these proceedings). Dramatic reductions in carcass and empty body lipid accretion rates and concurrent large increases in protein accretion rates are observed with daily administration of ST or SRF in both nonruminants and ruminants. Change in absolute yield and distribution of carcass tissues and possible changes in nutrient composition of the edible tissues of the carcass have only recently been investigated. Whether or not lipid, cholesterol or fatty acid concentrations are consistently altered in tissues of somatotropin treated animals is not known. The nature of sex or genotype interactions in these changes have not been well characterized. Therefore, this paper will evaluate recent information concerning yield, distribution and nutrient composition of edible tissues from pigs treated with porcine somatotropin (rpST) or somatotropin releasing factor.

Table 1. Dose-response effects of porcine somatotropin on carcass yield and wholesale cut distribution in barrows treated from 30 to 90 kg live weight.[1]

	Daily somatotropin dose, $\mu gkg^{-1}BWd^{-1}$				
	0	50	100	150	200
Dressing percentage, %	76.6^{a}	$75.5^{a,b}$	$74.1^{b,c}$	73.2^{c}	73.5^{c}
Chilled carcass wt, kg	67.2^{a}	66.2^{a}	65.0^{b}	64.1^{b}	64.2^{b}
Ham					
untrimmed	23.5^{a}	25.8^{b}	25.8^{b}	26.3^{b}	26.1^{b}
trimmed	21.4^{a}	24.5^{b}	24.3^{b}	24.9^{b}	24.8^{b}
Loin					
untrimmed	24.7^{a}	23.3^{b}	$22.5^{b,c}$	21.9^{c}	$22.6^{b,c}$
trimmed	17.9^{a}	20.4^{b}	20.0^{b}	19.7^{b}	20.4^{b}
Belly					
untrimmed	17.2^{a}	15.7^{b}	$15.5^{b,c}$	$14.9^{b,c}$	14.6^{c}
trimmed	13.5^{a}	12.4^{b}	$11.8^{b,c}$	10.9^{c}	$11.5^{b,c}$
Butt					
untrimmed	10.2	10.0	10.1	10.1	10.3
trimmed	7.9^{a}	8.6^{b}	$9.0^{b,c}$	$9.1^{b,c}$	9.4^{c}
Picnic					
untrimmed	10.8^{a}	11.3^{b}	$11.4^{b,c}$	$11.7^{b,c}$	11.9^{c}
trimmed	10.3^{a}	11.0^{b}	$11.2^{b,c}$	$11.4^{b,c}$	11.6^{c}
Jowl					
untrimmed	5.10^{a}	4.23^{b}	$4.13^{b,c}$	$4.01^{b,c}$	3.76^{c}
trimmed	2.87^{a}	2.19^{b}	$1.96^{b,c}$	1.73^{c}	1.76^{c}
Feet	3.38^{a}	$3.51^{a,b}$	$3.72^{b,c}$	3.86^{c}	3.99^{c}
Spareribs	3.09^{a}	3.42^{b}	$3.61^{b,c}$	3.85^{c}	3.82^{c}
Neckbones	1.56	1.63	1.76	1.74	1.81

[1] Least square means represent 10 pigs per rpST dose.
[a,b,c] Means within a row with different superscripts differ (P<.05).

Wholesale Cut Yield and Distribution

Early studies demonstrated a dose-dependent increase in weights of skinned hams from finishing pigs treated with pituitary derived rpST (Etherton et al., 1987), but these increases were influenced by increased live weight gain over the 35-day treatment period. We subsequently conducted studies, in which confounding effects of live weight differences were eliminated, and found differences in weights of trimmed wholesale cuts of pork carcasses from pigs treated with increasing doses of rpST (Table 1). When a large dose range was evaluated in barrows treated from 30 to 90 kg live weight, percentage of carcass weight in the ham, trimmed loin, picnic and trimmed butt were increased with rpST ($P<.05$), while proportions present in the belly and jowl (fat cuts) were reduced ($P<.05$). Differences increased with increasing rpST dose. These data are similar to those reported by Demeyer et al. (1989), and our previous observations in which weight of the trimmed ham was increased in a dose-dependent manner ($P<.001$) without significant effects on other trimmed wholesale cuts in pigs treated with 0, 30, 60 or 90 μg recombinant pST/kg live weight from 45 to 105 kg live weight (D. H. Beermann, unpublished data). Goodband et al. (1990) recently reported that trimmed ham and loin weights were not different in control and rpST treated pigs fed .6% lysine from 57.6 kg to 105 kg live weight, but increasing dietary lysine concentrations increased trimmed weights of both cuts in rpST treated pigs.

Table 2. Dose-response relationships between porcine somatotropin administration and dissected carcass tissue weights in 90 kg barrows.[1]

	Daily somatotropin dose, $\mu g kg^{-1} BW d^{-1}$				
Observation	0	50	100	150	200
Number of animals	10	10	9	8	10
	Percentage difference from control (%)				
Muscle mass, kg	30.92	+27.9**	+30.3**	+32.7**	+37.6**
Adipose mass, kg	22.78	-35.7**	-54.6**	-65.7**	-74.1**
Bone mass, kg	7.28	+10.2*	+14.3**	+16.2**	+17.3**
Skin mass, kg	3.66	+14.8*	+36.1**	+35.0**	+38.3**

[1] Somatotropin was administered by daily injections and adjusted biweekly to increased live weight. Carcass data are summarized from Thiel et al., (1990).

* ($P<.05$) vs. control

** ($P<.01$) vs. control

Separable Tissue Yield and Distribution

Although dressing percentage and carcass weight are reduced ($P<.05$) with high doses of rpST (Table 1), yield of physically separated skeletal muscle trimmed of adhering fat and connective tissue is increased in a dose-dependent manner by 28% at 50 g/kg to 38% more mass at a dose of 200 g/kg (Table 2). This magnitude of increase in skeletal muscle yield exceeds previous measurements of approximately 12% to 18% increases in weights of major muscles in the hind leg of pigs administered rpST (Beermann et al., 1990; Solomon et al., 1989). However, these data are in good agreement with recent observations by Bark et al. (1990), who observed 28% and 24% increases in muscle mass of rpST treated pigs (70 μg/kg BW) from genotypes expressing moderate or high rates of skeletal muscle growth.

Somatotropin administration at doses of 100 µg/kg or higher cause both a greater relative and absolute reduction in adipose tissue content of the carcass than is observed for the reciprocal effects on skeletal muscle (Table 2), suggesting independent effects on these two tissues. Weight changes of muscle and adipose were essentially the same at the lowest dose. Separable bone weight was increased by 10% to 17% with increasing rpST dose, and skin mass was increased to the same relative extent as muscle mass.

Table 3. Dose-dependent effects of porcine somatotropin on ham tissue distribution and proximate composition.[1]

	Daily somatotropin dose, $\mu g kg^{-1} BW d^{-1}$					
	0	50	100	150	200	Sx
SM/A/G[2]						
weight, g	1194.[a]	1527.[b]	1510.[b]	1557.[b]	1578.[b]	44.3
protein, %	21.7	22.2	22.1	22.0	21.8	0.27
water, %	74.3[a]	74.9[a,b]	75.4[b,c]	75.8[c]	75.9[c]	0.25
lipid, %	3.4[a]	2.0[b]	1.6[b,c]	1.3[c]	1.3[c]	0.18
ash, %	1.3	1.3	1.3	1.2	1.3	0.04
ST/BF[3]						
weight, g	1462.[a]	1860.[b]	1774.[b]	1779.[b]	1885.[b]	48.1
protein, %	20.8	21.7	21.6	21.6	21.2	0.25
water, %	73.4[a]	74.2[a]	75.0[b]	75.6[b,c]	76.2[c]	0.26
lipid, %	5.0[a]	3.2[b]	2.4[c]	1.9[c,d]	1.5[d]	0.24
ash, %	1.4	1.2	1.2	1.3	2.9	0.70
Quadriceps						
weight, g	825[a]	1004[b]	1025[b]	1057[b]	1048[b]	31.9
protein, %	20.9	21.2	21.4	21.3	21.5	0.17
water, %	75.3	75.6	75.8	75.9	76.0	0.18
lipid, %	3.1[a]	2.2[b]	1.9[b,c]	1.6[c]	1.8[c]	0.15
ash, %	1.3	1.3	1.4	1.4	1.3	0.06
Other Muscles						
weight, g	1323[a]	1678[b]	1715[b]	1759[b]	1800[b]	58.2
protein, %	20.6	21.1	20.8	21.6	21.2	0.28
water, %	73.2[a]	74.2[b]	74.3[b]	74.6[b]	75.0[b]	0.30
lipid, %	5.6[a]	3.8[b]	3.7[b]	3.0[b,c]	2.7[c]	0.27
ash, %	1.2	1.1	1.2	1.4	1.5	0.11
Adipose						
weight, g	1428.[a]	1017.[b]	772.[c]	633.[c]	470.[d]	
protein, %	5.0[a]	6.5[a]	8.4[b]	9.9[b]	12.5[c]	0.56
water, %	22.0[a]	28.9[b]	34.4[b]	42.2[c]	49.8[d]	1.97
lipid, %	72.6[a]	63.4[b]	56.2[b]	46.5[c]	36.6[d]	2.38
ash, %	0.3[a]	0.4[a,b]	0.5[b,c]	0.6[c]	0.7[c]	0.05

[1] Least square means represent 10 pigs per treatment group; data are expressed on a wet-weight basis.
[2] Semimembranosus, adductor and gracilis.
[3] Semitendinosus and biceps femoris.
[a,b,c,d] Means within a row with different superscripts differ (P<.05).

Table 4. Dose-dependent effects of porcine somatotropin on belly tissue distribution and proximate composition.[1]

	Daily somatotropin dose, $\mu gkg^{-1}BWd^{-1}$				
	0	50	100	150	200
Muscle					
weight, g	1827.[a]	2499.[b]	2508.[b]	2500.[b]	2751.[c]
protein, %	19.9	21.0	20.7	20.8	20.4
water, %	68.4[a]	70.8[b]	71.4[b,c]	72.6[c]	74.6[d]
lipid, %	10.9[a]	7.4[b]	7.1[b]	5.8[b]	3.7[c]
ash, %	1.2	1.2	1.2	1.2	1.2
Adipose					
weight, g	2285.[a]	1773.[a]	757.[b]	467.[b]	362.[b]
protein, %	4.4[a]	7.2[b]	8.7[b,c]	9.9[c]	14.3[d]
water, %	19.1[a]	26.9[b]	31.3[b]	38.2[c]	49.1[d]
lipid, %	76.0[a]	65.2[b]	58.9[b]	50.8[c]	36.1[d]
ash, %	0.1	0.5	0.8	0.5	0.3

[1] Least square means represent 10 pigs per rpST dose; data are expressed on a wet-weight basis.
[a,b,c,d] Means within a row with different superscripts differ (P<.05).

Table 5. Dose response effects of porcine somatotropin on longissimus muscle nutrient composition in boars and barrows.[1]

	Daily somatotropin dose, $\mu gkg^{-1}BWd^{-1}$				
	0	50	100	150	200
Protein concentration, %					
Fat strain barrows	22.8	23.5	23.4	23.3	23.3
Lean strain barrows	22.4[a]	23.5[b]	23.1[a,b]	23.3[b]	23.3[b]
Lean strain boars	22.3	22.7	23.1	22.6	22.9
Water concentration, %					
Fat strain barrows	73.0[a]	73.5[a,b]	74.0[b,c]	73.3[a,b]	74.8[c]
Lean strain barrows	73.2[a]	74.3[a,b]	74.2[a,b]	74.6[b]	74.9[b]
Lean strain boars	74.3	74.8	73.4	75.0	75.3
Ash concentration, %					
Fat strain barrows	1.4	1.4	1.4	1.4	1.4
Lean strain barrows	1.4	1.4	1.4	1.4	1.4
Lean strain boars	1.4	1.4	1.4	1.4	1.4
Lipid concentration, %					
Fat strain barrows	3.4[a]	2.5[a,b]	1.8[b,c]	2.6[a,b]	1.3[c]
Lean strain barrows	3.4[a]	1.5[b]	1.6[b]	1.2[b]	0.7[b]
Lean strain boars	2.6[a]	1.5[b]	1.0[b,c]	1.0[b,c]	0.5[c]
Cholesterol concentration, mg/100 g					
Fat strain barrows	56.0	58.9	55.4	62.2	57.2
Lean strain barrows	56.4	58.9	58.4	57.4	61.2
Lean strain boars	55.4	55.7	54.0	55.9	57.1

[1] Data reflect 10 animals per subclass; data are expressed on a wet-weight basis for muscle cross sections trimmed of all adhering fat and connective tissue.
[a,b,c] Means within a row with different superscripts differ (P<.05).

Tissue Distribution and Nutrient Composition

Nutrient composition of the tissues is best evaluated within subdivisions of the carcass. Wholesale cut muscle groups are separated for further processing (i.e. ham inside and outside cushion, tip and trimmings), and individual muscles comprise the major portion of fresh retail cuts. Therefore, proximate composition of a lean cut, the ham, was evaluated by muscle group and separable adipose tissues (Table 3). Proximate composition of separated skeletal muscle and adipose tissue was evaluated in a fat cut, the belly (Table 4), and more detailed nutritional composition information was assessed in an individual muscle, the longissimus (Table 5).

Ham Composition

The 50 μg/kg dose of rpST increased muscle mass approximately 28% in all muscle groups of the ham (Table 3), while the highest dose appeared to produce a slightly more variable response (27% to 36%). Percentage protein and ash were not significantly increased in any muscle group, and percentage water was increased about one percentage point ($P<.05$) in the larger muscles. Percentage lipid in the muscle groups was reduced in a dose-dependent manner by 29% to 70%. Although separable adipose tissue mass in the ham was reduced 28% to 67%, extractable lipid concentration was also reduced in a dose-dependent manner by 12% to 49%. This resulted in a 37% to 83% decline in absolute lipid content of the adipose tissue in the ham, across the range of rpST doses evaluated. As a result, percentage protein, water and ash in adipose tissue were more than doubled. Similar magnitudes of change in muscle and adipose distribution and composition were observed in the other lean cuts (data not shown).

Belly Composition

Skeletal muscle mass in the belly was increased 36% at the 50, 100 and 150 μg rpST/kg doses, and was increased 50% with the highest dose (Table 4), despite an 8% to 15% reduction in untrimmed or trimmed cut weight. Percentage protein and ash in the muscle was not affected, but water concentration was increased with each increment of rpST dose. Separable adipose tissue content was reduced in a dose-dependent manner by 22% at the lowest dose to a maximum of 84% at the highest dose. Percentage lipid was also reduced stepwise with increasing rpST dose, leading to a 33% to 92% decline in absolute lipid content of the belly. Percentage protein more than tripled and percentage water more than doubled across the rpST dose range, while ash concentration was unchanged.

Longissimus Composition

Daily administration of rpST at a dose of ≥ 50 μg/kg live weight clearly decreases intramuscular lipid concentration when administered during the final 50 to 60 kg live weight gain in finishing pigs (Beermann et al., 1988; Prusa et al., 1989a,b; Beermann et al., 1990; Mourot et al., 1990). This reduction of intramuscular lipid concentration is dose-dependent,

is observed in muscles from different regions of the carcass and generally parallels the relative reduction in other carcass fat depots. The effect appears to be no greater in fat-strain barrows, and no less in boars (Table 5). Percentage lipid in the longissimus was reduced to less than 1% in barrows and boars administered 200 μg rpST/kg live weight (Table 5), and in barrows and gilts administered 90 μg rpST/kg (Beermann et al., 1988). Protein and water concentration in the longissimus was increased less than one percentage point, and ash concentration remained unchanged.

Because consumption of cholesterol and saturated fatty acids have been identified as possible contribution to the development of cardiovascular disease in humans, we also evaluated the cholesterol concentration and fatty acid profile in longissimus samples taken from fat-strain and lean-strain barrows and lean-strain boars (Tables 5, 6). Cholesterol concentration was not affected by rpST administration, and was similar among all three genotype-sex groups. Therefore, it appears that nutritional contributions to total intake of calories as fat may be reduced with rpST administration in finishing pigs, but intake of cholesterol is not affected. These data are relatively low for fresh pork (USDA Handbook 8-10). Prusa et al. (1989) observed a significant (8% to 9%) increase in cholesterol concentration in broiled boneless loin chops of pigs treated with 8 mg rpST/day.

Few data are available for assessing the influence of rpST on fatty acid profile of lipids in the various adipose depots in pork carcasses. Prusa et al. (1989a) observed no significant change in percentage of saturated, monounsaturated or polyunsaturated fatty acids in the intramuscular fat of broiled, boneless rib chops from pigs administered 4 or 8 mg rpST per day from 45 to 100 kg live weight. Mourot et al. (1990) observed that backfat was more unsaturated in pigs either injected with 4 mg rpST daily from 60 to 100 kg live weight or implanted with a rpST preparation designed to deliver 2 mg per day. Significant increase in percentage of polyunsaturated fatty acids and significant decrease in percentage of saturated fatty acids was observed. Similar results were reported by Ender et al. (1989). Intramuscular lipid of the longissimus from rpST treated barrows and gilts exhibited significant reduction of nonpolar lipids, and no change in polar lipids in the studies by Mourot. Differences were also present in fatty acid profile. Barrows and gilts administered rpST exhibited 48% and 22% greater percentages of C18:2, respectively, when compared to their control counterparts. Very similar differences in percentage of total polyunsaturated fatty acids were also observed. Total saturated fatty acid percentage was approximately one percentage point lower in intramuscular lipid from rpST treated pigs. Interestingly, the increase in polyunsaturated fatty acid percentage was not observed, in lipid extracted from the adductor muscle from the same animals.

We evaluated the fatty acid profile of intramuscular lipid extracted from the longissimus of barrows and boars administered 0, 50 or 100 μg rpST/kg from 30 to 90 kg live weight. Our data confirm those of Mourot et al. (1990), indicating that percentage C 18:2 is elevated approximately 25% ($P<.05$), and percentage total monounsaturated fatty acids is reduced 5.7% ($P<.05$) in both sexes at both levels of rpST administration (Table 6). Because sex differences were not significant, data from barrows and boars were combined. Dose-response relationships were not evident.

Table 6. Dose-dependent effects of somatotropin on fatty acid composition of longissimus intramuscular lipid in 90 kg barrows and boars.[1]

	Daily somatotropin dose, $\mu gkg^{-1}BWd^{-1}$		
	0	50	100
Number of pigs	20	19	17
C14:0 (myristic)	1.45^{a}	1.13^{b}	1.22^{b}
C16:0 (palmitic)	$24.86^{a,b}$	24.24^{a}	25.42^{b}
C16:1 (palmitoleic)	3.80^{a}	3.28^{b}	$3.43^{a,b}$
C18:0 (stearic)	11.66	12.38	11.69
C18:1 (oleic)	45.78^{a}	43.47^{b}	42.61^{b}
C18:2 (linoleic)	12.62^{a}	15.80^{b}	15.50^{b}
Total saturated	37.96	37.77	38.34
Total monounsaturated	49.57^{a}	46.75^{b}	46.04^{b}
Total polyunsaturated	12.62^{a}	15.80^{b}	15.50^{b}

1 Data are expressed as percentages of the total lipid. The following fatty acid concentrations were below the level of detection: C12:0, C14:1, C18:3, C20:0, C20:1, C20:2, C20:4, C22:0, C22:1, C22:6, C24:0, C24:1. No sex effects were observed ($P<.05$).

[a,b] Means within a row with different superscripts differ ($P<.05$).

Discussion

The rapidly accumulating body of data indicates that administration of porcine somatotropin to finishing pigs alters the yield and distribution of wholesale cuts in the carcass, modestly increasing weight and percentage of lean cuts and significantly reducing the belly and other fat cuts. Greater changes in tissue distribution, toward greater skeletal muscle mass and less separable adipose tissue, are observed with the same rpST dose range. It is apparent that inadequate levels of limiting amino acids in the diet will reduce the magnitude of the response. Goodband et al. (1990) observed that stepwise increments of lysine concentration in the diet from .6% to 1.2% increased muscle mass, reduced carcass and muscle lipid concentrations and increased muscle crude protein and water concentration in pigs administered 4 mg rpST daily from 57.6 kg to 105 kg live weight. These data demonstrate the importance of supplying adequate nutrients to meet requirements for growth as defined by an animal's capacity for rate of protein accretion. It is possible that amino acid content or profile of diets used in some studies of rpST effects on tissue growth, distribution and composition may have influenced (dampened) the response to rpST.

Significant changes in yield and distribution of pork carcass tissues have also been demonstrated with daily administration of a synthetic human somatotropin releasing factor (hSRF) analogue in finishing barrows and gilts (Pommier et al., 1990). Muscle mass was increased 13 to 17% and adipose mass was reduced 13 to 30% in lean cuts from pigs administered 6.66 μg hSRF/kg three times daily from 50 to 105 kg live weight. These results are of smaller magnitude than those achieved with single daily administration of rpST. The transient elevation of circulating concentrations of ST which result from hSRF administration, and the lower mean concentration achieved over a 24-hour period most probably account for the differences.

The major change in nutrient composition of tissues from pigs treated with rpST appears to be the marked reduction in fat concentration and content. Percentage total lipids is reduced

in a dose-dependent manner in both skeletal muscle and adipose tissue from all wholesale cuts from pigs treated with rpST. At lower doses (50 μg/kg BW) absolute weight of skeletal muscle mass increase is nearly identical to the reduction in adipose tissue weight. The major portion of the reduction in absolute lipid mass is observed in the adipose tissue. Absolute changes in lipid content are greater for the fat cuts in the carcass. Differences in magnitude, or the lack of reduction which has been observed in some studies (summarized by Prusa, 1989) may be explained by administration of minimally effective doses or administration of fixed daily mass of rpST which results in declining effective dose (per kg live weight) during the treatment period. Our data indicate that large changes are achieved with a dose equivalent of 50 μg rpST/kg live weight injected daily, and that increments above this dose result in less rapid or lesser magnitude of change, although significant. Similar but smaller reductions of lipid concentration in muscle and adipose tissue are achieved with multiple daily administration of hSRF in finishing pigs (Pommier et al., 1990).

The rpST-induced reduction in intramuscular lipid concentration does not result in any consistent change in cholesterol concentration of longissimus muscle, at any dose tested. Fatty acid profile of backfat and intramuscular lipid is altered to increase the percentage of total polyunsaturated fatty acids, with the major change consisting of increased C18:2. These changes are relatively small, and they have not been consistently observed in some cases. Solomon and Pursel (1990) observed marked reduction in total lipid and total fatty acids, and similar shifts in fatty acid profile in transgenic pigs expressing a bovine growth hormone gene.

The sparse data available indicate that little if any change in mineral concentrations (Goodband et al., 1990) or vitamin content of muscle (Prusa, 1989) occur with administration of rpST. Therefore, we would conclude that the most significant effects of rpST on nutrient composition of edible tissues, excluding organ meats, is to reduce neutral lipid concentration. Several investigations indicate that cooking loss and sensory characteristics of fresh pork are not adversely affected by rpST administration, unless very high doses are employed (Beermann et al., 1988, 1990; Evock et al., 1988; Novakofski et al., 1988; Prusa et al., 1989a; Goodband et al., 1990; Thiel et al., 1990b).

Conclusions

Daily administration of porcine somatotropin during the finishing stages of growth markedly improve the nutrient composition of pork carcass through marked reductions in separable adipose tissue weight and lipid concentrations in all adipose depots evaluated, plus concurrent increases in skeletal muscle mass. Nutrient composition of skeletal muscle is altered toward reduced lipid concentration, however, cholesterol concentration is not changed and fatty acid profile exhibits small increases in percentage C18:2 and total polyunsaturated fatty acids.

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DOES RED MEAT HAVE A ROLE IN HEALTHY DIETS?

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Summary

The contribution of meat consumption to major chronic diseases -- CHD and cancer -- has not been adequately defined. Without question, the fat of meat contributes to a relatively high intake of saturated fatty acids in affluent countries, and high-fat meats may be one factor responsible for diet-induced, "mass hypercholesterolemia". Further, high-fat meats may enhance risk for certain kinds of cancer. Therefore, the general recommendation for the public to switch from high-fat meats to low-fat meats seems prudent. Another advance would be the development of techniques to specifically reduce the palmitic-acid content of both beef and pork. Such a process would specifically lower the one cholesterol-raising, saturated fatty acid in meat products.

Keywords: *Red meat, fat content, human health.*

Introduction

During the past two decades the idea has grown in the minds of many people that red meat is not healthy for the general public. Two concerns have been expressed. First, the consumption of red meat has been linked to the development of coronary heart disease (CHD), and second, it has been associated with increased risk for cancer. These ideas have led many investigators to recommend that consumption of red meat should be curtailed by the general public. However, the link between meat and major chronic diseases is based on limited epidemiologic evidence, and the validity of this connection can be questioned. Therefore, in this article, the nature of the evidence will be examined along with the strength of the link between consumption of red meat and chronic disease. CHD will be considered first, and then cancer.

Coronary Heart Disease

By what mechanisms might red meat increase risk for CHD?

If red meat raises the risk for CHD, the primary mechanism appears to be through an increase in the serum-cholesterol level. Many epidemiologic studies indicate that high levels

of serum cholesterol are a major risk factor for CHD (Keys 1970); thus, any factors that raise the serum-cholesterol concentration should increase the danger for CHD. Three dietary factors have been identified that increase the serum cholesterol. These are saturated fatty acids, dietary cholesterol, and obesity (Grundy et al., 1982 and Expert panel 1988). Therefore, if dietary consumption of red meat increases the risk for CHD by raising the serum cholesterol, it presumably would have to be due to its content of saturated fatty acids and cholesterol, or its high caloric density, leading to obesity. Of course, obesity increases CHD by ways other than raising the cholesterol level; it promotes the development of hypertension, predisposes one to diabetes mellitus, raises the serum triglycerides, and reduces high density lipoproteins (HDL) (Grundy and Barnett 1990).

Do the fatty acids of red meat raise serum-cholesterol levels?

The fat of red meat is widely considered to be "saturated", hence, it is a cholesterol-raising fat. However, the term "saturated" as applied to whole fat can be misleading, as it is in the case of meat fat. There are several types of fatty acids in the fats of different kinds of meat, as shown in Table 1. This table compares the fatty-acid composition of beef tallow and lard with other animal fats -- chicken fat and butter fat -- and three "saturated" fats from plant oils -- coconut oil, palm oil, and cocoa butter. The table shows that all of fats listed are relatively rich in saturated fatty acids, but all of them in addition contain unsaturated fatty acids, mainly oleic acid. There is abundant evidence that unsaturated fatty acids do not raise the serum-cholesterol concentration (Keys et al., 1965, Hegsted and McGandy 1965, Mattson and Grundy 1985, Grundy and Denke 1990.). In contrast, saturated fatty acids as a class appear to raise cholesterol levels, although growing evidence indicates that not all saturates are cholesterol raisers. Three saturated fatty acids -- lauric acid (C12:0), myristic acid (C14:0), and palmitic acid (C16:0) -- almost certainly are cholesterol-raising fatty acids (Keys et al., 1965; Hegsted et al., 1965). In contrast, medium-chain fatty acids (C8:0 and C10:0) seemingly are not cholesterol raisers (Hashim et al., 1960), and recent evidence (Bonanome and Grundy 1988) indicates that stearic acid (C18:0) likewise does not increase the serum-cholesterol concentration. With these relationships, we might look at the relative cholesterol-raising potential of different fats.

Table 1. Fatty Acid Compositions of Several Fats

	% Fatty Acid									
Fat*	4-10:0	12:0	14:0	16:0	16:1	18:0	18:1	18:2	18:3	Other
Butter fat	9.2	3.1	17.7	26.2	1.9	12.5	28.2	2.9	0.5	--
Palm kernel oil	8.2	49.6	16.0	8.0	--	2.4	13.7	2.0	--	0.1
Coconut oil	14.9	48.5	17.6	8.4	--	2.5	6.5	1.5	--	0.1
Palm oil	--	0.3	1.1	45.1	0.1	4.7	38.8	9.4	--	0.5
Beef fat	0.1	0.1	3.3	25.5	3.4	21.6	38.7	2.2	0.6	4.6
Pork fat (lard)	0.1	0.1	1.5	24.8	3.1	12.3	45.1	9.9	1.1	3.0
Chicken fat	--	0.2	1.3	23.2	6.5	6.4	41.6	18.9	1.3	0.6
Mutton fat	0.2	0.3	5.2	23.6	2.5	24.5	33.3	4.0	1.3	5.1
Cocoa butter	--	--	0.1	25.8	0.3	34.5	35.3	2.9	--	1.1

* The numbers for the fatty acids represent carbon chain length: number of double bonds.

Three fats emerge has highly potent for increasing cholesterol levels. These are butter fat, palm oil, and coconut oil (Table 1). Butter fat is particularly rich in palmitic acid and myristic acid, and it contains about 50% of its fatty acids as cholesterol-raising saturated acids (C12:0, C14:0, and C16:0); in addition, butter fat contains small quantities of trans monounsaturates which recently have been shown to increase the cholesterol level (Mensink and Katan 1990). On the other hand, some of the saturates (C8:0, C10:0, and C18:0) in butter fat do not increase the serum cholesterol. Likewise, the oleic-acid (C18:1) content of butter fat does not contribute to a rise in cholesterol levels (Keys et al., 1965; Hegsted et al., 1965; Mattson and Grundy, 1985; Grundy and Denke, 1990). Still, butter fat appears to be one of the more potent cholesterol-raising fats. Coconut oil is extremely high in cholesterol raisers (C12:0, C14:0, and C16:0), and should be the most hypercholesterolemic of all the fats; however, lauric acid (C12:0) may be somewhat less hypercholesterolemic than palmitic and myristic acids (Hegsted et al., 1965), and coconut oil hence may not raise the cholesterol level more than butter fat. Palm oil is extremely rich in palmitic acid (45% of calories), and it too is hypercholesterolemic (Mattson and Grundy, 1985; Bonaome and Grundy, 1988).

It is interesting to compare beef tallow with the three fats discussed above. Beef tallow has approximately 50% of its fatty acids as saturates. However, about 20% of these are stearic acid, which is not a cholesterol raiser (Bonaome and Grundy, 1988). Thus only about 30% of calories are of the cholesterol-increasing variety, i.e., palmitic and myristic acids. Hence, beef tallow should be less hypercholesterolemic than butter fat, palm oil, and coconut oil. The same is true for lard, which likewise has only about 30% of its fatty acids as cholesterol raisers. Indeed, from the point of view of fatty acid composition, beef tallow and lard are no more hypercholesterolemic than chicken fat. This is not to say that these animal fats have no cholesterol-raising potential. Thirty percent of their calories consists of cholesterol-raising fatty acids, and this effect is not offset by the other fatty acids. Although stearic and oleic acids do not increase the cholesterol concentration, neither do they lower it. Thus, they must be considered neutral in their action on cholesterol levels. Still, even though meat fats must be considered "cholesterol raisers", they are less hypercholesterolemic than widely believed.

Does the cholesterol in meat increase cholesterol levels?

Cholesterol is found both in muscle and fat of meat. The cholesterol content of both is similar, about 70 to 90 mg per 100 grams. In general, red meats (beef and pork) do not contain significantly more cholesterol than white meats (fish and poultry) (Expert panel, 1988). Thus, red meat is not uniquely hypercholesterolemic because of its cholesterol content. Furthermore, if consumption of red meat does not exceed six ounces per day, the intake of cholesterol will be in the range of 140 to 180 mg/day, which is within acceptable limits. The recommended intake of cholesterol is less than 300 mg/day. Normally, about one-third of dietary cholesterol comes from meat, one-third from eggs, and one-third from butter fat. It is relatively easy to essentially eliminate the latter two sources of cholesterol, and when this is done, consumption of meat in moderate amounts will not lead to an excessive intake of cholesterol. Thus, while the cholesterol content of meat/fat may raise serum-cholesterol levels, the rise will not be appreciable if other sources of cholesterol are eliminated. One way to reduce the cholesterol intake from meat is to remove excess fat.

Although the fat does not contain more cholesterol than the muscle, removal of excess fat will lower the absolute intake of cholesterol.

Does red meat promote obesity?

Yet another factor that may raise the serum-cholesterol level is obesity. Therefore, if red meat in the diet promotes development of obesity, it could contribute to higher cholesterol levels by this mechanism. There is the general impression that meat-eating populations are more obese than those that abstain from meat. There are several possible reasons for this impression. First, those who can afford meat tend to be more affluent than those who cannot, and affluence may promote overeating simply because people can buy more food. And second, if large amounts of fatty meats are consumed, they will be a concentrated source of calories; and in this way, meat can contribute to obesity. Fat-rich hamburger meat and processed meats are particularly high in calories, and their consumption could promote obesity if taken in excess. Thus, to the question of whether red meat promotes obesity, one must consider both the type of meat and amounts consumed.

If one restricts meat consumption to six ounces per day, this will provide approximately only 350 to 450 calories per day. Considering that red meat is high in protein and iron, this certainly is not a high caloric price to pay for a good source of protein and essential minerals. Thus, we must conclude that red meat *need not* contribute significantly to obesity. If anything, lean meat could be a valuable part of a weight-reduction diet.

How can meat be modified to reduce risk for CHD?

The major change that can be made in red meat to reduce risk for CHD is to reduce its total fat content. Certainly the outside fat should be trimmed away, and this is being done increasingly in the preparation of fresh meat for sale. In fact, the public is becoming unwilling to pay for this excess fat, which is perceived by many people to be unnecessary and unhealthy. When the meat industry realizes that it costs excess money to put on unacceptable fat and then have it discarded, then animal-feeding techniques will be adopted to minimize the amount of outside fat on meat. When this occurs, the fat contained within the muscle (i.e., marbling) likewise will be reduced. By decreasing the fat content of muscle, fat intake accompanying meat consumption will be reduced even more.

Once the idea is widely accepted by both the general public and the meat industry that low-fat meat is both healthier and less expensive, there are a variety of ways in which lower-fat meat can be produced. Use of recombinant somatotropin to stimulate protein accretion may be one way. Developing of new breeds of cattle that are more muscular and lower in fat may be another. Modification of the feeding pattern throughout the life of the animal may be yet another way to decrease the fat content of the whole animal. Still other ways may be found. The goal is to produce lean animals with a minimum of excess fat.

In the case of pork, the type of fat as well as amounts of fat can be altered. By feeding unsaturated fatty acids to pigs, their fat can be made less saturated, i.e., the content of

palmitic acid can be reduced. The fat that is fed can be rich in either polyunsaturated fatty acids (linoleic acid) or monounsaturated fatty acids (oleic acid). In our view, diets high in oleic acid are preferable because of several theoretical advantages of oleic acid over linoleic acid in the diet. Although lean pork is preferable to fatty pork, the latter can be acceptable if its content of palmitic acid is reduced from the usual 28 to 30% to approximately 15 to 17% (St. John et al., 1987). Still, high-fat pork, regardless of fatty acid composition, can promote weight gain if too much is consumed. Therefore, technology should emphasize the production of low-fat pork, although replacement of palmitic acid with oleic acid to the extent possible can be a secondary goal.

In the case of beef, it is difficult to modify the fatty-acid composition by feeding of unsaturated fats. In general, cattle do not readily absorb exogenous fat, and thus it is not possible to enrich adipose tissue with exogenous fat. And moreover, unsaturated fatty acids tend to be saturated in the rumen of cattle through bacterial hydrogenation. Previous research has shown that special treatment of feed will allow fat to pass through the rumen and thus be absorbed without alteration. By this procedure, the adipose-tissue content of unsaturated fatty acids can be increased (Nestel et al., 1973). Although this approach has never been appealing to the beef industry, more research is needed to develop ways to accomplish a change in fatty-acid composition of beef to a healthier pattern.

Cancer

By what mechanisms might red meat increase risk for cancer?

As reviewed recently by Prentice et al. (1990), several epidemiologic studies indicate that rates of certain types of cancer, particularly breast cancer and colon cancer, are higher in societies that consume large quantities of meat than in those in which intakes are low. These links have been noted in between-country studies, in migration studies, and to a lesser extent from within-country surveys. These relationships have led to speculations on possible mechanisms whereby high meat consumption might increase risk for cancer.

One question that has been raised is whether the putative "cancer-causing" action of meat is due to its muscle or fat component. Since high intakes of fat have been implicated in the development of certain cancers, the effects of meat in cancer causation could be related exclusively to its fat content. If this is so, then the relation between meat and cancer presumably could be eliminated by use of low-fat meats. In epidemiologic studies, the overall link between fat and cancer is stronger than for meat per se, and a reasonable first step to eliminating the meat-cancer connection would be to switch from high-fat meat to low-fat meat. This change should reduce the risk for CHD as well, which is another reason to support this approach. Some workers believe that dietary fat itself is not a cause of cancer, but rather obesity resulting from high-fat diets is the cause. If so, this provides still another reason to switch from high-fat meat to lean meat.

Alternatively, how might the muscle component of meat enhance the development of cancer? Are these substances in muscle that are directly or indirectly carcinogenic or cancer

promoters? Certainly, muscle contains a variety of compounds that theoretically might stimulate carcinogenesis. These compounds might become actively carcinogenic upon cooking, or they might enter meat during barbecuing. At present these possibilities are largely speculation, but perhaps are worthy of more investigation. On the other hand, theoretical carcinogens also exist in most other natural foods, especially fruits and vegetables. Thus, to condemn red meat as a *possible* carrier of carcinogens seems premature, and a recommendation to the public for dietary change cannot be made on the basis of a possibility.

If anything, red meat in principle should be relatively free of carcinogenic properties. Both fat and muscle components of meat should be protected from acquiring exogenous carcinogenic factors derived from animal diets. Thus, beef and pork should not differ in composition from human flesh, and hence should contain little carcinogenic potential. If red meat plays a role in human cancer, it most likely acts by the promotion of cancer, rather than initiation. And if red meat is a cancer promoter, the fat component probably plays a greater role than the muscle. In other words, lean meat probably is less of a cancer promoter than fatty meat. Thus, on theoretical grounds, recommendations to avoid lean red meat because of its potential to induce cancer or to promote carcinogenesis cannot be justified.

Does red meat increase risk for breast cancer?

If consumption of red meat increases the risk for breast cancer, a relationship most likely can be explained by its fat content. World-wide epidemiologic studies suggest that high intakes of fat are accompanied by increased rates of breast cancer (Prentice and Sheppard 1990). A relationship was not noted in a recent case-control study (Willnett et al., 1987), but many investigators still believe that high-fat diets predispose to breast cancer. Since consumption of high-fat meats is one contributor to high-fat diets, it is possible that fatty meats add to the dietary fat-cancer connection. It should be pointed out however that meat is only one of many sources of fat in the diet, and if the recommendation is made to curb meat intake to reduce fat consumption, this recommendation would have to extend to many other foods as well. There is no reason to single out meat as a source of dietary fat.

By what mechanism might a high-fat diet predispose to breast cancer? One possibility is that such a diet will lead to obesity, which in turn may enhance the risk for cancer. For example, obesity is known to raise oestrogen levels, and high levels of circulating oestrogens may promote breast cancer.

Some workers have suggested that high-fat diets promote growth early in life, and since tall women seem to be at higher risk for breast cancer than short women, rapid growth early in life might be diet related. Whether dietary fat in some way directly stimulates the growth of breast tissue and thereby predisposes to cancer is a matter for speculation. Another question is whether all types of fatty acids are potentially cancer promoting. For example, Prentice and Sheppard (1990) recently concluded that only saturated and polyunsaturated fatty acids predispose to cancer, whereas monounsaturated fatty acids do not have this potential. If this were true, it would suggest that specific fatty acids have a direct role in carcinogenesis, and further, the saturated fatty acids of beef might be a contributor. In spite of speculation about possible mechanisms, little or nothing is known with certainty about the

mechanisms whereby a high-fat diet might promote breast cancer. Until such a mechanism has been identified, there will remain serious doubt whether the apparent relation between dietary fat and breast cancer is real, or is merely the result of confounding factors.

Does red meat increase risk for colon cancer?

There are at least three ways in which red meat in the diet *might* predispose to colon cancer. First, the fatty portion of meat might be involved; second, the muscle of meat could contain carcinogenic substances that remain unabsorbed and pass into the colon; and third, meat might be consumed in the place of other foods that have a protective action against colon cancer. Each of these possibilities can be considered.

If the fat of meat promotes development of colon cancer, the mechanisms might be similar to those described previously for breast cancer, e.g., promotion of obesity. Some workers have speculated that bile acids may have cancer-promoting properties, and obese people definitely make more bile acids than thin people. As this excess of bile acids pass through the colon on their way to excretion, they could promote development of colon cancer. Note here should be made of the misconception that a high percentage of fat in the diet, independent of body weight, stimulates formation of bile acids; this is not the case (Grundy and Metzger 1972). But it is true that obesity stimulates bile-acid synthesis (Nestel et al., 1973), and if a high intake of fat promotes obesity, this response could favour any bile acid-cancer relationship. Of course, obesity might promote colon-cancer development in other ways, such as overstimulating cell division by providing high circulating levels of glucose and free fatty acids.

Second, does the muscle of red meat have carcinogenic substances, or cancer promoters? Little information is available to answer this question. In a recent case control study (Willnet et al., 1990), based on reported consumption at baseline, there appeared to be a relationship between meat consumption (independent of its fat content) and colon cancer in American women. This apparent connection however was relatively weak, and firm conclusions could not be drawn. Perhaps various substances might be extracted out of fresh meat (and cooked meat) to test in animals for their carcinogenic potential; but to date, little direct evidence supports the notion that the muscle portion of meat contains carcinogenic substances.

Finally, diets high in meat could be deficient in fruits, vegetables, and fibre, and if these foods have a protective action against colon cancer, this could explain a meat-cancer relationship. If so, meat would not be a cause of cancer but only would be guilty by lack of association. Certainly, protective foods could be added to diet without the elimination of meat.

How can red meat be modified to reduce risk for cancer?

The above considerations raise a serious question as to whether meat consumption truly is related to development of cancer. The evidence is not strong enough at present to make public recommendations for reduction in meat intake. If there is a connection between meat

and cancer, it is most likely related to a high-fat content. Whether a high-fat intake is related to cancer through promotion of obesity or by direct effect on susceptible tissues has not been determined. The available evidence suggests that saturated fatty acids are more closely related to cancer development than monounsaturates (Prentice and Sheppard 1990). Since a moderately high proportion of fatty acids in meat are saturated, and since some of these fatty acids also raise the serum-cholesterol level, it is reasonable to attempt to reduce intake of meat-derived saturated fatty acids. Actually, this can be accomplished best by reducing the total fat content of meat. Thus, the most appropriate modification of meat for the purpose of reducing risk for cancer is to reduce its fat content. At the same time, a general recommendation for liberal amounts of fruits, vegetables, and fibre can be made (Committee on Diet and Health Food and Nutrition Board, Commission on Life Sciences, National Research Council, 1989); in other words, meat eaters should not cut back on these other foods, which may offer some protection against cancer. Finally, further research should be carried out on the components of the muscle portion of meat to determine whether it contains substances of carcinogenic potential.

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SESSION V
SOCIAL AND CONSUMER ACCEPTANCE

* Communication between scientists and consumers
* Determinants of public acceptance
  - Australasia
  - North America
  - Europe
* Acceptance in production and processing

SUMMARISED AND ADOPTED CONCLUSIONS FROM PAPERS AND DISCUSSION

ON

SOCIAL AND CONSUMER ACCEPTANCE

Chairman:

M.A. Norcross, *United States Department of Agriculture, Food Safety and Inspection Service - USA*

Discussion moderator:

R.R. Straughan, *Department of Arts and Humanities, University of Reading - UK*

- *Participants readily agreed that* ***biotechnology is an emerging factor of great significance for the world food industry,*** *and that the way must be prepared if biotechnology is to be accepted smoothly and efficiently into our society and the world at large. If adequate preparatory work is not done, the benefits of biotechnology may be diminished or missed altogether.*

- *Preparation is necessary, the participants affirmed, because of* **potential consumer mistrust and fear of the process of biotechnology** *and its products. Harlander noted that educating consumers about biotechnology is crucially important, but may be difficult because of the decline of scientific literacy in our society and a deep-rooted mistrust of technology. Taverner reported that in Australia there is both a low level of knowledge of biotechnology and various concerns, differing among regions, as to its desirability. Hoban noted that consumer acceptance of biotechnology in meat and milk production is at best uncertain; significant percentages of major demographic groups - women, religious fundamentalists, the less educated - may be resistant to its introduction. Those who tend to be suspicious of institutional information and policies - seemingly, a growing number - are more likely to oppose the use of biotechnology. Foster stated that consumer anxieties centre on safety, but also include social and ethical issues and a strong fear of the new and unknown. She noted a study in the Netherlands indicating that increased knowledge of the subject is just as likely to lead to greater resistance. Meeker cited surveys showing a very low level of scientific literacy in the United States and the United Kingdom, and noted that decisions affecting the fate of agriculture are often made on the basis of a public opinion far more influenced by the news media than by actual scientific knowledge.*

All participants agreed that in order for biotechnology to be accepted, the critical task of educating consumers about biotechnology must be performed. This will not be simple or easy.

- *Harlander stated that* **scientists could play a vital role in educating the public**, *but few scientists are trained or experienced in such endeavours. Institutions seldom acknowledge the value of communicating complex scientific information to the public, and scientists who become "explainers" may be held in less esteem by their colleagues.*

  Harlander identified university scientists as the most appropriate individuals to interact with the public regarding biotechnology. University scientists who perform this role must be skilful at personal interaction, patient and imaginative. These individuals will likely require media training and substantial support from the university administration. Their key objective will be building coalitions that involve industry, government, and consumer groups in the making of biotechnology research policy. In conclusion, she quoted Abraham Lincoln who said that "Public opinion may not always be right, but it always prevails."

- *Taverner cited the commitment of the Australian government to a* **free and open public debate on biotechnology**, *but also noted that scientists seem to possess a low level of credibility with the public. Further surveys in this regard are needed.*

- *Hoban's research agreed with Harlander's, in that both identified academic scientists as the most appropriate educators of the public regarding biotechnology. Hoban affirmed the* **need for extensive educational efforts and for public involvement in decision-making** *on this issue, but cautioned that some segments of the population may remain sceptical.*

- *Foster detailed European Community and United Kingdom legislation designed to provide adequate safeguards in the approval of biotechnology applications. She further reported on the results of a recent workshop of the International Organization of Consumer Unions, which urged active government enlistment of consumer groups in impact assessment and decision-making and called for government support of consumer research. She noted that* **consumers' concerns and rights should be respected** *and considered, and paternalistic prescriptions and attempts at persuasion should be avoided.*

- *Meeker asserted that* **research scientists and administrators** *must assume some* **responsibility for communicating with the public,** *and noted that the public does perceive the world as being improved by*

the existence of modern science. Scientists must maintain the trust of the public in order to be involved as experts in risk-assessment. The public should be treated with respect, their concerns addressed, and their questions answered. Further, public confidence in regulatory agencies is crucial. Industrial organizations should support the decisions of the regulatory agencies, should make available to the public as much information as possible and should assist in consumer education to ensure the smooth implementation of biotechnology.

- *Summarizing the presentations, Straughan commented on three recurrent themes:*
  - *Safety*
  - *Naturalness and*
  - *Education.*

- **Safety can never be absolute**, *and in* **weighing potential risks and benefits**, *value judgements* **must enter in**. *Concerns about the "unnaturalness" of genetic manipulation stem from a variety of beliefs and value systems, which a significant number of consumers may share. Consumer education is needed to raise awareness, but it cannot guarantee consumer acceptance; scientific experts can explain the science but there are no moral experts to prescribe what is right and wrong.*

- *The cumulative thrust of these presentations is that biotechnology will pose* **major challenges** *to the scientific, regulatory, and industrial communities* **in educating the public regarding its benefits and risks** *and preparing the way for timely implantation. Many skills in the art of communication must be acquired and mastered and new working coalitions will be required. It is possible that even with the best efforts, the complete acceptance of biotechnology by the public may be an elusive goal. Clearly, the key individuals in this complex process are research scientists who, encouraged by government and industry, will work with the public toward a more perfect understanding of the benefits and risks of biotechnology. Further, there must continue to be a mutually respected working relationship between industry, academia and government based on impeccable scientific principles that are comprehensible to the layman.*

- *It undoubtedly would be beneficial to have the* **proceedings of this Symposium prepared in summary** *form for* **wide-spread distribution**. *In this way, the conclusions and recommendations resulting from this Symposium could be broadly shared with the public.*

COMMUNICATION BETWEEN SCIENTISTS AND CONSUMERS

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Summary

After years of speculation and promise, agricultural and food biotechnology are beginning to move from the research laboratory to the barn, the field and the processing plant. The orderly transition from research and development to application and commercialization will depend greatly upon acceptance by the consuming public. For this reason, educating consumers about biotechnology is critically important. Many believe this is an extremely difficult, if not impossible task, due to the erosion of science literacy in this country; a growing mistrust of technology, especially biotechnology; and, fear of the potential long term unanticipated effects of technological innovations. Scientists involved in biotechnology research in industry, government and academic institutions could play vital roles in fostering public understanding and rational discussion of biotechnology issues. Unfortunately, many scientists have had little or no formal training or practical experience in interfacing with the public or the press, and are often ill-prepared to meet the challenges posed by this new educational format. Few institutions recognize the need for and value of communicating complex scientific information in nontechnical and understandable language to the lay public, and the scientist who does become visibly involved in educating the public may be rebuked by fellow scientists. This paper will deal with the changing role of the scientist in society and will provide some suggestions for effective communication of biotechnology issues between consumers and scientists.

Keywords: *biotechnology, communication, scientists, consumers*

Introduction

Being a self-proclaimed cheerleader for biotechnology, I am frequently asked to discuss the potential impact of biotechnology on agriculture and food processing to diverse audiences. I vividly recall my first experience with an audience that was less than enthusiastic about the potential benefits of science and technology for improving the food supply. It was astonishing to me that not everyone shared my enthusiasm for genetically engineered dairy starter cultures, insect-resistant plants, and recombinant bovine somatotropin (rbST).

This audience was not enamoured with the technology I predicted would revolutionize agriculture and food processing in the next decade. They raised concerns about the potential long term unanticipated affects of impacts of products resultant from biotechnology being used to improve efficiency and quality of food production. They were concerned about the

escalating loss of plant germplasm and the potential negative effect of biotechnology on biological diversity, ecology and the environment. Although willing to accept risks imposed by nature, they were outraged by involuntary imposition of man-made risks, especially if risk would be disproportionately imposed on particularly vulnerable members of society -- infants, children, pregnant women, the elderly, or the chronically ill. They were frightened by the pace of discoveries in biotechnology and its pervasive impact on every scientific discipline.

The group was opposed to any technology that might undermine the survival of small family farmers and questioned why the public should support the development of technology that would line the pockets of large corporate agribusinesses while providing few tangible benefits for consumers. They were appalled at the amount of public and private funds being devoted to biotechnology at the expense of research on sustainable agriculture, alternative crops and groundwater contamination. They were disillusioned with the hype and the promises of agricultural biotechnology and the paucity of commercially viable products. They challenged the results of university research funded by manufacturers of biotechnology products and attacked the integrity of university scientists who accepted funding from industry.

They had lost confidence in the ability of federal and state regulatory agencies to protect the safety, wholesomeness and nutritional quality of the food supply. They wanted some reassurance that I and the other scientists and administrators involved in food biotechnology had considered the social, moral, ecological, environmental, economic and ethical implications of this new and revolutionary science. Obviously, the technical and scientific information that I felt most comfortable discussing were not the issues of utmost concern to that audience.

This experience was important to me for a number of reasons:

(1) It sensitized me to the complex issues that surround the acceptance and adoption of new technology, especially biotechnology, by the public.
(2) The issues raised by the audience were representative of the kinds of consumer concerns the scientific community must address in order to convince the public that the products of biotechnology are safe and effective.
(3) It made me painfully aware of the fact that nothing in my previous training or experience had prepared me to deal with these issues in an objective, rational, nondefensive, and compassionate manner.
(4) It marked the first step of a personal journey that has changed my view on the role of the scientist in society -- a view that is not necessarily shared by scientific peers or administrators.

To meet the challenges facing agriculture in the next decade will require the development of new and innovative technologies. Acceptance of these technological advances by the consuming public will be an important prerequisite to implementation. University scientists may be the most appropriate individuals to instill the enthusiasm, explain the benefits, and garner the trust of the public in agriculture and food biotechnology.

Challenges Facing Agriculture

The U.S. is one of the most efficient producers of food in the world; therefore, much of the burden for feeding the rapidly expanding global population may fall on our shoulders. It is predicted that the world's population will increase at a rate of approximately 90 million people annually. At the present time, most of the world's good agricultural land is already in production, and nearly all available irrigation water is being exploited.

In spite of the agricultural chemicals used to control plant pests, 37% of the food supply is lost annually to insects, weeds and plant pathogens. Developing countries experience losses as great as 60-80% of the annual food crops to plant pests and spoilage. The food supply is also vulnerable to natural catastrophes such as droughts, floods, and frost damage. Satisfying global food needs will require increased productivity and efficiency. At the same time, it is critical that increasing agricultural output be done in ways that will not degrade the environment and the natural resource base on which agriculture depends.

Understanding the Food Chain

In spite of these challenges, U.S. consumers have come to expect a safe, nutritious, abundant and affordable food supply. We are accustomed to spending less than 18% of our disposable income on food; yet, few understand how that food is grown, processed, or distributed. Eliminating the use of agricultural chemicals could result in produce that differs in appearance, taste, texture, nutritional quality, shelf-life, safety, and cost, when compared to traditional products. Only 2% of the population is involved in growing food for the entire nation. Unfortunately, although agriculture, food and nutrition are central to human existence, these topics are rarely emphasized, or even discussed, in elementary and secondary schools. With the lack of knowledge about food, one can understand why the public becomes outraged when they hear reports about Alar in apples, pesticides in ground water and *Salmonella* in poultry or eggs.

Assuring the Safety of the Food Supply

The United States enjoys the safest food supply in the world. The U.S. Food and Drug Administration has primary responsibility for insuring the safety of the food supply, and they have done an exemplary job. Unfortunately, few understand the regulatory process for approval of new food ingredients or animal drugs and biologics. As part of the approval process, companies are required to provide extensive evidence of human safety and efficacy. Although much testing may be done internally, results must be confirmed by independent laboratories. Human drugs are frequently evaluated by University Medical Schools that conduct well-controlled human clinical trials. In the same way, animal biologics may be evaluated by Animal Science departments or Veterinary schools; food ingredients may be tested for performance and nutritional impact by Food Science and Nutrition departments. Such testing is expensive and absolutely essential, and federal funds are not available. The expense is, and should be, born by the companies developing the products. Approval is dependent upon a rigorous review of all available data by the regulatory agencies. Although

this can be a painfully slow and expensive process for companies developing new products, it has worked very effectively for assuring the safety of the food supply. Such a system is absolutely essential.

Who Supports Your Research?

Just as few consumers understand how the safety of the food supply is ensured by regulatory agencies, how research is funded by industry at universities is also not well understood by the general public. Universities have developed guidelines for interaction with industry that protect the rights of University scientists to design research protocols, conduct research unhindered, and publish their data in peer-reviewed journals. Confidentiality, financial arrangements, and patent and licensing rights are established in agreements generated and approved by the University.

Despite these personal and institutional safeguards, some believe that it is inappropriate for universities to accept research funding from industry. They suspect that industry will control the outcome of research or suppress the open communication and dissemination of facts if the results are not favourable to industry's purpose. The integrity of an industry-funded University scientist may be questioned by consumer groups or the news media. This will become increasingly troublesome as federal funding for basic research continues to decline, and pressure for universities to seek alternative sources of funding from industry or non-profit institutions to support research and training activities increases.

It goes without saying that rigorous standards to guide industry funding of research at universities must be maintained, and these standards shared openly and honestly with the public. The vast majority of scientists will not jeopardize their most precious asset -- their scientific integrity -- and the public needs to know this fact. Industry must openly acknowledge and support the requirement that universities be objective and unbiased in their research pursuits.

In general, University scientists have enjoyed the confidence and support of the majority of the consuming public. Numerous surveys indicate that scientists are one of the most trusted sources of information; therefore, University scientists may be the most appropriate individuals to instill the enthusiasm, explain the benefits, and garner the trust of the public in agriculture and food biotechnology.

Who Should Communicate with Consumers?

Not all scientists should be involved in communicating with consumers. It is important to recognize that some scientists lack the communication skills necessary to simplify complex information in language that is understandable to the lay public. An arrogant and defensive scientist would not gain public trust. Scientists cannot expect to be trusted simply because they are the experts. When challenged or threatened, it is common for some scientists to resort to familiar technical jargon. These scientists best serve society by staying in the laboratory.

The scientists that communicate with consumers must be people-oriented individuals who are sincere and compassionate. They must be able to empathize without trivializing consumer concern. They must accept and affirm those concerns, even if they fly in the face of all scientific evidence or appear irrational to the majority of the scientific community. The concerns are real to the consumers who believe them, and it is the role of the scientist to bring to bear all of the scientific evidence available to address the concern. Scientists must also be willing to acknowledge where data is insufficient to answer the question. They must be open to divergent opinions, be honest, forthright and nondefensive, and not fearful of being personally and professionally challenged. Patience, a sense of humour, and a thick skin are also definite assets.

Interacting with Advocacy Groups and the Press

The public receives much of their science education from the news media. Advocacy groups are also frequently involved in educational efforts that espouse their particular cause. Consumers may perceive that advocacy groups and the press provide information not readily available from industry or government, or intended to counterbalance information provided by these agencies. Scientists are often reluctant to interact with the press for fear they will be misquoted. As a result, articles that appear in the press do not always contain balanced, factual information. To interact effectively with the press, it is essential that scientific information be presented in understandable language. Yet to the scientific purist, simplification of technical information could lead to misunderstanding by consumers, or worse yet, peers, who might question their motives for speaking to the press on controversial issues.

Many academic scientists who have had to respond to inquiries from the press or advocacy groups are quick to share their bad experiences. In addition, they are frequently ill-prepared to be challenged and may respond very defensively if they perceive they are being attacked. If the press handles an issue unfairly or incorrectly, it is important that they be challenged and corrected. Scientists need to be encouraged to develop personal relationships with science or food editors of local newspapers and take time to educate them on complex scientific issues, realizing that it will take a proactive approach and lots of time will need to be invested.

The scientist must be recognized as a trusted, responsive and reliable source of information to the news media. Although we are often quick to criticize the press, it is important for scientists to understand the pressures and time restraints inherent in the job of reporting the news. Advocacy groups have developed sophisticated communication systems to keep the press informed on various issues. Scientists, on the other hand, rarely communicate with the press unless contacted. If scientists are not available or willing to provide balanced information on an issue, the reporter has little choice but to report what information is available. Scientists should and must provide accurate and objective information to the press and assist in their efforts to translate the technology for the general public.

Professional Training

For those scientists that elect to become involved in educational outreach activities, professional media training on the most effective ways to communicate with the public and the press must be provided on an ongoing basis. It is important to recognize that classroom teaching is very different than communicating with consumers or the press, and few faculty members have any practical experience in these areas. Any scientist who has been misquoted may likely avoid future encounters with the press, and few understand how to control an interview. Proficiency comes only with a great deal of practice. Role playing, video and audio recording of mock interviews, testing of responses to hostile questions or personal attacks, assistance in capturing key thoughts in "sound bites", instructions on how to effectively communicate key points in interviews with newspaper, radio and TV reporters, and peer evaluation, are critical activities for improving communication skills. Each successful experience builds confidence and reinforces the value of the activity for the scientist.

Administrative Support

It is critical that administrators recognize and affirm that communication with the public is an obligation of University scientists and is a highly valued activity. Administrators must provide continuous and visible support for those scientists willing and able to participate in outreach activities. This could include release time from other academic responsibilities, verbal support, and recognition of contributions as an expected and valued activity for promotion and tenure considerations. Highlighting consumer education as an integral part of the mission statement of the unit is also important. In at least some cases, the best communicators may also be the best researchers and teachers, and commitment to consumer education will necessarily detract from these activities.

Building Coalitions

Academic institutions could serve a vital function by bringing together groups with divergent opinions to discuss issues related to agriculture and food biotechnology. Although this may be a painful process, particularly if advocacy groups with radical or anti-technology viewpoints are represented, this activity is extremely important. Open discussion of the concerns of farmers, consumers, advocacy groups, industrial scientists, and government agencies provides valuable information that could help guide research programs at land-grant institutions. These groups do not need to control the research agenda at academic institutions, but their input should be actively sought and acknowledged. If these groups participate and take ownership in the process of providing input and feel their opinions are valued, implementation of biotechnology in agriculture and food will be more readily accepted. Not all scientists and administrators need to participate in this process. Individuals who are compassionate, sensitive to the needs of people, and unafraid of being challenged should be encouraged to participate.

Prospects for the Future

Biotechnology appears to offer viable solutions to many of the challenges that face agricultural and food systems; however, if the public does not accept the technology, it simply will not be used. Eroding scientific literacy coupled with growing mistrust of technology creates an enormous educational challenge -- a challenge that demands our attention. To be successful, we must:

- Encourage enthusiastic, communicative, and caring scientists to discuss biotechnology with consumers.
- Communicate in language understandable to the general public.
- Acknowledge public concern and listen to consumer fears in a sensitive, compassionate and sincere manner.
- Involve the public in making decisions that will impact their communities and their lives.
- Provide both sides of the story to the public so they can make informed choices.
- Reassure the public that appropriate regulatory systems are in place to protect the safety of the food supply.
- Provide administrative support and training for those scientists who are willing and able to communicate with the public.

In the long term, it is essential that we begin to address the problem of eroding scientific literacy in this country. We must institute educational programs at the elementary and secondary school level on how food is grown, processed and distributed. Colleges and universities need to recognize that a basic understanding of agriculture, food and nutrition should be a component of a liberal arts education, and work to develop appropriate courses of general interest to all students. It is also important to recognize that industry, government and academic scientists must share the responsibility of educating the public about challenges that face agriculture and food systems and the potential benefits of science and technology.

Suggested Readings

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DETERMINANTS OF PUBLIC ACCEPTANCE IN AUSTRALASIA OF BIOTECHNOLOGY FOR THE CONTROL OF GROWTH AND PRODUCT QUALITY IN MEAT PRODUCTION

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Summary

Within this region there is extreme variation in the methods of meat production and marketing. Different socio-economic conditions throughout the region will affect public attitudes to biotechnology.

In determining attitudes to biotechnologies affecting the production and quality of their dietary meat, the public will "weigh" perceived advantages of price and product quality against perceived disadvantages of product safety, animal welfare, ethical and moral issues and environmental concerns.

The public is making this assessment with little understanding of biotechnology: in NZ, only 9% of the public claimed they could explain biotechnology to a friend.

Scientists, environmental groups, authoritative public agencies and government will help form public perceptions regarding the acceptability of biotechnology in the production of meat. However, studies in NZ show that scientists have poor credibility with the public while in Australia, environmental groups have gained high exposure and credibility.

There is a need for greater public awareness of the social and economic benefits, possible hazards and the controls used to minimise these risks. However, the task is made difficult by the lack of clear government and meat industry policy on the issue and the lack of specific studies of public attitudes to biotechnology in meat production.

Keywords: *Australasia, biotechnology, acceptability.*

Introduction

Australasia is a very diverse and rather ill-defined region. In the past, it has been taken to include Australia and its geographical neighbours New Zealand (NZ), Papua New Guinea, Indonesia, Singapore, Malaysia and the major island groups in the Pacific Ocean.

While the production and marketing of meat in Australia and NZ have much in common, these two countries have little in common in this regard with other countries in the Australasian region.

In Australasia, the major and distinct markets likely to influence the production and marketing of meat and hence public acceptance of new biotechnologies in meat production, are those in Australia and NZ, S.E. Asia and Japan.

This paper will cover the general features of these markets, but will focus on the situation in Australia and NZ where there is more data, experience and activity in the area of biotechnology for the control of animal growth.

Features of the meat markets

The meat markets of Australasia and other countries around the Pacific rim have little in common. They vary from the extremes of finesse in presentation and hygiene in Japanese supermarkets to the market stalls of South East Asia where the consumers demand freshly slaughtered (warm) pork.

The consumers of Australia and NZ purchase the majority (70%) of their meat from specialist meat retailers (butcher's shops) rather than supermarkets.

The projected per capita consumption of meat (excluding fish) in 1990 in these regions is greatest by Australians (77 kg) and New Zealanders (79 kg) with considerably lower figures in countries such as Taiwan (39 kg) and Japan (27 kg).

The countries also vary in their self sufficiency for meat. Australia exports nearly half (46%) of its total red meat production, while Japan is only 70 - 80% self sufficient for meat.

In competing for this share of the lucrative Japanese meat market, the Japanese standards and expectations for meat quality and safety become highly influential. They influence events in the Asian region and beyond.

Features of consumer perceptions of biotechnologies in meat production

In assessing their acceptance of biotechnologies affecting the production and quality of their dietary meat, consumers will be looking at the "trade-offs" i.e. balancing the advantages and disadvantages from their perspectives.

Perceived advantages

Price

Studies of the economic impact of agricultural biotechnology, such as that reported by Lemieux and Wohlgenant (1988) for porcine somatotropin suggest that through its influence in reducing pork prices, the net benefits to the consumers will be between 2 and 3 times greater than to the producer.

Biotechnologies are expected to have a major influence in ensuring minimal meat price increases. The extent to which this advantage is perceived by consumers has not been established. Indeed, ironically it might be that by making food cheaper than it would be otherwise, biotechnology could be encouraging consumers to become more indulgent in their demands of food products.

Product quality

In most markets and for most meats, the major determinants of quality appear to be colour and leanness.

For example, surveys of consumer behaviour with pork in Japan in both 1983 (Takase et al., 1985) and 1989 (Koizumi et al., 1990) found that meat colour and the amount of fat in the meat were the most important determinant of quality - in both surveys between 19 and 20% of housewives judged fatness to be a major determinant of quality. Pork colour however, was judged by more than one third of respondents as the most important determinant.

The Australian public is well exposed to the health benefits of lean meat. Consumers have been under constant pressure to decrease dietary intake of saturated fats.

Although in the early 1980's consumers had overriding concerns regarding the adverse health implications of eating meat, advertising has changed consumer attitudes towards meat. Recent consumer research reported by the Australian Meat and Livestock Corporation in its Meat Marketing Trends (March 1990), indicates that consumers now believe that they had earlier been misinformed by the media on meat.

More consumers now regard nutritional value as a reason for their continual use of meat. For example as shown in Figure 1, the proportion of consumers throughout Australia who believe beef and lamb to be "good for you", increased from 69% in 1985 to 87% in 1988.

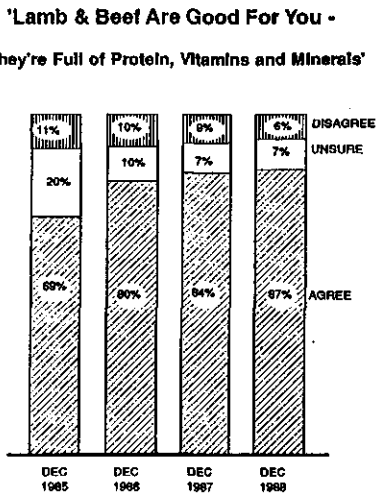

Figure 1. Consumer awareness of the nutritional benefits of meat (from Meat Marketing Trends (March 89)

Advertising in Australia has promoted "new" meat i.e. lean and served in smaller portions, in contrast to "old" meat described as thick and fatty, i.e. created the impression of a new meat with improved quality. There are possible analogies for meat produced using new biotechnologies.

In their survey of over 2,000 of the New Zealand public, Couchman and Fink-Jensen (1990) found that 66% of respondents perceived benefits on genetic engineering of animals. (In contrast, 88% perceived benefit from the genetic engineering of plants.)

Of those who recognised the benefits, only 11% said it would contribute to better meat. The most recognised benefit of genetic engineering (38%) was that it would help improve stock and animal products.

Perceived disadvantages

The debate on these biotechnologies for meat production will inevitably be associated with the increasingly public debate in Australia and NZ on genetic engineering.

Couchman and Fink-Jensen(1990) found that while 73% of the NZ public had heard of genetic engineering, just over half (57%) had heard of biotechnology. Furthermore, although only 9% claimed they could explain biotechnology to a friend, more than 20% said they could explain genetic engineering.

Among the NZ public, the survey indicated that the highest level (48%) of concern among various products of genetic engineering was for the use of meat. However, more than half of the respondents were **not** concerned about eating meat of genetically engineered animals.

Table 1. Incidence of concern about using genetic engineered produce (%)

Subject	Incidence %
medicine	34
meat	48
vegetable	38
dairy	43

(Couchman and Fink-Jensen, 1990)

The nature of the concerns of the public with eating this meat were primarily that the meat was unnatural (27%). However, they were also concerned that there may be unknown effects from eating such foods (21%), that they did not know what they were eating (15%), product safety (9%), lack of information (9%), animal cruelty (5%) and other minor concerns.

Product safety

In Japan, consciousness among housewives of the 'sanitary condition of pork' rated 3.2 on a scale of 1 to 7.

In both 1983 (Takase et al., 1985) and 1989 (Koizumi et al., 1990), nearly 40% of Japanese housewives considered the safety/sanitation of pork an issue. Of these, the major problem (86%) was thought to arise from the use of medicines for the pig.

In another survey conducted in Japan by a Consumers Co-operative who provide "chemical free" meat to their members through special contracts with farmers, about 40% of their consumers were concerned about the residue of "hormone and antibiotic".

Although this might be an extreme group and while the Japanese housewife might be more sensitised to food safety than those in Australia, there does appear to be a growing public awareness of potential residues in meat.

Nevertheless, while media prominence in Australia has been provided to pesticide residues in beef and while about half of Australia's beef is produced using hormone therapy, public attitudes towards beef in general have maintained a positive profile.

Animal welfare issues

Couchman and Fink-Jensen (1990) asked an open-ended question regarding the nature of concerns about using meat from genetically modified animals. Only 5% of respondents mentioned animal cruelty and these concerns were with the wellbeing of the animal as well as the moral issues of animal use. Similarly, of those (58%) who considered that there were serious risks involved in genetic engineering of animal cells, only 6% identified the risk of animal abuse.

Thus in New Zealand, animal welfare issues appear not to be perceived by the public as a major disadvantage of biotechnology in meat production.

Ethical and moral issues

In a recent Australian report, the Victorian Law Reform Commission focused on identifying aspects of genetic manipulation work that may present particular risks or arouse particular public concern.

They found general moral concerns about genetic manipulation; despite the achievements of genetic manipulation and its future promise, some people are deeply concerned about the fundamental moral implications of this technology.

Because it "interfered with nature", genetic manipulation of human cells was least acceptable to all groups in the NZ survey (Couchman and Fink-Jensen 1990). However, more than half (56%) of the respondents considered that the manipulation of the genetic material of animals was acceptable.

Environmental concerns

The apparent concern of Australian consumers for environmental issues was reflected in recent consumer research that identified the desire of consumers for "environmentally friendly" packaging of meat products.

Indeed, the Victorian Law Reform Commission identified widespread public concern about the potential environmental effects of releasing recombinant organisms.

This is an emotive area upon which pressure groups have seized for their advantage.

Major influences on public opinion

There are a number of major influences which help form these perceptions of consumers regarding the acceptability of biotechnology in the production of their meat.

Scientists

Couchman and Fink-Jensen (1990) assessed the credibility among the NZ public of both public sector and corporate sector scientists. They sought the reaction of respondents to statements of either public or corporate sector scientists endorsing the safety of a research project. While 36% would believe the public sector scientist, only 28% would believe the company scientist.

There were 20% of the respondents who would not believe the public sector scientist, and the remaining 52% remained undecided.

Despite a strong positive perception of science among New Zealanders, Couchman and Fink-Jensen (1990) found strong concerns about possible hazards of science and the desire among the public for tighter regulation.

Clearly, because of their poor credibility in relation to product safety, scientists may not be the most appropriate group to influence public opinion.

Environmental groups

The environmental movement has the Australian farming community on the defensive. Everyday farming practices are under scrutiny from a lobby movement and a media that is suspicious of the environmental credentials of scientists and farmers.

For example, the Australian Conservation Foundation (ACF) issued a press release stating that there had been a cover-up with regard to the release of transgenic pigs in Australia. They indicated there had been unauthorised sale of genetically modified pigs in South Australia.

They were concerned with three points:

- the possible impact of biological diversity if extra hormone genes transferred into feral pigs or other domestic animals;
- human health aspects of eating engineered animals and,
- welfare considerations.

The media reported this story with enthusiasm: following this press release there was a front page headline, "Mutant Meat", describing the ACF release in some graphic detail.

Three or four days later on page 13 of the same newspaper there were some further stories which presented a more reasoned and detailed account of the whole incident. It was clear, for example, that many of the allegations made by the ACF were not true but in fact that the National Health & Medical Research Council (NH&MRC) had assessed the human health aspects of eating these particular animals and approved them for human consumption.

All the correct protocols involved in transportation of these animals so that there was minimal risk to their release to the environment were followed and, similarly, in terms of animal welfare, this aspect had also been covered.

Indeed it seemed that many details of every transaction had been scrutinised by ethics committees at various levels.

The NH&MRC and the State Health Commission both approved the slaughter and sale of the pigs which they agreed were no different to normal animals. This has been public information. Nevertheless this manipulative misreporting of the incident has almost killed this research project.

The ACF has now called for a moratorium on the further release of genetically engineered organisms "into the environment".

Environmental groups such as the ACF, will ensure that developments in genetic engineering in agriculture will be a debate that will occupy the nation in the 1990's.

However, apart from this incident with transgenic pigs, the Australian public have had little exposure to these biotechnologies and there is little general understanding or knowledge of biotechnology.

While the NZ study of Couchman and Fink-Jensen suggests that the concern and an apparent lack of knowledge of these new technologies in agriculture may hamper vital research, this same lack of knowledge could used to the advantage in their introduction.

There has been little reporting in Australia of research relating to the use of hormones in animal production. There has been no rbST issue and no public reaction and alarm concerning perceived risks to human health through milk supplies etc.

Public health authorities in Australia and New Zealand have not stated any clear position for or against the technologies.

Authoritative public agencies

The Australian National Heart Foundation has endorsed lean meat as a healthy product. The support for biotechnologies leading to leaner meat production from respected groups such as these would be extremely influential with the public.

In recommending legislation on the issues involved with genetic manipulation, the Victorian Law Reform Commission recommended:

- Genetic manipulation should not be limited in any general way.
- The Genetic Manipulation Advisory Committee should continue to advise and monitor genetic manipulation work.
- Specific legislation should be enacted to control experimental releases of recombinant organisms into the environment.
- Regulation of products manufactured by genetic manipulation techniques should not be specifically regulated for quality control. They should continue to be regulated on the basis of their intended use in the same way as other biological products.

The Law Reform Commission did not believe that genetic manipulation was wrong on either religious or ethical grounds:

- The use of genetic manipulation to improve agricultural animals was judged to be basically a more controlled and refined means of the long-established practice of planned breeding.
- DNA is not a sacred substance.

They did recommend however, that to assuage public fears on this issue there is a need for community education on recombinant DNA techniques. Despite the fact that public information and participation:

(a) might unduly hinder and delay scientific progress;
(b) might seem unnecessary considering that government agencies generally approve and oversee the work and represent the public;
(c) would impinge on the confidentiality of new procedures and products that must be protected for commercial reasons,

the Commission believed it is not justified to withhold information from the public about proposed releases.

The Australian Shadow Federal Minister for Science and Technology, Mr Peter McGauran stated:

"We must endeavour to ensure the public discussion takes place in a sober atmosphere which enables a balanced assessment of both the risk and benefit of genetic engineering.

Public confidence is essential and it must be built on an understanding there will be a rational and scientifically based assessment of all risks associated with the release of genetic material."

3.d.Government policy and legislation

The Australian Government Agricultural and Veterinary Chemicals Committee are currently considering their policy on rbST and rpST.

Trade issues will clearly play a major role in deciding government attitudes to specific biotechnological products.

As Australia exports nearly half of its total red meat production, the relevant requirements of importing countries regarding the use of these biotechnologies will influence regulatory authorities in Australia on this issue. The Australian Quarantine and Inspection Service must comply with importing country requirements for the purposes of export trade. For example, with the EEC ban on the use of hormonal growth promotants, a system has been developed to ensure that meat and offals from animals treated with growth promotants are not exported to the EEC.

Government policy on these issues is currently being formed: the Australian government are currently holding a Parliamentary Inquiry into genetically modified organisms.

The timing of this inquiry would appear to be stimulated by the publicity surrounding the "unauthorised release" i.e. the transporting of genetically altered pigs from the research facility to the abattoir (see 3.b). Preliminary statements from the inquiry committee include:

" Clearly the time has arrived for a detailed public examination of these issues and of the regulatory framework that should be in place to provide whatever safeguards might be needed

In NZ, legislation governing the release of genetically modified organisms is to be tightened under a new environmental body - the Hazards Control Commission, which will be responsible for all phases of genetic engineering.

Conclusion

The public in various parts of this diverse region of Australasia could be assumed to have different determinants of non-acceptance of new biotechnology in meat production. In Japan, food safety appears to be the major factor; in Australia and NZ, ethical and environmental issues appear to be important; while in Southeast Asia there appears to be very few specific public attitudinal barriers to new biotechnology. In all cases however, there is a lack of data to support these assumptions.

Experience in Australia with public reaction to genetically engineered pigs indicated that the risk to human health was not the major issue. At the heart of the controversy concerning the sale of meat from genetically engineered pigs to South Australian consumers was the community's concern that it be involved in decisions about products arising from controversial biotechnologies such as genetic engineering.

The data presented by Couchman and Fink-Jensen (1990) indicate that in NZ, the level of public understanding of genetic engineering is low and that of "biotechnology" even lower. It would be expected that the level of public awareness and understanding of biotechnology in Southeast Asia would be even lower than in NZ or Australia.

As suggested by Couchman and Fink-Jensen (1990) a dialogue between scientists and the public is needed to:

- inform the public of the social and economical benefits of biotechnology, the possible hazards, and the controls in place to minimise these risks;
- ensure that research organisations are aware of public concerns and that they take account of them in their research practice (especially ethical and safety considerations).

It would seem however, that because of the low credibility of scientists with the public, research is required to determine how to implement an effective and credible dialogue.

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DETERMINANTS OF PUBLIC ACCEPTANCE IN MEAT AND MILK PRODUCTION: NORTH AMERICA

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Summary

Consumer response to the products of biotechnology is neither well understood nor fully appreciated. Relatively little attention has been paid to public attitudes about biotechnology, relative to the time and money spent on research and product development. This is problematic because consumer acceptance will determine the ultimate success of any new biotechnology products used in meat and milk production. Such acceptance is, by no means, assured.

This paper presents a case study of public attitudes about the use of biotechnology in meat and milk production. Results are presented from a telephone survey of 332 North Carolina consumers. We examine consumer attitudes toward animal biotechnology along four main dimensions: desirability of bovine somatotropin; desirability of genetic engineering to produce larger or faster growing livestock; belief that genetic engineering of animals is morally wrong; and concern over eating genetically engineered meat or dairy products. We develop and test a theoretical model that analyzes the factors that influence these attitudes. Our model builds on theories of risk perception and ethics.

Definite concerns exist among consumers along a number of dimensions. We find that certain groups will be less likely to accept the use of biotechnology in meat and milk production. Women and people with less formal education will find genetically engineered products to be less acceptable. Acceptance of the use of biotechnology will be conditioned by underlying beliefs and values. People who are more concerned over the risks of biotechnology will be more likely to find the products less desirable. Finally, people who have more trust in institutional information and policies are more likely to accept the use of biotechnology in meat and milk production.

Keywords: *public attitudes, consumer acceptance, social implications, ethical values.*

Introduction

Biotechnology is clearly developing under intense public scrutiny. Citizens are becoming increasingly concerned about new technologies. In particular, the public now considers certain agricultural technologies (e.g., farm chemicals) as potentially dangerous because residues and byproducts have been identified in the food and water supply. The use of biotechnology in meat and milk production could elicit concerns like those expressed about

agricultural chemicals. In addition, other dimensions of biotechnology will also raise public concerns. Bentley (1987) argues convincingly that public opinion will influence the future direction of biotechnology.

We need to realize that some people may react negatively to the perceived impacts associated with anything new. If the gap between public understanding and technological advance becomes too large, research and development will be slowed. Our challenge is to explain biotechnology in a way that the public can understand. This presents a serious challenge given the complexity of biotechnology and the prevailing climate of public opinion about science and government. Public attitudes and concerns should be more thoroughly researched, understood, and considered before developing new products, educational programs, and public policies. It is clear that the public and scientists need more information so our society can determine whether biotechnology will have any adverse impacts.

Because very few products have yet reached the market place, it is very difficult at this point to accurately describe public opinion about biotechnology. Berrier (1987) suggested that because we are early in the development of agricultural biotechnology public awareness is still very low. Another problem is that the public is very heterogeneous in its attitudes and knowledge toward biotechnologies (Klassen 1987). The few attempts that have been made to anticipate public concerns over biotechnology have been based more on informed speculation than careful analysis.

The Office of Technology Assessment (1984) summarized five main arguments frequently raised in public debates about genetic engineering and biotechnology. The first involves debate over what levels of health, environmental, or social risk should be considered acceptable and allowed. Benefits and risks are complex and difficult to systematically evaluate. A second reason biotechnology may prove controversial is that scientists will be increasingly able to modify and manipulate living organisms. Some opponents of genetic engineering argue that humans should not "play god" by manipulating the genes of humans or other organisms. Proponents of genetic engineering argue that we have manipulated genes for thousands of years through selective breeding. Opponents respond that genetic changes have so far been limited and did not involve crossing fundamental species barriers. Moral and ethical issues associated with biotechnology, therefore, deserve greater attention.

A third area of controversy involves concerns over loss of genetic diversity. Opponents of biotechnology argue that genetic manipulation may result in decreased genetic diversity with a resulting loss of species' resistance to future threats. Others argue that biotechnology will, instead, increase the gene pool available for human exploitation. The fourth controversial area involves freedom of scientific inquiry. Some people argue that scientists should be able to pursue any line of inquiry they choose. Others feel that some forms of research should be subject to greater restraint. As science starts to involve some form of action (rather than just thought) it becomes subject to legal and moral constraints like all types of action. The debate centres over who should regulate scientific inquiry and technology development. The final area of controversy described by OTA involves the notion of a technological imperative. Some argue that what is technologically possible will

eventually be done, regardless of ethical or moral guidelines. A variety of factors, including the profit motive, influence the development of scientific knowledge and technology.

Several specific factors could limit consumer acceptance of the use of biotechnology in meat and milk production. Recent public concerns over risks associated with food safety may cause consumer opposition if they are led to believe their food is "contaminated by biotechnology". We must realize that the public does not respond to technology based on a rational calculation of the actual hazards (Sandman 1987). They respond based on values, emotions, and outrage rather than rational and scientific analysis. Public understanding of science and technology is low, even among people with a lot of formal education. Public reaction to technology is easily manipulated by mass media coverage and special interest groups. Rogers (1987) explains that "we are faced with a level of scientific illiteracy in this country that is truly frightening." Biotechnology is moving too quickly for the public to integrate its advances into their existing educational, religious, and social frameworks. As the gap between public understanding and scientific advance grows too wide, people may try to slow progress in order to have time for further analysis and understanding.

Moral or ethical issues could also limit consumer acceptance of the use of biotechnology in meat and milk production. People with strong, fundamental religious convictions may oppose genetic engineering, especially when applied to animals and humans. They may feel we are "playing god". The growing animal rights movement can be expected to become very concerned with genetic engineering of animals. Moral and ethical concerns also arise over equity issues. Many groups are concerned about potential socio-economic impacts on farmers and rural communities. Some members of the public will believe that biotechnology may lead to an uneven distribution of benefits and costs.

Even if public concerns do not fit technical reality, (in terms of the health, ecological, and social impacts) these concerns could greatly limit the application of even safe biotechnological applications. MacKenzie and Berrier (1987) explain the public's perceived risk of genetic engineering experiments or products may not necessarily be the same as the real risks. A portion of that perceived risk will represent fear created by lack of knowledge or understanding. Although these risks may not be well founded from a scientific standpoint, they deserve to be addressed. In most cases, what people **believe** to be real is often translated into real consequences, especially as related to public policies and consumer behaviour.

Wyse and Krivi (1987) argue that biotechnology is "destined to become a major component of our society, one that will greatly impact our lives, one that can stir people's strongest emotions, and one they know little about." They argue that biotechnology has the potential to elicit strong public outrage for the following reasons:

1. The public does not now understand biotechnology or its potential uses. A huge non-attentive public exists that can be easily influenced by emotional appeals.
2. Biotechnology has important social, economic, ethical, and moral implications associated with its use. Therefore, it has the potential to arouse strong public reaction.
3. Some products of biotechnology could have a component of environmental risk associated with the release of engineered organisms into the environment. Although the probability of this risk is low, the potential impacts are high.

There can be little doubt that the new biotechnology has generated, and will continue to generate, considerable controversy and debate both within the scientific community and in the larger public forum. Agricultural biotechnology and its commercial products are in their infancy relative to the medical and pharmaceutical fields. However, consumer advocates, environmentalist groups, and even some farm groups have begun to challenge the legitimacy of certain types of research and product development. Lawsuits have been brought against both public and private researchers and research institutions. Two state legislatures (i.e., Wisconsin and Minnesota) have placed a moratorium on the marketing of a biotechnologically-produced product (i.e. rbST). Other state governments (e.g., North Carolina) and the federal government have become involved in the oversight of this technology to an extent unprecedented except perhaps for nuclear technologies.

Although debate and disagreement have long surrounded science and technology development, agricultural biotechnology will provide a major "test case" for a variety of long-standing ethical and public policy issues associated with the practice of agricultural science and the larger public interest. Among these are:

1. The mission of agricultural research: Toward whom and to what ends should publicly-sponsored science be directed?
2. Agenda Setting: How are and should the clientele and goals of agricultural research be determined?
3. Technology transfer: What is the proper role of public institutions, private industry and individual scientists in transferring the technologies that agricultural science produces?
4. Science and technology policy: What are the legitimate roles of government at all levels in supporting, promoting, or constraining agriculturally-related technologies with an eye toward the public interest?

A full examination of these and related issues is beyond the scope of this paper (see Busch et. al., 1991). There is, however, a deeper background issue, that could help orient discussion of these kinds of questions. This issue concerns the larger public context in which decisions on agricultural science and technology are now made. Observers have noted for many years that agricultural science is no longer an "island empire" (Mayer and Mayer, 1974). Decisions about research goals, clients, extension efforts and even farm-commodity policy are now made with an eye toward the larger public, both rural and urban. Indeed, decisions must now recognize that various groups are monitoring the real or potential effects of science and technology on a variety of "publics." Consideration of these effects, and these nonfarm publics, must increasingly be a part of the agenda for decision-makers from the Federal level down to the bench science level.

There are both philosophical and practical reasons for this. Philosophically, both public and private science should ultimately serve and not undermine the public interest, however that might be defined. From a practical standpoint, failing to consider these publics may result in reduced levels of support, lawsuits, rejected patents, and even enforced redirection of the research effort. We believe that public attitudes and beliefs about the use of biotechnology in meat and milk production must be given greater attention for both philosophical and practical reasons.

There can be little doubt the larger public has revealed preferences for biotechnology products, as well as deeper attitudes toward science and technology. Public reliance on communication, transportation, and biomedical technologies is a given. The rate of adoption of new consumer technologies is staggering. Our culture has been characterized as having a pro-technology or "technophilic" attitude (Drengson, 1982). Nevertheless, there is an undercurrent of "technophobia" as well, particularly among some groups. In this paper we describe research on the extent of technophilia and technophobia with respect to the use of biotechnology in meat and milk production. We offer some tentative explanations for these differential attitudes. We then draw some conclusions regarding the significance of these differential attitudes for the agenda-setting, extension, and governmental oversight efforts with respect to biotechnology.

The goal of this paper is to analyze some factors that could influence consumer acceptance of the use of biotechnology in meat and milk production. To do this we develop and test the conceptual model shown in Figure 1. We have included several demographic variables and religious orientation as background characteristics that reflect inherent differences among respondents in our sample. Two sets of intervening variables are included that mediate the influence of background characteristics on acceptance of biotechnology, in meat and milk production: awareness of and attitudes toward genetic engineering; and confidence in institutions to manage genetic engineering.

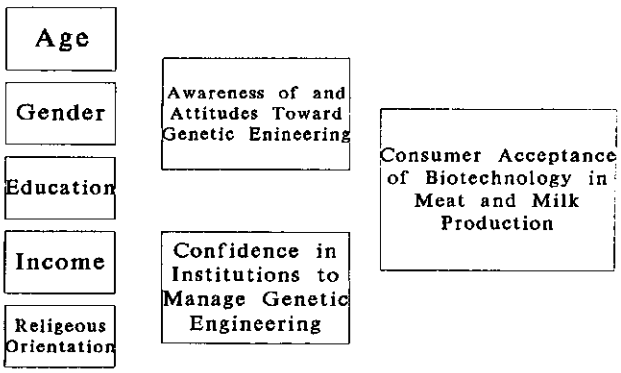

Figure 1 Conceptual model of determinants of consumer acceptance of the use of biotechnology in meat and milk production.

Research methods and results

After we describe our data collection procedures, we present our analysis at three levels. First, we present the univariate frequencies for all the variables included in the model. Second, we describe the bivariate relationships among certain independent variables, as well as the relationships between the independent variables and a four-item scale of consumer acceptance. Finally, we use multiple regression to analyze the relative influence of the various independent variables on consumer acceptance of biotechnology in meat and milk production.

Data Collection Methods

This research involved telephone interviews with a random sample of people over 18 years old drawn from specific areas of North Carolina[1].

Telephone interviews, lasting about 20-25 minutes, were conducted during December of 1988. A total of 332 telephone interviews were completed. After removing ineligible phone numbers, the overall response rate for the survey was 62 percent. Telephone interviews were conducted by the Applied Research Group at North Carolina State University which has extensive experience conducting these types of interviews.

Our goal was to interview respondents from two main areas: highly agricultural rural areas and the state's three largest urban areas. Counties ultimately included in this study were selected based on several criteria. The three largest urban areas in North Carolina (by population) were selected: Charlotte, Raleigh, and Greensboro. Our goal was to complete the same number of interviews (55) in each metropolitan area. Selecting the rural agricultural areas presented more of a challenge. Given the diversity of North Carolina agriculture, we wanted to obtain information from counties representing the full range of agricultural enterprises and geographical areas in the state. We sampled counties to represent major conditions in the state. Our goal was to balance crop and livestock areas and complete about the same number of interviews (32) in each of the rural counties. Five highly agricultural rural counties were selected that had 70 percent or more of their population living outside of incorporated areas. Telephone numbers were generated using random digit dialling from the telephone exchanges from the areas of interest.

One other methodological point is important to note. The interviews focused exclusively on genetic engineering, instead of the more general set of techniques included under the term "biotechnology". We made this decision for two reason. First, genetic engineering is a more concrete concept then biotechnology. On the other hand, biotechnology" means different things to different people. The second reason for focusing on genetic engineering was that it will be the most controversial type of biotechnology and will, therefore, raise the most public concern. We defined genetic engineering for respondents, as follows: "Scientists have new knowledge about biology that they can use as tools to solve problems. Genetic engineering is one of these new tools. In genetic engineering, genes are taken from one kind of plant or animal and put into another kind."

Univariate results

Several background demographic variables (i.e., age, gender, education, and income) are included in the model. More (59%) women were interviewed than men (41%). Respondents' ages ranged from 18 to 85. The average age of all respondents was 42 years. Respondents'

[1] *Support for this research was provided by the following: the N.C. Biotechnology Center, the N.C. Agricultural Extension Service, The N.C. Agricultural Research Service, and Ciba Geigy. The conclusions presented in this paper are those of the authors and do not necessarily reflect those of the sponsoring organizations.*

educational levels were as follows: eight years or less (4%); eight to eleven years (8%); high school graduate (29%); some college (24%); college graduate (24%); graduate work or degree (10%). Mean family income was between $25,000 and $30,000.

We anticipate that certain religious beliefs will influence public attitudes about biotechnology. Religious salience was measured by asking "How important is religion in your daily life?" Religion was a very important part of most (63%) respondents' lives. Another 23 percent indicated religion was somewhat important. Only four percent said religion was not important. Fundamentalism in religious orientation was measured by two questions. Most respondents (79%) believed that the story of creation as recorded in the Bible is true. Almost three quarters (74%) believed the biblical version of creation should be given equal weight with the theory of evolution in public schools. We combined these two questions to form an index of religious fundamentalism. This index is moderately reliable with a Cronbach's Alpha of .59.

We also measured a number of indicators of respondents' awareness of and attitudes toward genetic engineering. Respondents varied in their awareness of genetic engineering. Over one third of the respondents had read or heard either a lot (7%) or some (32%) about genetic engineering. Almost half (44%) said they had heard a little about genetic engineering. Another 16 percent claimed to have heard or read nothing about genetic engineering. Two statements were used to assess respondents' general orientation toward genetic engineering. To assess the tradeoffs between the benefits and risks of genetic engineering, respondents were asked how much they agreed or disagreed with the following: "The potential benefits of genetic engineering are greater than the possible risks." Almost three quarters (71%) agreed that the benefits will be greater than the risks. Just over one fourth felt that the benefits will not be greater than the risks. Respondents were also asked how much they agreed or disagreed with the following statement "It would be better if scientists did not know how to use genetic engineering." Only three percent of all respondents strongly agreed with this statement. Another 13 percent agreed. Most (64%) disagreed that it would be better if scientists did not know how to use genetic engineering. In fact, 19 percent strongly disagreed with this statement.

The final set of intervening variables involves the level of trust or confidence that respondents have in the ability of government and other institutions to inform and involve the public in decisions about biotechnology. To determine concerns with too little regulation, respondents were asked how much they agreed or disagreed with the following statement "Too little regulation of genetic engineering poses serious risks to human health." Over one fourth (29%) of the respondents strongly agreed with this statement. The majority (55%) agreed that too little regulation is a risk to human health. Only 13 percent disagreed with the statement, while three percent strongly disagreed. Respondents were asked the extent to which they thought the public should play a greater role in genetic engineering regulation by voicing their agreement with the following "The public should have more say in government regulation of genetic engineering." Over 20 percent strongly agreed and about two thirds agreed with this statement. Few consumers feel that the public should not have a greater role in the regulation of genetic engineering.

In order to determine how much confidence consumers have in information provided by institutions, respondents were asked how much trust they would have in information about

genetic engineering provided by different individuals or organizations. Respondents would have the most faith in university scientists. Respondents reported the next greatest amount of trust in environmental groups. Of the three levels of government, respondents would have the most faith in local public health officials. The next most trustworthy source would be state government. Public confidence in the federal government would be slightly lower. The public will clearly have relatively little faith in the company making the product. We developed an additive scale including these six information sources. This scale is reliable with a Cronbach's Alpha of .73.

We measured consumer acceptance of biotechnology in meat and milk production by four questions. Respondents were asked how desirable they thought two applications of genetic engineering would be. The first application was bovine somatotropin (rbST). Respondents were not asked about the product by name; but were asked how desirable it would be if "genetic engineering were used to produce a hormone that increased the amount of milk that dairy cows produce." Only 10 percent of the respondents thought rbST would be very desirable. Many (40%) felt rbST would be somewhat desirable. However, half the respondents (50%) believed that rbST would be undesirable. Less than one third (32%) of all respondents thought the use of genetic engineering to produce larger or faster growing livestock would be very desirable. Almost as many (31%), in fact, thought this would be undesirable.

The two final indicators of consumer acceptance of biotechnology in meat and milk production involve two related issues. Respondents were asked how concerned they would be about eating genetically engineered meat or dairy products. Most respondents would be either very concerned (45%) or somewhat concerned (37%). As a final indicator, respondents were asked if they thought that genetic engineering of animals was morally wrong. Respondents were almost evenly divided on this question. A significant number (45%) of respondents thought genetic engineering of animals was morally wrong. Almost as many (43%) did not think genetic engineering of animals was morally wrong. A sizeable number of respondents (12%) did not have an opinion about the morality of animal genetic engineering. They were coded intermediate to the two other responses. These four items are combined into an additive scale. This scale is reliable with a Cronbach's Alpha of .73. This four item scale appears to be normally distributed which indicates that it can be treated as almost a continuous level variable for purposes of our analysis. The four-item scale just described will serve as our main measure of consumer acceptance of biotechnology in meat and milk production.

Bivariate Relationships

This section will provide a preliminary interpretation of the determinants of consumer acceptance of biotechnology in meat and milk production. Results of this bivariate analysis are given in Table 1. We will first describe some of the observed relationships between certain groups of the independent variables themselves. We will consider how the background characteristics are related to the intervening variables. Finally, we will turn our attention to the relationships between the independent variables and consumer acceptance of biotechnology in meat and milk production.

Table 1. Bi-variate relationships (zero-order correlation coefficients) among variables in conceptual model

		X_2	X_3	X_4	X_5	X_6	X_7	X_8	X_9	X_{10}	X_{11}	X_{12}	Y
X_1	Gender (Female)	.10	-.14*	-.12	.19**	.15*	-.18**	-.11	.18**	-.01	.18**	-.13	-.34**
X_2	Age		-.17*	-.18**	.19**	-.00	-.10	-.01	.05	-.08	-.00	-.13	-.07
X_3	Education			.40**	-.19**	-.31**	.34**	.18*	-.24**	.16*	-.18**	.14*	.31**
X_4	Family Income				-.18*	-.21**	.25**	.17*	-.24**	.02	-.16*	.17*	.20**
X_5	Religious Salience					.44**	-.19**	-.14*	.21**	-.02	.05	-.02	-.24**
X_6	Religious Fundamentalism						-.22**	-.19*	.20**	-.03	.10	.01	-.23**
X_7	Awareness of Genetic Engineering (GE)							.17*	-.23**	.10	-.16*	.17*	.25**
X_8	GE Benefits Exceed Risks								-.24**	.00	-.19*	.08	.31**
X_9	Better If No GE									-.02	.13	-.15*	-.43**
X_{10}	Too Little Regn Is Risk										.15*	-.03	-.15*
X_{11}	Greater Role for Public											-.06	-.26**
X_{12}	Faith in Information												.27**
Y	Acceptance of Biotechnology												--

* means that correlation coefficient is significant at p< .01
** means that correlation coefficient is significant at p< .001

Several demographic characteristics appear to influence awareness of genetic engineering. Male respondents had heard or read more about genetic engineering than had women. Those with higher levels of education and income also reported greater awareness of genetic engineering. Respondents who held more fundamental religious beliefs or who believed religion was more important reported less awareness of genetic engineering.

Several types of respondents were more likely to believe that the benefits of genetic engineering will be greater than the possible risks. People with higher educational and income levels were more likely to express this view. Greater awareness of genetic engineering was also positively related to the belief that the benefits will exceed the risks. On the other hand, respondents with stronger and more fundamental religious beliefs were more likely to disagree that the benefits will exceed the risks.

Similar relationships were found when we examined agreement with the statement that "It would be better if scientists did not know how to use genetic engineering." Women were more likely to feel this way, as were respondents with lower income and educational levels. Religious fundamentalism and salience were also positively related to this viewpoint about genetic engineering. Disagreement was greater among those respondents with greater awareness of genetic engineering and those who thought the benefits of genetic engineering would be greater than the risks.

Only one variable is related to agreement that "Too little regulation of genetic engineering is a risk to human health." In this case, respondents with more education were more likely to agree with that statement. On the other hand, people with less education were more likely to agree that "The public should have more say in the regulation of genetic engineering." Income was also negatively related to agreement with this statement. Women were more likely to want more public involvement in regulation, as were respondents who had read or heard less about genetic engineering. Respondents who did not agree that the benefits of genetic engineering will exceed the risks wanted a greater public role in regulation. Those who wanted more public involvement in regulation were also more likely to believe that too little regulation posed risks for human health.

Certain groups of respondents claimed to have greater overall faith in sources of information about the risks of genetic engineering. Respondents with higher education and income levels reported greater faith in the information sources, as did respondents who had heard or read more about genetic engineering. People with greater faith in information sources were also more likely to disagree that it would be better if scientists did not know how to use genetic engineering.

Finally, we can examine how the background characteristics and intervening variables are related to consumer acceptance of the use of biotechnology in meat and milk production. Women were less likely than men to accept biotechnology. Higher education and income levels were positively associated with acceptance of biotechnology. Religious salience and fundamentalism had a negative relationship with consumer acceptance of biotechnology. People who had read or heard more about genetic engineering were more likely to accept products, as were respondents who believed the benefits of genetic engineering were greater than the risks. On the other hand, people who felt it would be better if scientists did not know how to use genetic engineering were less likely to accept biotechnology. Respondents who felt that too little regulation posed a risk to human health were less likely to accept biotechnology, as were those who felt the public should have a greater role in the regulation of genetic engineering. Finally, respondents who had more faith in information sources appear more likely to accept the use of biotechnology in meat and milk production.

Multivariate analysis

We have observed inter-relationships among a number of the variables in our conceptual model. It will, therefore, be useful to analyze the relative contribution of the background characteristics and intervening variables as determinants of acceptance of biotechnology in meat and milk production. We do this through multiple regression of these various factors on our four-item scale of consumer acceptance (see Table 2). This section tries to paint a fairly

Table 2. Multiple regression of the relative influence of independent variables on consumer acceptance of biotechnology in meat and milk production.

		Standardized Regression Coefficient	T-Value
X_1	Gender (Female)	-.20	3.72**
X_2	Age	.01	.14
X_3	Education	.16	2.56**
X_4	Family Income	-.05	.81
X_5	Religious Salience	-.08	1.30
X_6	Religious Fundamentalism	-.04	.62
X_7	Awareness of Genetic Engineering (GE).	.04	.63
X_8	GE Benefits Exceed Risks	.15	2.73*
X_9	Better if No GE	-.27	.85**
X_{10}	Too Little Regn is Risk	-.17	3.17**
X_{11}	Greater Role for Public	-.09	1.57
X_{12}	Faith in Information	.16	3.03**

* means that standardized regression coefficient is significant at $p < .01$
** means that standardized regression coefficient is significant at $p < .001$

clear picture of which types of consumers will be more likely to accept the use of biotechnology in meat and milk production. We will also suggest some reasons why such acceptance may not occur. In fact, we are able to explain much of the variance in consumer acceptance of biotechnology. The adjusted r-square value for our full model is .37, indicating that the variables in our model account for over one-third of the differences between respondents in terms of acceptance.

In terms of the background characteristics included in our model it seems clear that certain groups of consumers will more readily accept the use of biotechnology in meat and milk production. Men will be more likely to accept biotechnology than will women. This could be problematic in that most food purchase decisions are made by women, not men. Even if the male in a household buys food, he will rarely go against a woman's wishes when it comes to whether or not certain foods are purchased. People with higher educational levels will be more likely to accept biotechnology. Years of formal education is a reasonable indicator of technological sophistication and scientific literacy. This findings presents a challenge for educational efforts because those with less education will be less interested in or knowledgeable about scientific issues. Family income is no longer significant which indicates that educational levels account for most of the influence of income. The items measuring religious orientation are no longer significant after controlling on the other variables. This indicates that the influence of religious orientation is probably accounted for by differences in education and gender.

Acceptance of the specific application of biotechnology to meat and milk production will be conditioned by consumers' general attitudes toward genetic engineering. Respondents who agreed that the benefits of genetic engineering will be greater than the potential risks were more likely to accept biotechnology in meat and milk production. On the other hand, those who feel the risks of genetic engineering are greater will be less likely to accept these uses. As another indicator of general orientation toward genetic engineering, it is clear that people who believe it would be better if scientists did not know how to use genetic engineering will be less likely to accept the use of biotechnology in meat and milk production. This indicates that consumer acceptance or rejection of the use of biotechnology in meat and milk production reflects underlying beliefs or values about the appropriateness of genetic engineering in general.

Our results suggest that a higher level of confidence in the institutions responsible for developing and controlling biotechnology will be an important determinant of consumer acceptance of the use of biotechnology in meat and milk production. We found that consumers who believe that too little regulation of genetic engineering poses serious risks to human health will be less likely to accept the use of biotechnology. Those respondents who have a higher level of trust in statements about genetic engineering made by various groups will be more likely to accept the use of biotechnology in meat and milk production. It is important to keep in mind that consumers will have a lot more trust in some groups (i.e., university scientists and environmental groups) than they will in others (i.e., the company making the product).

It is interesting to note awareness of genetic engineering is no longer significantly related to acceptance of biotechnology in meat and milk production. After controlling on the background characteristics (e.g., educational level and gender), respondents who had heard

or read more about genetic engineering were not more likely to accept biotechnology. It could also be that awareness influences acceptance indirectly through the attitudes that people hold about genetic engineering and the confidence they have in government to manage genetic engineering.

Conclusions and implications

Consumer acceptance of biotechnology in meat and milk production is uncertain, at best. As we draw our conclusions, it is important to recognize that the evidence from social science research is far from conclusive. We have very little empirical research on which to recommend policies or programs. To date, far too little attention has been paid to consumer acceptance of biotechnology. More social science research, like the type described in this paper, is clearly needed if the agricultural biotechnology enterprise is to succeed in winning consumer acceptance.

Our results suggest that certain groups of consumers may either support or oppose the use of biotechnology in meat and milk production on several grounds. We find that men will be more likely than women to accept the use of biotechnology in meat and milk production. As a group, men tend to be more interested in and supportive of new technology than do women. On the other hand, women tend to be more concerned about health risks of new technologies than men. Respondents with higher educational levels will also be more likely to accept biotechnology products. This suggests that knowledge and intellectual sophistication could prove to have a positive relationship with acceptance of biotechnology. It is not, however, necessarily true that more information about biotechnology will change existing attitudes. Increased information may, in fact, strengthen already held beliefs (positive or negative).

We also predict that consumer acceptance of biotechnology in meat and milk production will be strongly influenced by attitudes about genetic engineering more generally. This indicates that more general orientations toward science and technology may be at the root of beliefs about animal biotechnology. Finally, it seems clear that consumers confidence in the organizations that manage biotechnology will have an important influence over whether or not they accept the use of biotechnology in meat and milk production. We can conclude that opposition to biotechnology could become intense unless the public is confident that the organizations involved with biotechnology are "playing by the rules."

Concerns related to human health and environmental risks can be addressed through public policies and regulations. If the public can gain confidence that government and industry are doing their best to protect human health and the environment, these types of concerns may not present a serious obstacle to consumer acceptance. However, if government and industry are unable or reluctant to take all necessary safety precautions, consumer acceptance of biotechnology could be justifiably low. Based on recent experience with Alar, and other food safety concerns, we can predict that if the media publicizes any real or perceived risks to human health from the products of biotechnology consumer opposition will become intense. How deep or sustained such opposition will be depends on a number of factors. One of the key determinants will be consumer confidence in government to adequately protect them from risk. Education about government regulation and oversight

could play an important role in addressing consumer concerns about health and environmental risks.

Concerns over moral and ethical issue could represent much more serious and challenging obstacles to consumer acceptance of the use of biotechnology in meat and milk production. These are not, however, the kind of issues that can or should be addressed through government regulations. Even if government agencies and lawmakers were willing to address these types of ethical concerns, it is unlikely that they would be able to satisfy the opponents of biotechnology. Likewise, it is unlikely that educational efforts will be very effective in attempts to address the difficult moral and ethical issues raised by biotechnology. This will be especially true if educational efforts continue to be grossly under-funded and aimed at public relations, rather than public education. We will need, instead, to foster meaningful dialogue among all parties. This must include a greater role for the public in the decisions about new technology.

From the standpoint of the overall biotechnology enterprise, rbST may prove to be a poor choice as a test case. It will be much more difficult to obtain consumer acceptance of rbST than it will be for some plant-related products such as disease resistant fruit. The public tends to be more opposed to genetic engineering of animals than they are to plant applications (Hoban and Woodrum, 1990). Furthermore, rbST may suffer from the stigma of being a "hormone in milk." Milk has always had a strong tie to children and, therefore, it is important to maintain a wholesome image. Adverse public response to rbST may adversely affect that image. Moreover, rbST has drawn a lot of attention because of potential socio-economic impacts on dairy producers. Whether the socio-economic impacts of rbST will actually materialize will depend on many factors, including the price of rbST for dairy producers and the effectiveness of educational programs to help producers learn how to use rbST. The point is that rbST has already become a lighting rod for considerable controversy. This may have unfortunate consequences for consumer acceptance of other biotechnologies used in meat and milk production.

We will now try to put some of the ethical issues in a larger context and offer some insights into the role of social science and philosophy in this important area. In general, public attitudes toward biotechnology may ultimately be connected with attitudes toward acceptable levels of risk (Berrier, 1987; Heimer, 1988). Attitudes toward risk are conditioned by a variety of factors, including knowledge level, age, gender and the like. However, attitudes toward biotechnology and science in general are also conditioned by ethical beliefs, (i.e, beliefs about what is right and wrong). As we have suggested, some of these beliefs may be based on religious convictions. In the case of biotechnology, some are based on beliefs about the "naturalness" or appropriateness of genetic engineering with respect to animals, whether these beliefs are religious or secular in origin. Some of these beliefs may be based on concern for the environment, or food safety. Moreover, some are based on beliefs about the value or virtues associated with family farming. Indeed, whether the general attitude toward science and technology is pro or con, deeper beliefs about values are undoubtedly involved.

Values can be variously defined as ideals, standards, or principles. In practice, they are sets of beliefs to which people implicitly or explicitly appeal in making decisions. People's beliefs (particularly their ethical values) are notoriously vague, inconsistent, and transitory.

Ethical values clearly vary among people. One person's or group's values may appear irrational or myopic to others. Nevertheless, our society has a long-standing commitment toward respecting each other's differences. Ours is a pluralistic society. Different and even conflicting ethical values make public decision-making in a democracy so delicate. Value differences also can make the role of the scientist an extremely complicated matter. It is one thing, for example, to communicate research information to an ethically like minded community of scholars, that has either explicitly or implicitly accepted the legitimacy of research in the first place. It is quite another to communicate that same information to a group whose ethical values are in stark contrast to one's own. This would appear to be the case for people whose values lead to a scepticism (if not outright rejection) of biotechnological research.

Philosophers have long noted that one cannot derive an "ought" from "is". Increased knowledge and information will not logically lead to an ethical judgement. New knowledge or information may cause individuals to change their ethical beliefs: reprioritize them, render them consistent, or even abandon them. As intimately connected as facts and values may be, they remain different categories of experience. Public debate on such issues as abortion illustrate the depth of divergence between fact and value. People may agree on the fact that a fetus is a living being, yet hold profoundly different beliefs about the morality of aborting it.

Pluralistic, democratic societies typically resolve value conflicts in terms of tradeoffs and balancing of interests. Conflicting values are evaluated based on available information and potential consequences of pursuing a given value. Within the scientific community, there is also a tendency to think in terms of tradeoffs. Alternative courses of action are considered in light of relevant information and ethical values. Indeed, many feel this "weighing of alternative values" is the only rational way to make decisions, at whatever level those decisions are to be made (Aiken, 1987).

When subjected to this sort of risk-benefit or cost-benefit appraisal biotechnology arguably comes out on the plus side. However, our research suggests that when it comes to public attitudes about biotechnology, different values and rationalities may be involved. For some people and groups, it may be fundamentally unreasonable to even consider trading some values for others when some things, (e.g., the environment or the sanctity of life) are thought to be placed at risk. Many people believe, right is right and wrong is wrong, whatever the harmful or beneficial consequences of the action. As Thompson (1988) has shown, some individuals and groups believe that any change from the status quo represents an unacceptable risk.

These points suggest some profound challenges for scientists, administrators, and policy makers at all levels of authority and responsibility. Ethical issues arise with respect to most new technologies. Public attitudes vary, often for reasons beyond the influence of more or better information about potential personal, environmental, or socio-economic consequences of the technology. Recognizing this is a first step. Some values and attitudes are affected by more and better information. As we have suggested, more highly educated and better-informed individuals will likely have more favourable attitudes toward biotechnology. An important question is whether more information will lead those with less education to accept certain applications of biotechnology. If so, this would suggest that

certain kinds of information should be made available to the public in usable form. Information about public knowledge and attitudes must also be provided to scientists, extension personnel, and administrators at all levels.

The danger in all this is that scientists, extension educators, and administrators may find themselves in the role of advocating not only particular products such as rbST, but the unfettered practice of science and technology development as well. And this, ultimately, may place "pro-science" individuals in the role of advocating what can be called an ethical world view (i.e., a view of what is both ultimately right as well as how that should be decided). To this we can only note, that all communication is essentially persuasion. Even the communication of ostensibly value-neutral data or scientific results has the element of "buy this" (Knorr-Cetina, 1981). Even within a scientific discipline or community there is an element of persuasion and trust. We are persuaded to accept the data as real. We have confidence that the results are truly reported, because we trust the author or purveyor of that information.

In the area of public attitudes, and the larger public agenda for agricultural research, the matter of trust is the key. As we have shown, people are inclined to trust academic scientists, but not trust privately-employed ones. Perhaps this is because academic scientists, for all their jargon and occasional obfuscation, have told the truth in the past. This suggests an ethical responsibility that we must continue to foster and act upon. We must be honest with those who are concerned about rbST and about genetic engineering in general. Let us tell them honestly and candidly about both the benefits and the risks. Let us recognize and admit up front that our concerns are with more knowledge, better technologies, and a stronger agricultural economy. Let us also recognize that despite the hidden agendas of some critics of agricultural science and technology development, there can be honest disagreement about both facts and values.

In the final analysis, it is up to decision-makers to determine and acknowledge the public interest in science and technology development. Policy-makers will dictate whether rbST or any other product of the new biotechnology will be allowed on the market. Awareness of public attitudes can provide some assistance in this task. However, given inevitable ethical conflicts in a democratic and pluralistic society, some people's values must invariably be "discounted." Some publics will win and some will lose, despite the prima facie legitimacy of most, if not all, the values people hold. That is perhaps the tragedy of public decisions in a pluralistic, democratic society. It is neither a new problem, nor an issue we can resolve here. We can only hope that social scientific research can contribute toward a more open and complete discussion of ethical issues and scientific knowledge in the public debate.

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DETERMINANTS IN PUBLIC ACCEPTANCE - EUROPE

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Summary

Public perception will be of paramount importance in determining the growth and progress of biotechnology. The depth of public feeling should not be under-estimated. Some consumer concerns relate to the safety of the process or product, others are based on social or ethical issues, but most probably relate to "the fear of the unknown". These concerns have to be acknowledged and addressed by appropriate policies and strategies.

Keywords: *consumer acceptance, biotechnology*

Introduction

Biotechnology embraces a wide and complex set of scientific and industrial disciplines. Biotechnology is usually interpreted as involving some element of genetic manipulation of plants, animals or micro-organisms, even although at present this aspect represents a small proportion of the total range of activities classed as biotechnology. The Organisation of Economic co-operation and Development (OECD) refers to a "new biotechnology" which embraces recent developments such as genetic engineering and cell fusion. In its recent report, "Biotechnology and Wider Impacts", OECD states that, "The new biotechnology is distinguished from other major technologies of the 20th Century by the fact that its impact on the quality of life, its human and social consequences, are arriving earlier and may go deeper than macro-economic impacts measured by productivity, investment or GDP growth".

The impact will be pervasive. Biotechnology will be used extensively in food production to enhance the useful and desirable characteristics of plants, animals and micro-organisms. The overall aim will be to improve the yield, performance, quality and, ultimately, profitability of food products.

In principle, the techniques of improvement in the selection and breeding of plants and animals have been around and accepted for centuries. But biotechnology will add a new dimension, achieving a greater speed and precision than ever before. It will also be possible to achieve certain outcomes, which were previously impossible. It is these aspects which create uncertainty and unease in consumers. Their concerns fall into two broad categories, those relating to safety issues and those relating to the social and ethical issues. These concerns must also be seen against a general background of "fear of the unknown". In other words, are the scientists pushing out the boundaries of scientific achievement towards

unknown and uncharted territory, where unforeseen consequences and catastrophes could occur?

The Challenge

The challenge to all of those involved in the biotechnology industry is to find the correct balance between meeting these concerns and creating the appropriate environment for industries to develop, innovate, and take full competitive advantage of the commercial opportunities open to them.

The Problems

The problem is that very little is known about the likely attitudes and behaviour patterns which consumers will adopt in relation to biotechnology. Nor do we have a real understanding of how these attitudes and behaviour patterns are developed and influenced. Recent experience of consumer attitudes in Europe towards the potential use of recombinant bovine somatotropin (rbST) in milk production and the use of irradiation as a food preservation technique suggest that biotechnology will become a highly sensitive area, likely to attract strong opinions and inspire polarised views.

Consumer Research

Some useful research in this area has been carried out by the Netherlands Institute for Consumer Research (SWOKA). For this research 1729 Dutch consumers over the age of 16 were interviewed by means of a tele-panel. The results of this research indicate that while more than half the respondents, had heard of the word biotechnology, only about one third knew its meaning. Opinions about biotechnology - either the risks or the benefits - were poorly formed, and they were only able to explain positive or negative reactions in very general terms. The research results do, however, highlight the gap between the scientists' and the public's perception of biotechnology. The English language summary of the results concludes,

"The arguments that were brought out up by the participants in the interviews differ from the arguments that are used by biotechnology experts and other authors who write about the benefits and risks of biotechnological developments and applications. Experts can weigh detailed information about specific applications, while consumers - with their low level of knowledge - have to depend on more general feelings and expectations about technology in general and some rough information (mostly from the news media) about some biotechnological applications".

The study also went on to test the assumption that more information and knowledge will lead to lower levels of anxiety and, hence, greater public acceptance of biotechnology. The SWOKA study suggests that this is not the case. Increased knowledge is just as likely to lead to greater resistance. It should be remembered that the purpose of education is to open up

people's attitudes and encourage them to question and challenge. The biotechnology industry sometimes appear to fall into the trap of believing that the function of information and education is solely to ensure acceptance. Clearly, much more research needs to be undertaken and it should focus on the following objectives;

- to review the current levels of knowledge and consumer perceptions of biotechnology in food and agriculture.
- to develop methods of measurement of perceived risks and benefits.
- to understand how such perceptions of risks and benefits are formed.
- to develop and test information strategies.

Risk Perception

It is essential that this kind of research is carried out so that it will be possible to identify with greater certainty the crucial determinants of consumer acceptance. It may be a difficult concept for scientists to grasp, but for the vast majority of people, it is the perception that counts, not necessarily the facts and it is essential to address these perceptions. If consumers perceive biotechnology to be a more unpredictable science, therefore in need of more safeguards and controls, then this must be the starting point for addressing the consumer protection requirements.

Consumers are only likely to accept biotechnology if they perceive the benefits to be greater than the risks. They are likely to make this assessment in relation to themselves as individuals, other people or animals, society as a whole and the worldwide environment. So if biotechnology can offer them benefits, can benefit other people and does not do harm to other parts of society or the environment then acceptance is likely to be greater.

Safety Assessment

Clearly, safety is the most important aspect for consumers. As individuals, they are in no position to make that assessment for themselves, so they must rely on others to make that decision on their behalf and in their best interest. This places considerable demands on the *system* of safety assessment. This implies a rigorous assessment procedure, and a system of assessment that is open, accountable, independent and representative. This is the only way to reassure people that a proper balance is being drawn between commercial interest and consumer protection.

Labelling

Consumer organisations believe that biotechnology products should be clearly labelled (eg rbST milk) so that individual consumers can exercise an informed choice in a free market. The labelling argument becomes less clear cut the further back in the process the biotechnology application occurs.

EC legislation on the development and use of genetically modified organisms

The European Community adopted two Directives in April 1990 to regulate the development and use of genetically modified organisms. These Directives have to be implemented by Member States by 23 October 1991.

I Council Directive 90/219/EEC on the Contained Use of Genetically Modified Micro-Organisms.

The *Contained Use Directive* establishes a common regime to protect humans and the environment regarding the use in laboratories and industry of genetically modified micro-organisms (GMM's). Although "micro-organisms" are not defined in the Directive, the terms would include yeasts and bacteria but not vertebrate animals or seed-bearing plants.

The Directive requires users of GMM's to prepare a safety assessment, to notify the competent authority 90 days in advance of proposals to work with GMM's, obtain consent to the proposed work in specified (less safe) cases, keep records and prepare emergency plans (again for specified, less safe cases). The Member State's competent authority has to provide the EC Commission with summary information, publish information (not commercially sensitive) and arrange inspections of the sites where the work is carried out.

II Council Directive 90/220/EEC on the Deliberate Release into the Environment of Genetically Modified Organisms

The *Deliberate Release Directive* establishes a common regime for the release into the environment of genetically modified organisms (GMO's) (eg planting a (GMO) crop) and for the marketing of GMO's and products containing GMO's. Unlike the Contained Use Directive, all living things are included in its scope.

As with the Contained Use Directive, a system of safety assessment, prior notification and prior consent in appropriate cases (including all proposals to market GMO's) is established. The competent authority of any Member State in which a proposal is made to market a GMO for the first time in the EC takes an initial view on whether the Directive's safeguards have been complied with. If the Member State is satisfied that they have, the proposal (and supporting evidence) is sent to the Commission who will send it to all other competent authorities. Any competent authority may present a reasoned objection to the proposal within 60 days and, if the two competent authorities are unable to reach agreement within this 60 day period, the Commission has to decide (subject to regulatory committee process) whether the GMO may be marketed throughout the EC. Once approved for marketing, the GMO's would be given free circulation within the EC. Provision for the public availability of certain information, and for reports to be made (annually by competent authorities and triennially by the Commission) on approvals, is included.

Directive 90/220/EEC thus provides a common market for GMO's throughout the EC from October 1991. Although Member States' competent authorities may object to a proposal, the objection has to be on the basis of a reasoned argument. As the basic purpose of the Directive is to protect human health and to safeguard the environment, it is unlikely

that an objection would succeed solely on the grounds of public disquiet about the GMO's unusual parentage or that there was a possibility that it would suffer discomfort.

The EC Commission's draft proposal on novel foods is similarly directed at ensuring consumer safety and so, if a GMO-sourced food were demonstrably safe, would offer no greater opportunity for banning GMO's which might cause some public disquiet for other reasons.

EC draft novel foods regulation

The draft Community proposal on novel foods (which is yet to be published) defines a "novel food ingredient" as one which 'in the Community has not been used hitherto for human consumption or which has been consumed in only small amounts or has not been used for that purpose.' The Community proposal would establish a Community-wide prior approval system for all novel foods. All novel food ingredients would have to be notified to the Commission and a decision on their approval given by vote of a regulatory committee made up of Member Stages. Any novel food ingredient likely to "have an effect on public health" would be referred to the Community's Scientific Committee for Food for their advice before a decision on its approval was made.

EC climate of opinion

The general climate of opinion in Europe on the application of biotechnology to food and agriculture is cautious. There is a deep suspicion about more intensive methods of production and that is a clear indication that political and socio-economic arguments may overrule the strict scientific assessment. These attitudes have already been reflected in recent decisions about growth hormones and rbST.

UK legislation

Food Safety Act 1990

Section 18 of the Food Safety Act contains the provisions relating to novel foods.

All food produced by genetic modification are likely by their nature to fall within the definition of "a novel food" in section 18(3) of the Act in that they have "not previously been used for human consumption". However, at least in theory, it might be possible to produce virtually the same food by conventional breeding. A further difficulty could arise in controlling any conventionally bred off-spring of a genetically modified plant etc which might not be considered "novel" because of the passage of time since the original modification. The purpose of sub-section (4) is to clarify the scope of section 18 to ensure that all foods produced by genetic modification are covered whether or not they are similar

to foods produced by conventional breeding or cease to be strictly speaking "novel" because of the passage of time.

Ministers made clear during the passage of the Food Safety Bill that they proposed to use these section 18 powers to introduce a prior approval system for foods produced by genetic modification based on advice from the Advisory Committee of Novel Foods and Processes.

Section 18 Food Safety Act 1990 (extract)

Section 18(1)The Ministers may by regulations make provision

(a) for prohibiting the carrying out of commercial operations with respect to novel foods, or food sources from which such foods are intended to be derived, of any class specified in the regulations;

(b) for prohibiting the carrying out of such operations with respect to genetically modified food sources, or foods derived from such food sources, of any class so specified; or

(c) for prohibiting the importation of any food of a class so specified, and (in each case) for excluding from the prohibition any food or food source which is of a description specified by or under the regulations and, in the case of a prohibition on importation, is imported at an authorised place of entry.

Section 18 (4)For the purposes of this section a food source is genetically modified if any of the genes or other genetic material in the food source-

(a) has been modified by means of an artificial technique; or

(b) is inherited or otherwise derived, through any number of replications, from genetic material which was so modified;

and in this subsection "artificial technique" does not include any technique which involves no more than, or no more than the assistance of, naturally occurring processes of reproduction (including selective breeding techniques or in vitro fertilisation).

Social and Ethical Concerns

The social and ethical concerns cover a wide area of issues which raise questions about moral values, principles, obligation and rights. These issues can be summarised by four key questions

- Is it fair?
- Is it right?
- Is it natural?
- Do we need it?

The social, ethical, economic and even political implications of biotechnology raise fundamental questions about individual choice, freedom and rights. New techniques, whether or not they are "unnatural", are not necessarily wrong. Difficult value judgements may have to be made, balancing potential benefits for one group of people against potential disadvantages for others. Many of the arguments which will undoubtedly be used for and against biotechnology may rest upon shaky foundations, and obscure concepts and are likely

to be presented in emotive terms. Important issues about animal welfare also have to be addressed.

In many cases, answers to questions may not even be possible. Against such a background, how can a wider view be taken? Various suggestions have been made, usually along the lines of establishing "Ethical Committees", whose task would be to consider these issues and draw up guidelines for the industry and the legislators. Some observers have gone further, suggesting that a "fourth hurdle" (after safety, quality and efficacy) should be a condition of approval. These issues underline the conflict between the ability of individual consumers to make their own "value" judgements about food products and processes and the need for certain limitations to be placed upon that individual freedom in the interests of society as a whole.

IOCU views

Many of these issues were discussed at a recent workshop (May 1990) in the Hague, Netherlands organised by the Regional Office in Europe and North America (ROENA) of the International Organisation of Consumer Unions (IOCU). The participants discussed the aspects of biotechnology on which IOCU and individual consumer organisation should concentrate. That summary is as follows.

IOCU workshop - the Hague - Netherlands - May 1990

Government level

- governments should be more open for consumer input. Consumers sometimes are allowed to sit on advisory committees, but this kind of representation should be stepped up.
- governments should also fund research carried out by consumer organisations.

Consumer aspects

- IOCU and national organisations should establish a 'platform', as working group and forum for exchange of information and ideas.

Such a group should seek information on the progress and status of biotechnology in their countries. The example of the consumer founded platform was mentioned.

- novel products of biotechnology should be assessed for social, economic, and environmental impact. Expert committees involving consumer organisations should be established to evaluate these aspects.
- full labelling is important.

Environmental aspects

- need for information on the effects of genetically manipulated products and the processes involved.
- need for information on how decisions are reached and what kinds of criteria are used.
- need for more safety research.
- more public participation in decision making.

Criteria for evaluation

- clarify the most important criteria for evaluating biotechnology.
- calling for manufacturers to be required to publish a justification at the early stages of the approval process.
- request more money for consumer research.

Conclusion

Progress on biotechnology must take place - preventing such progress would not be in the consumer interest. Nor would it be in anyone's interest to ignore the factors which will determine consumer acceptance. The emphasis must be on learning from the past, identifying consumer requirements and ensuring that the appropriate policy and strategy is in place to satisfy these requirements.

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DETERMINANTS OF ACCEPTANCE IN PRODUCTION AND PROCESSING

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Summary

Biotechnology is playing an increasing role in nearly all scientific fields. The decision to reject these tools in any one industry or country will leave that industry or country noncompetitive. It is vital that new products and processes be developed and publicly and commercially accepted.

Producers and processors will implement new technologies if they will benefit from them. The public will accept new processes and products if they perceive them as safe. If consumers do not perceive a new technology as being safe, producers will hesitate to implement the technology.

Public opinion is the consensus derived from open discussion of food safety, risk assessment and cost-benefit analysis. However, science education and communications among scientists, producers and the public must improve if consensus is to be based on informed decisions.

Keywords: *biotechnology, education, communication, agriculture, public opinion.*

Introduction

A workable definition of biotechnology can be derived by examining the two parts of the word. "Bio" stands for biology, the science of life that includes all living things. "Technology" is collectively the tools and techniques which include animal breeding, embryo transfer, genetic engineering, fermentation, tissue culture, and so forth. Biotechnology is applying those tools to living organisms to get them to do what you want them to (Witt, 1990).

Biotechnology can be used to improve the performance and composition of animals, value-added processes, diagnostics for disease, vaccines and other aspects of animal production. These tools have the potential of improving the animals' well-being, in addition to improving industry competitiveness. Increased efficiency also decreases waste production and can improve the environment.

Biotechnology is playing an increasing role in nearly all scientific fields. To choose not to implement these tools in any one industry or country will leave that industry or country noncompetitive. The application of biotechnology to agriculture has lagged behind human

health applications due to a lack of investment which would yield needed basic knowledge in animal physiology, biochemistry and microbiology (National Agricultural Research and Extension Users Advisory Board, 1990).

It is vital that new products and processes be developed and that they become publicly and commercially accepted so the growing world population can be provided a reliable food supply.

Farmers and processors base their decisions to purchase and implement new technology on its expected benefits. These benefits are normally in the form of increased efficiency, decreased input costs, lower labour requirements or higher quality of production. The bottom line is that producers must see increased profits or improvement in their quality of life to justify changes.

The Decision Making Process

Today's world presents few new concepts in the decision-making process of producers. However, the information age we live in, with its instant communications, changes the formula somewhat (Sweet & Meeker, 1990). The average citizen has more media awareness now than ever before, but at the same time is woefully ignorant of science and technology. If someone of notoriety has something important to say or if someone famous has anything at all to say, that opinion of technology is heard around the world almost instantly. Little time is spent verifying stories or finding perspective. It is news because someone said it, not because the message was important.

Producers are aware of consumer needs and expectations and are responding well to the market place. At the same time, political activists are attempting to shape consumer perceptions of safety, quality and risk with little regard for scientific thought. Thus, for perhaps the first time in history, producers are considering consumer perceptions as they ponder the use of new technologies. Some critics use their own "science" or find a scientist who agrees with them but not the majority of other scientists. Producers fear the market consequences of public misunderstanding.

We have heard much about the standards to be met for the approval process in recent years - safety (to humans, the target animal, and the environment), efficacy and quality. The credibility of government agencies responsible for making these decisions must be maintained.

The FDA recently departed from tradition by publishing information on the safety of recombinant bovine somatotropin (rbST) prior to approval of the drug. This new, more open attitude of the agency improves public opinion of the FDA and reduces concerns about the quality of the data or the safety of rbST (Juskevich & Guyer, 1990). Publishing rbST safety data in the scientific literature moves the debate away from the popular press. This improved openness and responsiveness by a government agency should be applauded and encouraged.

Safety is important to everyone. However, it must be defined in reasonable benefit versus risk terms. Zero risk is not possible for any presently used technology or any other facet of

life. It should not be expected of new technology either. As Voltaire said, we should not let the perfect be the enemy of the good.

The "fourth hurdle" - socio-economic impact of new technologies - has not been added to the list of criteria for agencies such as the FDA to evaluate. Anti-technology critics consider socio-economic impact to be second only to safety. The evaluation of socio-economic impact should be made by the public or third party experts, not the FDA.

Perhaps the arguments about socio-economic impacts should be raised to a higher level. Is it fair to society to reject technology because it may change the structure of an industry? What industry is saved and what industries are prevented from developing? What about the socio-economic impact on a large portion of the six billion people that will inhabit the earth in the early 21st century? Can we be so selfish as to protect existing societal and industrial structures and not address the food needs of the future?

One pork producer urged caution with respect to the use of "hormones" (Braaten, 1990). He said negative consumer perception would combine with the increased tonnage of pork due to increased efficiency to lower pork prices. He acknowledged rpST would make pork more competitive with chicken, but was not interested in pork becoming capable of mass producing cheap meat if profit margins are less. In his eyes, the consumers would benefit, the drug companies would have a new market, and producers would be the victims. His arguments cannot be ignored. Those scenarios should be considered. However, I believe the majority of producers who agree with this point of view would still adopt the technology if they were comfortable that consumers would accept their products and demand would not suffer. A longer term view could be developed if a world food policy showed promise that a large world population would, in fact, have access to abundant production and producers would be fairly compensated.

We should learn lessons from history. Robert Cassens (1990), in his new book about the ten-year struggle over nitrites in cured meat said three forces contributed to the "shock wave" which almost destroyed the meat industry. These forces were:

1. An unsuspecting and unprepared industry which was basking in previously achieved technological advances and preoccupied with business, marketing and labour.
2. A fundamental scientific community delving into toxological and analytical areas and knowing something, but not enough.
3. The consumers being swept along in tremendous sociological changes and being led by a new breed of activist who received vital assistance from the media.

These three well-explained forces could be summarized as such:

1. An unprepared industry;
2. A weak commitment to basic research;
3. Consumer concern.

Education and Information

Those of us associated with animal agriculture should design a strategy to enlighten the consuming public about useful technologies that result in the production of wholesome, safe, nutritious food. People who produce food should be proud and project a positive public image.

The National Science Foundation, through Northern Illinois University, recently surveyed 2,041 people in the U.S. and found that 5.6% were sufficiently literate in the sciences to make informed decisions about issues such as nuclear power or toxic wastes. In the U.K., 7.1% of respondents were scientifically literate (Miller, 1989). But, in spite of these findings about the level of public knowledge, decisions affecting the fate of agriculture are being made on the basis of public opinion. That opinion is influenced more by public education and the news media than it is with knowledge of production technology. This tells us that both producers and biotechnology companies need to be more involved in informing the consumer. More important, however, we all must work to improve our educational systems so more citizens can responsibly understand and participate in the formulation of public policy.

The authors of Megatrends 2000, Naisbit and Aburdene (1990), say that the issue of biotechnology will not go away and that it is too important to delegate to the experts! The experts should improve their credibility. An observer of the ozone layer issue (Brodeur, 1986) said the failure of society to deal with technical issues depends on: indecisiveness of the scientific community, timidity of regulatory agencies, ignorance of the public, inconsistency of the press, indifference of many nations, and obstruction and obfuscation of industry.

Research scientists and administrators must assume some responsibility for communicating with the public. The public continues to believe the world is better off because of science. The scientific community is generally highly regarded, ranking second only to medicine among 13 institutions surveyed (Anon, 1989). They should explain biotechnological principles in understandable terms. Predictions of the impact of new developments should be realistic. Unrealized promises hurt the credibility of science. The public should be treated with respect, their concerns addressed, and their questions answered. Scientists must maintain the trust of the public so they are allowed to help make risk assessments.

NPPC Plans on Biotechnology and Communication

NPPC plans to be involved in consumer attitude research and focus groups to determine what aspects of technology development concern the public. Briefing sessions with opinion leaders and government officials, keeping them informed, will help alleviate surprise. Regular contact with researchers, manufacturers and regulators will keep up-to-date information flowing among these groups and help NPPC keep its member producers well informed.

When a new product such as somatotropin is approved, fast action to get correct information to the public will be needed before marketing of the product. This may include news releases, advertising and briefings to widely disseminate the facts about the new product or process.

The industry is best served if the public has full confidence in the FDA and USDA. Industrial organizations and commodity groups should support the decisions of these agencies, supply them with industry information, and assist in consumer education to ensure smooth implementation of new technology.

Conclusions

Producers and processors will implement new technologies if they will benefit from them. The public will accept new processes and products if they perceive them as safe. Public opinion must be the result of informed consensus derived from open discussion of food safety, risk assessment and cost benefit analysis. However, science education and communication among scientists, producers, media and consumers must improve to accomplish this.

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SESSION VI
ENVIRONMENTAL AND SOCIO-ECONOMIC IMPLICATIONS

* Environmental implications
* Socio-economic implications
* Implications for animal production system

SUMMARISED AND ADOPTED CONCLUSIONS FROM PAPERS AND DISCUSSION

ON

ENVIRONMENTAL AND SOCIO-ECONOMIC IMPLICATIONS

Chairman:
D. Lister, *CAB International - UK*

Discussion panel:
L.M. Crawford, *USDA Food Safety Inspection Service - USA*
J. van Hemelrijck, *FEDESA, Brussels, Belgium*
V.W. Ruttan, *University of Minnesota - USA*

- *Session VI reviewed the environmental and economic issues and the role governments might have in determining the* ***prospects*** *for, and* ***acceptability of the developing technologies.***

- *The first paper by Colin Tudge took the view that considering rST* **technology in relation to environmental matters** *was largely a question of what was sought from agriculture in general which might be to feed the world's population whilst* **maintaining the biodiversity of species.** *This could be achieved by approaches based on intensive systems of agricultural production in which rST would have an obvious role but there were strongly held beliefs emerging that greater reliance should be put on extensive agriculture where a role for rST might be more difficult to support. The use of rST in intensive systems not only permits a reduction in the number of animals required for a given level of production but is nitrogen sparing and gives rise to* **less pollution from nitrogen sources. Land could be freed for other purposes** *and the risk of decline in predominantly animal species reduced.*

- *Dr. Boussard presented the argument that, based simply on economic grounds,* **rST technology** *was likely to prove* **beneficial perhaps especially** *so in* **developing countries.** *For milk, the cost of rbST use is very much less than the anticipated returns although the net costs per extra unit of yield of milk are little changed. rpST ought also to provide economic benefit and such complications as are conceivable pertain to land use and availability. Using* **rpST will save land** *which will create problems where land is plentiful but can offer solutions where land is in short supply.*

Technical progress will be increased by rST technology but its adoption will depend on politico/socio/economic pressure to support or deny it. Either way there will be transitional difficulties caused by the freeing of land, manpower and capital. There will, therefore, be a **pressing need for ameliorative government intervention** *to accommodate the changes which the introduction of rST into animal agriculture will inevitably generate.*

- *The* **socio/politicial dimension** *was brought into more immediate focus by Drs. Fallert and Crawford who had concurrent involvement with the NIH hearings on somatotropin. Dr. Fallert recounted the agricultural scenario into which the new technology would need to be fitted. In particular there is a national and international reduction in the number of farms matched by a compensatory increase in the size and output of those remaining. There is universal pressure to reduce agricultural support and make agriculture more responsive to market forces.*

- *History acknowledges the effective uptake of new inventions, developments and technologies by farmers but recently concerns have been voiced by the* **general public which have impeded and even halted the introduction of new science into agriculture**. *The safety and wholesomeness of food are matters which are widely felt not to be safely left to government. The same applies to animal welfare, safety and pollution. But governments and regulatory authorities find difficulty in accommodating these socio-economic issues in the regulatory process. Professor Ruttan felt that many of the background problems to be of our own making and that* **scientists should have prepared the way** *for the current innovations rather* **more carefully**. *rST technology, it can be argued, is in essence no different so far as its role in agricultural production is concerned from any other development presented to the agricultural and food sectors in previous times. It is the rate of progress and the changing public perceptions which are at heart of today's problems and the agricultural science community should recognise this and take the appropriate action.*

- *Dr. van Hemelrijk pointed out that there are further features of the debate which have emerged in the European Community though they are also readily acknowledged in other regions of the world. The* **notions of efficacy, safety and environmental impact are paramount** *in the acceptability of any new product or technology. They are dealt with in various ways from one regulatory authority to another and there is some overlapping of the standards to be met. In the U.S.A, the Animal Health Institute concerns itself with public education. In the European Community more emphasis is placed on Community law. The chain of legislation is, however, adequate by itself and must be accompanied by effective control measures which*

unfortunately are not always policed. There are now **moves in Europe** *to create quality assurance schemes for the food chain as a whole rather than its component parts.*

- *Whatever the concerns, there was a clear recognition that intellectual arrogance, political naivete and lack of public awareness by scientists will neither help the cause of science nor the introduction of new technologies for the public good.* **Science,** *at least, can begin to* **put its own house in order.**

GROWTH HORMONE BIOTECH AND THE ENVIRONMENT

Colin Tudge

London - UK

Introduction

I am very much on the side of the environment, which I suppose is why I have been invited to talk at this meeting. But I do not share the view that I felt is held by many who apparently espouse the same cause. I am not anti-science and anti-high tech (which I define as the kind of tech that depends upon science and comes out of science). I am certain that the world's food and environmental problems, which are so closely linked, cannot be solved without the application of some very fine science indeed, and some very sophisticated high tech. Specifically, I have no doubt that molecular biology in general, and genetic engineering in particular, will play many important roles in helping human beings to feed themselves and in helping us to protect the rest of nature. So, that means I am not prejudiced against the specific high technologies that surround growth hormones. But at the same time the needs of the environment and the needs of humanity are more important than any one technology or any one industrial company, and if we find any technology lacking, we should not be afraid to throw it out. "If thy right hand offends thee, cut it off".

To be sure, at first sight - or as a ploughman might say, "at the first pass" - the growth hormone technologies look very good from an environmental point of view.

Intensive livestock production

First, we should observe that these technologies, as they now stand, and as they have been developed, are geared towards intensive livestock production. This is inevitable. Intensive production concentrates cash as well as output, and makes it possible to finance technological innovation. Secondly, of course, in intensive systems the many variables are largely controlled, so it becomes possible to measure accurately the impact of any new development. Hence we can see that treated animals convert more of the nitrogen they are given into protein; we can see that they produce relatively less fat; we can see that their urine contains less nitrogen, and hence may be less polluting; all as described to us by Pieter van der Wal.

We should obverse, too, that nitrogen pollution - like most forms of pollution - is in general far more complicated and potentially even more pernicious than it is usually given credit for. Thus, people commonly think of N pollution purely in terms of run-off. But that is only a small part of the tale. Recent studies at Rothamsted Experimental Station in England have shown that every hectare of Britain - except perhaps in the remotest areas - receives 40 kg of nitrogen *from the atmosphere.* This is a staggering amount; perhaps a third of what a farmer might apply to an arable field. Some of these nitrogen compounds come from car

exhausts but much originates as ammonia and oxides of nitrogen released from agricultural fields. For commercial foresters and organic farmers (who don't like to add artificial fertilisers) this nutrient from the sky is a bonus. However, its effects on wild floras have not been directly assessed but are likely to be disastrous.

The indirect effect of these oxides of nitrogen is their contribution to acid rain - which has been widely discussed, although there are still several mysteries to clear up. In addition, however, wild plants in general are adapted to soils with a very *low* nitrogen content. Infertility is the usual order of things in nature. Most wild plants languish if N is too high, or simply fail to respond to it - and thus they are ousted by that minority of plants that are adapted to a high N input, and do grow rapidly in response to it. These, of course, are the plants that customarily flourish on agricultural land and are classed as "weeds".

In semi-arid Australia the native flora is of the kind known as "bush". It is extraordinarily varied. The bush of Western Australia includes 9000 species of flowering plants - about six times the number found in Britain. However, in much of Western Australia the bush is reduced to 'remnants', dotted among arable fields. Studies at the CSIRO's Division of Wildlife and Rangelands Research in Western Australia have shown that species variety is declining rapidly within these remnants - in other words, many species are becoming locally extinct - and that one of the main reasons for this is the encroachment of N from surrounding fields. Now this probably is, mainly, a direct seepage effect, rather than a descent of oxides from on high. It seems likely, too, that wild plants in other parts of the world might not be quite so nitrogen-sensitive as those of Australia - which is an ancient continent that is fabulously infertile. But the point is made nonetheless. Wild plants flourish in infertile soils. Indeed, we might even infer an inverse relationship between number of species and degree of fertility - a point that seems paradoxical at first but becomes less so as you start to think about it. But we can sensibly extrapolate from the Australian studies; and infer that the showering of nitrogen compounds on to the wild floras of the world in general is liable to prove extremely damaging simply because of over-nutrition. Reducing the amount of N that is wasted by cattle and is ripe for sublimation may not make a huge contribution. But the generalisation is that surplus N is even worse than is usually appreciated; and anything that reduces it is helpful.

But we should never be content to discuss any issue simply in its own terms. We should always ask about content. Given that - at present - growth hormone technologies are part of intensive livestock production, we must ask, "is intensive livestock production good for the environment?". In other words, "are the growth hormone technologies being used in a 'good' context?"

Well, to many people who think of themselves as "environmentalists", intensive livestock production is the bete-noire. But again, we can make very powerful environmentalist arguments in its favour.

In general, there are two main ways in which to design an environmentally friendly agriculture. The first is to produce as much food as possible from the smallest possible area, and so leave a great deal of other land for other purposes, including wildlife conservation. The second is to devise "extensive" systems, producing far less food per unit area, but hospitable to other species. Let us compare these two approaches.

In terms of production per unit area, intensive systems look very good indeed. They commonly produce several times as much food per unit area as extensive systems - and in the case of livestock, often several hundreds of times more per unit area. "Per unit area" is what counts, for of all the inputs of agriculture, land (together perhaps with light) is the one that is least expandable; and the one whose expropriation effects other species most directly.

Of course, to some extent - even to a large extent - the land economy of intensive systems is deceptive. Intensive units are like factories: they process inputs from far and wide. In ecological terms, intensive livestock units are like estuaries: the animals within them convert nutrients brought in from entire catchments.

The true area of an intensive livestock unit is its own patch of land plus all the hectares of cereal, pulse, and other fodder that feed into it. This of course will be many times - even hundreds of times - greater than the unit itself. Even so, though, if you do all the sums, well run intensive livestock units that are supplied by intensive arable systems come but very well in terms of animal energy and protein produced per unit area.

Then again, all production systems, livestock or factory, produce waste. Intensive livestock units have often pushed out effluent in offensive and damaging quantities. this, too, is deceptive, however. Extensive systems seem far less polluting because the organic nitrogen produced by the animals is processed locally by soil bacteria, and most of the inorganic nitrogen thus released is taken up by pastures or oxidised into the atmosphere. Cows in a field do not smell, as those in an intensive dairy unit may do.

But each individual animal in an intensive unit is liable to process its food more efficiently than an extensive animal, because it spends less energy moving about and keeping warm, and because it will probably have been bred specifically for feed conversion efficiency rather than for the ability to survive in the great outdoors. So the total amount of effluent N produced will be less in an intensive system than in an extensive, *per unit of feed consumed*, and per unit of meat, milk, or eggs produced. When intensive unite are polluting it is because the appropriate technology has not been installed. But in general we could say - at least if we kept our fingers crossed while saying it - that the effluent from intensive systems should in principle be *more controllable* than from extensive systems.

In general, then - intensive systems are often under-engineered, and therefore can be polluting and non-friendly to the environment. But this is not inevitable. If they are designed and operated properly, they can, taken all in all, be *less* polluting.

Extensive production systems

What of extensive systems? How friendly are they to the environment?

Well, some extensive farming systems have been around for so long, and are so interesting in their range of species, that they have become accepted even by biologists as part of the proper order of things. Some extensive systems create ecosystems that are in some way *richer* than the pristine environment. Thus plants are still surviving on the chalk downlands of England that in other parts of Britain became extinct soon after the Ice Age. Reason?

They are plants that naturally grow north of the tree line - which in the last Ice Age was in Southern England. But trees have been kept at bay from the downs in the millennia since the Ice Age by grazing sheep. Similarly, the loss of sheep from around England's south-west coast has endangered the local chough, which like to take invertebrates from grassland - but prefer *short* grass. Admittedly, deer probably did the job before there were sheep (not rabbits, which came to Britain some millennia after sheep); but it's the sheep that kept the chough in business.

Australian aborigines are thought of as the world's great hunter-gatherers; not as farmers at all. But Rhys Jones, anthropologist from Canberra, argues rather that for the past 40.000 years aborigines have practised what he calls "firestick farming"; setting fire to the bush at regular intervals and in a very orderly fashion, to encourage fresh growth and provide foci of huntable animals. That is extensive farming of a kind; and it has created a flora and fauna that must be profoundly different from that of pre-aboriginal times (when there were many mega-marsupials and giant reptiles in addition to the present fauna) but is a rich end "valid" ecosystem in its own right. And anything 40.000 years old deserves to be called "natural".

On the other hand, we know that extensive farming systems can be extremely delicate; and if extensive farming is insouciantly carried out, or if too many people farm extensively at once, then extensive farming can be very destructive indeed. Vast areas of Australia have been laid waste by excess cattle brought in by Europeans; Africa's Sahel and India's commons are severely overgrazed; much of South America rushes straight from tropical forest, through pampas to desert in a few brief years; and so on.

In Britain, at present, under the auspices of the Agricultural and Food Research Council, there are quite a few projects to reconcile extensive agriculture with environmental friendliness and stability. Scientists at what is now the Macualey Land Use Research Institute seek to optimise the use of heather and gorse, as well as of grass, by sheep, to create an upland landscape that is also hospitable to other species such as grouse. At the Institute for Grassland and Environmental Research there was until recently a prolonged study of the effects of grazing by cattle on the native pastures of the Somerset moors - the notion being to reconcile the two.

Extensive farming at its best, in short, can be beautiful, species-rich, and productive - though only at its best; and in general, the more productive it becomes the more the wildlife suffers. Wildlife in significant numbers plus food in significant amounts is a very difficult - interesting, but difficult - equation to get right. Much of extensive agriculture in Britain at least is a whited, or rather a greened, sepulchre. It looks terrific, but there's not a lot living out there, except the cows and the grass.

Systems between the extremes

There are, I should say, positions between the extremes, in which areas of land on farms of whatever degrees is intensity are ear-marked for wildlife - such as hedgerows and areas of marsh; the trick being (again under study by AFRC) to know which wild species need what. For example, a scheme masterminded from Oxford University currently seeks to define

stopping-off spots for wildfowl, as they migrate through Britain, and farmers will no doubt be compensated in some way for keeping those spots intact.

In short, our second pass suggests that there are good environmentalist cases both for intensive farming and for extensive. In general, the world's *land should be laid out as a mosaic*; some land *devoted to food production*; some *devoted to wilderness*; and some seeking to *combing the two*, with extensive regions artfully - ideally - designed to accommodate wild creatures as well as to produce food. The model, perhaps, is already provided by Australia's Great Barrier Reef, some of which is devoted to intensive fishing, some of which is apportioned for tourists, and some of which is left pristine.

What is intriguing, though, - and contrary to many "environmentalists" expectations - is that intensive agriculture probably should play a much bigger role in this mosaic, than extensive. The loss of efficiency in extensive systems (in terms of amount produced per unit input) is rarely balanced by overall environmental friendliness, and in practice, extensive systems can be extremely unfriendly to the environment, and often downright destructive.

Thus, at this second pass too, it seems that the specific technologies surrounding growth hormones come out of environmentalist discussion very well. They increase éfficiency. They reduce inputs relative to outputs. They reduce wastes, relative to outputs. Even if they are considered solely in the context of intensive livestock production they come out well, because intensive livestock production itself comes out well. If they can be extended to livestock in extensive systems - well, that is a bonus.

What do human beings actually need?

But if we are really taking the world's problems seriously; if we are, really seeking to feed the many billions of people who will soon be on Earth and at the same time to save the majority of other species, we cannot leave matters there. So far, after all, we have tacitly assumed that the world's agriculture, taken all in all, is already producing the right things. All we have asked, is how those things can be produced most efficiently. The bigger question - if we are really taking the planet's problems seriously - is whether, in fact, the things we are now producing are the right things.

To answer that larger question, we must go back to basics and ask, "what do human beings actually need?"

The answer that is now forthcoming from nutritionists runs roughly as follows: 2000 kcals of energy per head per day, of which 5 - 10 per cent should be protein; plus a mixed bag of minerals, vitamins, and essential fats, all laced with fibre. Some commodities - notably non-essential fats - should be avoided in excess; and even protein in enormous quantities, has its detractors. Why de-aminate what shouldn't need de-aminating? Why burden yourself with surplus organic nitrogen?

To be environmentally friendly, we should contrive to produce these nutrients with minimum resource - and, in particular, with minimum input of land. So how can that be done?

Well, as everyone now appreciates, *human* beings *eat most economically* (in terms of environmental input) if they derive the *bulk of their energy and protein directly from seeds*; which usually though not necessarily means cereal and pulse. Vegetables, fish, meat and dairy products then serve merely as trickers-out - suppliers of vitamins, minerals, and essential fats; and, essentially, of flavour. You may argue that such a diet would be tedious in the extreme. In fact, of course, *all* the great cuisines of the world - Indian, Chinese, South East Asian, North African, Mediterranean including French Provincial, North European, Central American - are based on precisely this apportionment of foods. The basis of Chinese and Indian cuisine is the bowl of rice or the wheat-based "pancake" or bread - chapatti, nan, paratha, dosa and the rest. Scotland has haggis and neaps - oat-based. French cooking in its present form - which is the root of *haute cuisine* - is remarkably austere; excellent bread, cassoulet, etcetera. There is no hardship, no austerity, no real self-Manial in eating the way that the modern nutritionists recommend. We merely have to re-discover traditional cooking.

Now- here's a revolutionary thought. Wouldn't it be a good idea to design agriculture expressly to feed people? Designed, that is, to meet nutritional needs and also to respect gastronomic aspiration? In the recent history of the world, funnily enough this has not been attempted very often. Britain did it in World War II, when we were under seige. China attempted it in the years after Mao's revolution - and although the Chinese did not succeed in feeding everybody, they did a lot better than the pundits predicted. In general, though, present-day agricultures are designed (or at least they "happen") in response to a whole number of different pressures; those of the west in accord with the business demands of capitalism (albeit much modified); those of Soviet Russia designed to show that collectivism works (which in this context it clearly didn't); and those of the Third World, a series of political footballs.

Suppose, though, we did design agricultures primarily to feed people - and to do so while making best use of land. Such an agriculture could truly be called "rational"; and all agricultures that were not so designed, could properly be considered "irrational". Rational agriculture would by definition be the most environmentally friendly that we could conceive of. How would it be designed?

Well, clearly, the most suitable areas would in general be devoted to cereal and pulse, which would be eaten directly. Especially favoured areas would produce vegetable and fruit. Much as at present.

The major change, however, would be in livestock. There wouldn't be none at all, as the vegetarians advocate. *Nutritionists demand livestock* - if only as a *source of minerals and essential fats*, though *it also has advantages as a source of energy and protein.* But there need not be much: meat in a "rational" diet would be the *garnish, rather than the centrepiece.*

In general, then, livestock would primarily be raised either on odds and ends - agricultural by-products such as pigeon-pea stalks, or swill; or it would be raised on land that could not reasonably be used for major crops, such as the Scottish or the Ethiopian hills. In the latter cases, it would be raised in extensive systems that were designed to be friendly.

There would be two exceptions to this, however. First, a society that elected to subsist primarily on cereal and pulse should strive to produce surpluses, Because yields are innately variable, and in some years there will be shortfall. But in most years there will, indeed,

be surpluses; and livestock should be kept as a sump population, to mop them up. Of course, if animals are kept through the winter on surplus cereals and pulses, there will be more around to make better use of grazing in the following summer, so this makes sense on two counts.

Secondly - and very importantly - animals in the Third World are not mere food. They are also sources of fuel and clothing (as they are everywhere, of course) and, vitally, of transport and traction. neither is it the case what animal traction is merely a stop-gap, waiting for tractors to be introduced. Many engineers as well as agriculturalists, including some at the AFRC's institute of Engineering Research, feel that animals are the best form of transport and traction in may Third World contexts.

So - where does this leave growth hormone technologies?

Clearly, the crucial question is not, "how do these technologies affect the friendliness of present-day agriculture?"; but, "how could they be Fitted into "rational" agriculture, that was truly designed to feed people without wrecking the environment?"

And there, it seems to me, the jury must remain out.

Clearly, the growth hormone technologies do enhance the efficiency of animals in intensive livestock systems, which, environmentally, is a good thing. But it remains to be seen whether and how much importance would be attached to intensive livestock production in a truly rational system. I suspect it will have some importance; there will, after all, be cereal and pulse surpluses. But I suspect, too, much less than at present; because cereal and pulse would not, in a rational system, be grown in large amounts specifically for livestock, as it is at present.

On the other hand, FAO now advocates zero grazing in the Third World. If fodder is taken to animals in byres, they do not poach the ground or trample what they do not eat, and their dung-can later be distributed much more evenly. Zero grazing also provides labour, which in Third World countries is almost always a good thing. In general, zero grazing is environmentally friendly, because it increases efficiency (the same food for less input) and because it should increase control over potential pollutants. There seems to me no reason why growth hormone technologies should not improve the efficiency of animals eating pigeon pea stalks. But there could be a price to pay. So far as I know, the necessary research has still to be done.

Then again, cattle are not and would not be kept in the Third World just to eat pigeon pea stalks. The desire, now, is for multi-purposes animals; cows, indeed, that can pull a plough while pregnant. produce a beefy calf, and give milk, all at the same time. Would these new technologies enhance the abilities of such animals in such a context? If so, then this seems to be a social and an environmental plus. But again, the research has to be done. Among the possible caveats are the other variables; the difficulty, for instance, of controlling disease in Third World livestock, without which it becomes hard to measure the impact of any refinements.

One last environmental point. One reason for keeping cattle intensively is that it enables the world to keep more cattle than they could if they simply grazed on natural pasture. It is

now clear that methane contributes significantly to the greenhouse effect: nothing like as much as carbon dioxide, but still enough to be measurable. It is also clear that significant amounts of methane are generated in the guts of termites and of cattle. There is an argument - perhaps not a huge one, but still and argument - for keeping fewer cattle, to alleviate global warming.

Conclusions

At first sight - pass one - these new growth hormone technologies seem environmentally excellent. They reduce unit input per unit output. They reduce pollution per unit output.

At second sight - pass two - they still hold up. They are at their best - we may presume - in the context of intensive livestock production. And if we set out to produce the kind of food we produce now by the most friendly methods, then intensive livestock production emerges as a valid and extremely valuable system.

At third sight, however - pass three - the picture becomes murkier. If we truly took the problems of humanity seriously, and those of the planet as a whole; if we truly set out to provide food for the 10 billion people who could inhabit this Earth by the middle of the next century, and for several centuries after that: and if we truly set out to conserve the larger proportion of the 30 million or so other species with whom, at present, we may share this planet - then we would set out to design a new kind of agriculture. This could be called "rational" agriculture; and rational agriculture would be different in several highly significant ways from those of the present. In particular, livestock production would be less significant, and multi-purpose animals would be more significant.

How the new technologies would fit into a system that was truly rational remains to be explored. Clearly, though, if the new technologies are employed merely to enhance systems that are not rational then they cannot truly be considered to be environmental friendly.

I think it would be possible, if we applied our best science in a rational context, effectively to re-create Arcadia. But as they say in Ireland, if I was going there, I wouldn't start from here.

SOMATOTROPIN: AN ECONOMIC VIEW

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Summary

The land, capital or labour saving character of somatotropin is discussed. In the case of bST, the innovation is moderately land saving, whereas it saves capital, and substitutes skilled for unskilled labour. In the case of pST, it is firmly land saving, thus encouraging intensification. As a consequence, in Europe, it will exacerbate the detrimental consequences of the Common Agricultural Policy. In the US, it may provide pork producers with additional comparative advantages, but depress the price of land, and increase regional specialisation. It is not sure that the technique can be made use of by developing countries. If it were true, livestock production could be transformed in a way similar to the transformation of cereal production by the "green revolution", the more as the two movements are likely to mutually reinforce themselves.

Keywords: *Technical progress, land use, production location, farming intensity, Common Agricultural Policy.*

Introduction

The possibility of administering large quantities of elements of the somatotropin (ST) family to most domestic animals undoubtedly opens a new era of technical progress in the livestock business. But because developed countries agricultures have a general tendency to overshoot demand expectation, and since, most of the time, public budget are in charge of creating artificial demands for unwanted quantities, most public decision makers will consider the mere possibility of any productivity increase in agriculture as, at least, a mixed blessing. As a consequence they will actually make considerable efforts to prevent such an event to occur. The point of view of an economist is somewhat different, however. In fact, no economist would deny technical progress its virtues. The real problem, with ST as well as with any similar change in the production possibility set, is whether is it really a technical progress, with which consequences. In addition, it is also to assess to what extent adverse consequences, if any, could be avoided by suitable policies. This is the subject of this paper.

The notion of technical progress

For an economist, "modernization" is not necessarily a technical progress. In fact, two very distinct kinds of change are involved in what is commonly called a technical progress,

such as, for instance, harvesting with a combine harvester instead of with a scythe. First, there is a substitution of capital to labour. Such kind of technical progress occurs in response to price movements, for instance an increase in the price of labour, and a decrease in the price of capital. Such changes do not necessarily imply any change in technology, that is, in the stock of human knowledge. Actually, horse powered harvesters were put in use as early as during the 4 th century BC, in what is now northern France, precisely because, for many reasons which encompass the scope of this paper, labour was going to be scarce at that time. In technical economic language, this is moving along an isoquant.

Second, there are also "true" technical progresses, that is changes which occur because the new technique, for a given production level, uses less than at least one input, without requiring more of any other. This is described in technical language as "move of the isoquant toward the origin". Such moves take place whatever the price system, because, in that case, the advanced technology dominates the other ones for any price setting. Of course, such technical improvements spread over very quickly as soon as farmers are aware of their existence.

Actually, most of actual technical progresses are complex moves, combining both kinds of change[1]. For instance, modern harvesters associate a capital/labour substitution effect with a true change in the production possibility set, because all the capital which would be necessary to sustain the army of workers required for scythe harvesting the area which is processed by one such craft would probably be enough to buy two of them. For that reason (and for that reason only), combine harvesters represent a true technical progress over scythe.

In addition, it is clear that the discussion just outlined must not be reduced to the case of a two input / one output problem: Agriculture produces many outputs from many inputs. As a consequence, the preceding observations must be considered within a multidimensional setting, with as many dimensions as the total number of inputs and outputs.

Is somatotropin a technical progress?

In this context, what can be said of ST? I have not the honour of deserving the name of a biologist, and I may be wrong in interpreting your discussions. For that reason, I do not pretend that what follows is factually correct. What is true is that it represents the idea (right or wrong) that many economists have presently about the technical effects of ST. To some extent, this conference will precisely serve to determine whether this interpretation is correct[2]. In short, this interpretation is as follows: The consequences of ST are quite different for meat and milk productions. In the case of milk, there is a production increase per animal. But there are no significant changes in the quantities of energy and of protein which are

[1] see especially, the classical work by Hayami and Ruttan (1971).

[2] My technical information comes from synthesis, second hand, papers from which such an august audience is not likely to learn anything, but which are invaluable for an ignorant as I am: Chillard et al (1989) or Colleau (1990) for bovine somatotropin, Bonneau (1990), Bonneau et al (1990) for porcine somatotropin. See also the important and comprehensive report of the USDA, as well as an unpublished document (CREA, 1990)

necessary to make one additional kg of milk. As a consequence, it reduces the costs which are genuinely tied with the existence of one individual animal: In the case of milk, this is mainly the working time necessary for milking, as well as milking parlour number, stables, etc... .This is also the nutrient requirements for the maintenance of one animal. Given the already high ratio: production requirement/maintenance requirement, this last item is not very large. In addition, this lowering of the maintenance feed requirements is offset by a corresponding reduction in meat production of the milk cows.

From another point of view, bovine somatotropin (bST) is generally considered (Mouchet, 1989 ; Cordonnier and Bonnafous, 1989 ; Cordonnier, 1989) as a potential regulating device in herd management: Since it is possible to give or not to give the drug to animals, it is possible to use it for increasing production when markets or general conditions are good, and decrease it in the opposite case. Again, such a usage would increase the general efficiency of a farm, and improve most of input/output ratios.

Thus, somatotropin, in the case of milk production, saves capital and labour, mainly unskilled. Conversely, it requires skilled labour, and some capital to buy and administer the drug. Will this skilled labour be that of a veterinarian? As far as I know, this point is still pendant. This is important, because, if a veterinarian is required, this implies a large lumpy cost for a herd (obviously, the veterinary will charge travel costs on a lump sum basis), thus making economy of size important. Otherwise, there is no reason for the innovation not being adopted by very small part time farmers. In any case, since these costs are very small, and almost negligible by comparison with benefits, ST, in this context, is a quasi true labour and capital saving technical progress, the adoption of which is likely to be very quick if the drug is to be authorized.

In the case of meat the problem is slightly different: The effect of ST is to reduce the proportion of fat in meat. Since fat is more demanding in energy than muscle making, the net result is an increase in the conversion coefficient of starch to meat. Again, this is a technical progress, but very different from the previous one.

First, bovine meat does not seem to be affected, insofar as bovines in general do not produce much fat. This is an exception for third world herds, with some breeds (such as African Zebus) which could very quickly benefit from the innovation, if not too costly. But since data are scarce on that point, the discussion, here, will be mainly focused on pigs. For pig enterprises,in addition to the reduction of animal related costs, (labour and capital, as seen above), ST will significantly decrease the quantity of nutrients required for a given meat production. The importance of this observation will be made apparent after a discussion of the production intensity concept.

The notion of production intensity

An agricultural production process is said to be more intensive than another if it uses more non land inputs per unit of output. The importance of the concept spurs from the fact that land is always the ultimate fixed factor in agriculture: It is always possible to increase the capital or labour involved in agricultural production, if the price of output justifies it. But land, this "free gift of nature", is fixed by the boundaries of states, or even by the radius of the earth.

Thus, even if the agricultural production function is genuinely "with constant returns to scale[3]. "the fixity of land makes it "with decreasing returns to scale", implying, in a fixed technology context, the necessity of increasing prices to increase production, unless free land be available.

Conversely, in case of excess production, the fixity of land guarantees that decreasing agricultural prices would decrease production, by inducing farmers to choose more extensive production techniques. Thus, in a fixed technological environment, the farming intensity level seems to be the key determinant of agricultural production, and the instrumental variable which will govern the correspondence between needs and production possibilities.

Now, technology is never constant, and is basically unpredictable. It turns out that the recent evolution of technical progress in agriculture is such that, at current agricultural prices, intensifying, hence increasing per ha production, is often profitable, up to the point that current food solvable needs are much more than met. As a consequence, in developed countries, land is presently in excess, as shown, among other symptoms, by the existence of land set aside programs in operation on both sides of the Atlantic. This raises a host of problems, the discussion of which is clearly out of the scope of this paper, but the existence of which helps to understand the importance of answering the question about the nature of the relationships between land and somatotropins. In effect, if ST is a "land saving" technical progress, it will exacerbate the above mentioned difficulties. In the opposite case, it will alleviate them.

Bovine somatotropin and land: the interferences of international trade

From the above discussion, it is clear that rbST is practically neutral with respect to land in the case of milk, (because it requires basically the same quantity of nutrients per kg of milk, and assuming no change in the per ha yield of nutrients), and noticeably land saving in the case of pork. As a consequence, rbST should leave political decision makers rather indifferent. On the contrary, rpST should be a matter of concern. Things are a little more complicated than that, especially with rbST, and especially in Europe.

In effect, in Europe, milk cows nutrients are seldom produced "on the farm". This is partially a consequence of the inconsistencies of the Common Agricultural Policy: For various reasons, the starch equivalent has two quite different prices when locally produced (as a grain crop) or imported (as a "cereal substitute"). As a consequence, the European farmer has all the reasons to sell his grain to the government (this grain will eventually be reexported at the expense of the treasury, which will pay the difference between the international and guaranteed prices) and to buy back American or Brazilian soybean, to feed his cows. For that reason, the European produced milk is not only made of European land, but also of the American, or Asian land which is necessary to produce the large quantities of

[3]Technically, it is said "homogenous and of degree one", for if it is possible to produce a given quantity of agricultural commodities with 1 ha of land, 10 hours of labour, etc...., then it is possible to obtain twice this quantity with 2 ha of land, 20 hours of harvester, 40 hours of labour, etc... In that case, production can reach infinity if all inputs are available and if outputs are sold at fixed prices.

imported feedstuffs used in European agriculture. The magnitude of these surfaces are enormous: between 10 and 30 millions of ha, that is, the same order of magnitude as the french agricultural area.

In that context, since the introduction of ST is likely to increase the proportion of concentrates in the total herd calories intake, it will be viewed by European authorities as an additional trouble, since it will increase the chances of Brazilian, Asian, or northern American land to substitute to European land in the feeding of European cattle.

It must be noticed that this particular problem arises only as a consequence of the unfortunate decision of stopping halfway in the protectionist policy which was decided at the beginning of the common market: Without any protection, or with a full, starch content based, protection of feedstuffs, the difficulty of indirect import of non European land in Europe would vanish almost completely.[4]

Apart from this problem, rbST may actually increase intensity, but through a slightly different process, because of the limited stomach capacity of cows. Because of this limit, the quantity of roughage a given cow can ingest is limited, and, therefore, all feed increases will be made of concentrates, either cereals or oilseeds. Now, it turns out that these commodities are relatively easy to transport and stockpile (which means that the location of milk cows will be easily made distinct from the nutrients producing land) and also that the technical progress is quicker in their case than for rough fodders (which means that, in addition to the slight land saving effect of the small reduction of nutrient requirements at the cow level, there will also be a land saving effect due to the substitution of land extensive grains and oilseeds to the land intensive rough fodders in total cows calories intake). In that sense, rbST will reinforce an evolution which it did not trigger. In addition, in view of the large number of involved parameters, it is very difficult to assess the extent of its role in this evolution, and to predict its direction in the future.

Thus, the general impression coming out of this discussion is that rbST will have an effect toward more intensive farming, but that this effect is slight, and without many practical consequences if one is not too worried that European cows can use more Brazilian land, or that Wisconsin can produce milk from Iowa maize.

The case of rpST is quite different.

Porcine somatotropin and land: toward important reallocations

In the case of pork, clearly, rpST, in addition of being capital and labour saving, is also land saving. The consequences are important. First, geographical reallocations will occur, because all kinds of pork will not react in the same way. Maybe the Danish pork, already

[4]It must be added that such a rebalancing of Common Agricultural policy, so "wishable" as it may be, (and whatever its sense, that is, toward more or less protectionism) would create serious transition problems: The dutch herd, for instance, which relies mainly on foreign land through imported feedstuffs, would be submitted to very hard pressures, involving dramatic reallocations of virtually all agricultural assets.

selected for their ability to produce small quantities of fat and large quantities of muscle, will loose a part of their comparative advantage, by comparison with many middle western pork plants. Although such reallocations may trigger interesting discussions at government level, they may not be the most important. Two other consequences deserve consideration.

First, large areas of land will become available for other usages. Of course, if the gain in feeding efficiency is 15 %, this does not mean that 15 % of the surfaces presently devoted to pork feeding will be made free. With such a gain in productivity, a similar fall in average price is to be expected. This will encourage pork consumption, and create a comparative advantage for this meat against its direct competitors, mainly chicken meat. In the present situation of our knowledge about consumption and consumption demand elasticities, it is certainly premature to give too precise figures in this respect, for consumption models are still too dependant on secondary assumptions for that we could have a full confidence in their numerical results. Yet, it is possible to imagine that a permanent fall of, say 10 % in the price of pork will induce a shift in the quantities of demanded pork and chicken of the same order of magnitude. This means that not only will land be released by the technical progress in pork production, but additional areas will come from displaced chicken production. In the whole, this should lead to significant falls in land prices, in locations which remain to be determined, unless new demands emerge for other usages.

Second, there is the question of the geographical concentration of pork production plants. In the case of pork, the reasons for having production geographically disconnected from the corresponding land are the same, and even much stronger, as in the case of milk. ST will reinforce these reasons, by decreasing the cost of transporting the feedstuffs necessary for a given meat production. As a consequence, pork production plants should become larger. But the consequences of larger pork production plants are well known. Not only do they produce meat, but also unwanted and bad smelling effluences which, with small plants, would easily be dispersed in the wild life, but which, because of their size, are very difficult to dispose of. And since the society detrimental externalities thus produced are not charged to them, they have no incentive to adopt different, less harmful techniques.

In this context, by reducing the number of pigs per kg of pork meat, rpST will decrease the overall pig generated pollution. But by encouraging larger pork production plants, it will locally increase this problem in the vicinity of surviving plants (In effect, the above reasoning implies that some plants will disappear).Is this a reason to forbid rpST use in pork production? Probably not, because the problem does not arise from the drug itself. It arises from the pollution market failures, and should be solved at this level, rather than by indirect and imperfect restrictions on secondary aspects.

Conversely, if efficient steps were taken in order to prevent too large pork production plants, would the incentives to make use of rpST be lowered? Probably not, because this would not suppress the yield increase effect of rpST. Simply, in that case, the production cost of pork would be higher, and even more without than with rpST.

Somatotropin and sheep production

As far as I know, ST has not been envisaged for sheep, and, of course, there is still a possibility for that the technique does not work at all with that species. The above analysis, however, suggests that it could be highly valuable if it were feasible: sheep are more likely to develop undesired fat than young bovine. They are less likely to have exhausted their possibilities for roughage ingestion increase. Therefore, they may represent a unique possibility of non intensifying somatotropin-like substance usages. Of course, I admit that the technical basis for such a statement are lean. But dreaming a little is not necessarily forbidden in an international meeting.

Who will adopt somatotropin?

Thus, the introduction of rST is a true technical progress, always capital and labour saving, moderately land saving in the case of rbST, definitely land saving in the case of rpST. No doubt it will be quickly adopted if allowed, although the adoption pace may depend upon a variety of secondary circumstances, such as the availability of veterinarians to administer it, if the intervention of such skilled manpower is really necessary.

The political problem tied with such an innovation is that it will reshuffle many cards, be harmful to vested interests, and create real adaptation costs, as any other technical innovation. It fact, it will modify the technical basis of comparative advantage. For instance, if it is true that the response to rpST is smaller for highly selected (such as Danish pigs) than for more traditional (as many midwestern) animals, then it will suddenly provide the latter with some of the laboriously acquired qualities of the formers. And since midwestern pigs have other, different qualities of which the Danish ones are deprived, and which will not disappear from the introduction of rpST, they may very well override them in international competition. However, in the present state of our knowledge about the effects of ST, such a precise forecast is probably rather premature. In fact, the completely opposite view could be supported as well.

More important is the discussion about which kind of farmer will adopt the innovation. There is a pervasive creed according to which the "most advanced farmers" will adopt it [5]. This opinion is supported by the observation that the introduction of ST will raise many day to day problems for animal feeding schemes tuning, and that only very skilled and informed people can be successful in such a task. Obviously, this is at least partially true. Another observation leading to the same conclusion is that "the most advanced farmers" are those having already pushed all possibilities of substituting land and (or) capital to labour as far as possible, and who will therefore be the most anxious to go further in the same direction.

But these reasonings do not preclude the possibility of ST being used by more traditional farmers, especially in the third world. Actually, in many countries, it is difficult to know

[5] Cf, for instance Mouchet (1989) who provides an estimate of proposition of adopting farmers in France: 15-25% before 1995, assuming an authorisation this year.

whether fodder resources or genetics are the real limiting factor to meat or milk production, even if it is possible to assume that both of them are important.

The genetic potential of a herd is difficult to improve in most third world countries, because this would require heavy and difficult to operate projects that governments are generally unable to properly manage. If the lack of suitable genes was demonstrated to be the most binding factor for livestock production increase in these countries, then ST could be a suitable runabout. In that case, it could play a role similar to (and, in fact, perfectly complementary with) the "green revolution".

The latter was extensively developed in many countries of the third world, mainly in the South Asia, as a "package" including irrigation, credit and fertilizer supply. It succeeded in massively increasing agricultural supply, especially wheat and rice. It had severe drawbacks, displacing poors and making the rich richer (Griffin, 1974 ; Petit, 1990). But it helped in favouring the displacement of manpower from agriculture to industry and services. In the whole, it was rather beneficial to most consumers, especially the poorest.

Similarly, ST is complementary with other techniques, especially fodders cultivation, with which it could constitute a "package". It will also release manpower, and, more importantly, capital, which is particularly scarce in developing countries. It is therefore possible to imagine significant increases in milk and meat supply due to ST in these countries. I admit this is an optimistic view. I am an optimist.

Conclusion

Finally, ST will create difficulties in the transition period before full adoption. If it frees manpower, will this manpower find alternative employment? If it frees capital, where is this capital to be reinvested? If it frees land, what to do with this land? Here is the classical debate about any innovation:In the long run, it is beneficial. But in the short run, it may even create ruin and misery. The history of the 19th century is full of stories of workers burning new pieces of machinery, or opposing technical progress. Often, these actions were not without justification, simply because these people were fighting for their own survival or out of fear of change. In principle, the correct functioning of markets should avoid such detrimental effects of innovation. But markets, often, fail to perform their tasks, and public intervention is required to substitute for their shortcomings. This is the case, especially, for large innovations, such as steampower, or electricity. Is ST of this size? obviously not ! In addition, the state intervention in failing market should never be directed toward forbidding innovation: The problem is not to prevent it, only to alleviate the damages it could cause. From this point of view, it is to be hoped that, rather than forbidding ST, governments will be able to find different means of intervention, and imagine new agricultural policies capable of avoiding the detrimental effects of not only ST, but also all kinds of technical progresses in agriculture, without preventing them to take place.

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APPLICABILITY AND REPERCUSSIONS RELATED TO THE ANIMAL PRODUCTION SYSTEM IN INDUSTRIALIZED COUNTRIES

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Summary

This paper examines the perceived differences between recombinant-DNA and earlier technology, the likely economic effects of commercial use of both rbST and rpST, and why both rbST and rpST used for meat production may have less difficulty in gaining the market's confidence. Contrary to typical new animal drug applications with the U.S. Food and Drug Administration (FDA) where the industry and the general public are not generally aware of the individual pharmaceutical company applications, rbST has been in the public's eye almost continually since the mid-1980's. Critics have attempted to discredit the potential benefits of rbST in milk production, and to spurn biotechnical development in general. In contrast, criticism of both rpST and rbST for meat production has been less visible, less vocal, and less persistent. The primary reasons appear to be: (1) rbST was one of the first areas of recombinant-DNA research in animal agriculture and was a prime target for activists and critics, so early reports of its likely effects were over-dramatized; (2) milk has been promoted as a natural, healthful and unadulterated product for both infants and adults, so critics of rbST have taken advantage of this image and have attempted to portray milk from rbST-treated cows as being unsafe; (3) rbST and rpST use for meat production results in products having attributes perceived by consumers as being more healthful--less fat, less cholesterol, and fewer calories--in contrast, rbST use does not significantly alter the composition of milk; (4) there is a larger selection of meat and meat substitutes for consumers to choose from than in the milk and dairy products area; (5) efficiency gains are more likely to be passed on to consumers in the more market-oriented meat industries than in the regulated dairy industry; and (6) socio-economic issues may differ between the meat and dairy industries because of differences in the structure and organization of the sectors.

Keywords: *biotechnology, somatotropin, dairy, swine, meat, acceptance.*

Introduction

Both recombinant porcine somatotropin (rpST) and recombinant bovine somatotropin (rbST) have been under review by the U.S. Food and Drug Administration (FDA) under the program of New Animal Drug Application (NADA) for several years to determine whether or not these products meet the requirements for approval of a new drug. Under this procedure, all data derived from studies conducted under the Investigational New Animal Drug Applications (INADA) must be submitted to FDA's Center for Veterinary Medicine (CVM) to obtain a final determination as to whether or not the new animal drug is

efficacious; is safe for the target animal; has no adverse effect on the environment; has acceptable quality control; and most critical of all, that edible products from the treated target animal are safe for human consumption.

Each company interested in developing and marketing a new animal drug in the United States must submit sufficient data for CVM to make a determination. In contrast to the usual procedure, the four companies filing INADAs for rbST gave the FDA permission to inform the general public that investigational studies were underway. This action on the part of the companies in the mid-1980's, in conjunction with rbST being one of the first major products of the science of biotechnology for animal agriculture, set the stage for considerable academic, industry and public scrutiny that continues today. This paper examines the underlying issues fueling the controversy surrounding rbST use for milk production and why both rbST and rpST used for meat production would likely have less of a problem in gaining public acceptance. Other than the issue of more likely consumer acceptance of rbST in its potential role in meat production rather than milk production, this paper will focus primarily on issues related to rbST use in milk production and rpST use in pork production. Unless specified otherwise, rpST and rbST refer to the recombinant-DNA product.

Overview of the pork and dairy industries

The pork industry in the United States, and in most developed countries, relies primarily on market forces rather than government regulations to generate signals for guiding pork production, processing and marketing. In contrast, the United States and almost every major developed dairy-producing nation operates government programs which regulate their domestic dairy industries. Many subsidize part or all of domestic production, imports are commonly restricted, and exports are frequently subsidized.

History has shown that price enhancement above market-clearing levels by dairy programs in many major milk producing countries generates excess milk supplies. The Government costs of handling the excess add to budget pressures. In some instances, subsidized exports are required to maintain price-enhancing domestic dairy programs.

The U.S. dairy industry

Federal dairy programs play an important role in the pricing and marketing of milk in the United States (Fallert, Blayney, and Miller, 1990). The major dairy programs are dairy price supports, Federal milk marketing orders, import restrictions, and State regulations. The U.S. dairy industry is primarily a domestic industry. Restrictive import quotas are used to prevent lower cost and subsidized dairy products from undercutting U.S. dairy price supports. The import quotas on manufactured dairy products normally limit imports to just under 2 percent of U.S. milk production. Exports of around 2 percent of U.S. milk production have historically been concessional sales or food aid donations from Government supplies.

Since the mid-1980's, there have been significant strides taken in some major producing countries to address dairy industry problems. The implementation of production quotas in the

European Community (EC-12) in 1984 dramatically reduced the world's largest dairy product surpluses. Legislation authorizing the milk diversion program and the dairy termination program in the United States are examples of alternative approaches for attacking the excess supply issue. In addition to the voluntary supply management programs, the United States implemented a flexible dairy price support mechanism.

The history of excess resources in dairying leads some to suggest that further cost-reducing and output-enhancing technology such as rbST will only exacerbate dairy industry problems. Ironically, other emerging milk production technology such as artificial insemination, embryo transfers, computerized feeding, total mixed rations, and nutritional supplements appear to have the industry's blessing. For example, a recent article on total mixed rations (TMR) in a large regional cooperative's newsletter (MID-AM, Aug. 1990) indicated that "Most nutritionists and dairy scientists feel comfortable in projecting a five to ten percent increase in milk production when implementing TMR." It is difficult to sort out the reasons for the entirely different perceptions and reactions to rbST and TMR technologies.

Other controversial dimensions of the changing structure of the U.S. dairy industry are the issues of larger herd sizes, a decline in "family" farms, and the changing location of milk production. The number of farms with milk cows dropped from 2.8 million in 1955 to around 205,000 in 1989. Commercial dairy farms declined from 600,000 to around 160,000 (Table 1.). The number of milk cows declined from 21 million in 1955 to 11.1 million in 1975, and 10.1 million in 1989. A 143-percent increase in milk production per cow enabled milk production to more than keep pace with commercial needs over the 1955-89 period.

Table 1. U.S. dairy industry changes, 1955-89

				Change per year	
Item	1955	1975	1989	1955-75	1975-89
		Thousand		Percent [1]	
Cows	21,044	11,139	10,127	-3.1	-0.7
Farms with milk cows	2,763	444	205 [2]	-8.7	-5.4
		Number			
Average cows per farm	8	25	49	5.9	4.9
		Pounds			
Milk per cow (annual)	5,842	10,360	14,244	2.9	2.3
		Million pounds			
Total milk production	122,945	115,398	145,252	-0.3	1.7

[1] Compound annual rate.
[2] Commercial dairy farms (farms with 10 or more milk cows) are estimated at around 160,000 in 1989 with an average of around 65 cows per farm.
Source: Fallert et al., 1990.

A regional shift in milk production from the traditional dairy areas of the Upper Midwest and Northeast to the West and Southwest began about three decades ago and has accelerated in the last 20 years. Wisconsin is still far ahead as the number one milk producing State, but California is rapidly closing the gap. Some critics of rbST assert that the trends toward larger dairy farms and the shift in milk production to the Southwest would be accelerated with rbST use. The question again arises as to why there is this concern about rbST when use of other

technologies such as TMR--which would likely have similar structural effects as rbST--do not appear to generate these same concerns.

The U.S. pork industry

The United States ranks second to China in pork production, is the world's largest pork importer and a major pork exporter (Shagam, 1990). Pork production in the U.S. has increased slightly over the past 29 years, despite a small decline in the hog inventory. More effective use of the breeding herd appears to be a major factor in the growth of pork output, along with some increase in the average dressed weight of hogs (Futrell, forthcoming).

Like the dairy industry, U.S. pork production is taking place on fewer and larger farms. The National Agricultural Statistics Service (NASS), USDA defines a hog operation as any place having one or more hogs and pigs on hand during the year. By this measure, the number of U.S. hog operations declined from 871,000 in 1970 to 309,700 in 1989. However, a better indicator of commercial hog operations is Census of Agriculture data which shows that the number of farms that sold hogs and pigs decreased from 1,273,000 in 1959 to 230,000 in 1987. Forty six percent of the farms selling hogs in 1987 sold 99 head or less but accounted for only 3.7 percent of the total sold. In contrast, 10 percent of the farms sold 1,000 head or more and accounted for 57.5 percent of the hogs sold. This was a significant change from 1969, when 6.1 percent of the farms had sales of 1,000 head or more and marketed one-third of the hogs (Tables 2 & 3).

Table 2. Farms with sales of hogs and pigs, by number sold per farm, U.S.

	Total farms	Hogs sold per farm			
Year		1-99	100-499	500-999	1,000+
		Percent of farms			
1969	536,351	53.6	40.3	4.8	1.3
1974	449,841	57.9	33.9	5.8	2.4
1978	470,518	59.8	30.5	+6.4	3.3
1982	315,095	51.8	31.8	9.5	6.9
1987	238,819	46.0	32.5	11.5	10.0

Source: Futrell, forthcoming; derived from Census of Agriculture, Bureau of the Census, U.S. Department of Commerce.

Table 3. Hogs and pigs sold, by number sold per farm, U.S.

	Total hogs	Hogs sold per farm			
Year	sold	1-99	100-499	500-999	1,000+
		Percent of Hogs Sold			
1969	86,771	13.6	53.5	19.6	13.3
1974	79,897	11.1T42.1	21.7	25.1	
1978	92,141	9.6	34.9	21.8	33.7
1982	94,784	5.4	24.7	21.7	48.2
1987	96,569	3.7	19.2	19.6	57.5

Source: Futrell, forthcoming; derived from Census of Agriculture, Bureau of the Census, U.S. Department of Commerce.

According to a University of Missouri study (Rhodes, 1990) one of the dramatic changes in structure is the increasing size of that boundary line between hog farms that decline and those that grow. The boundary line is now at 1,000 head annual sales--and approaching 2,000--whereas in the 1960's it was at 200 head. Another dramatic change in structure is the growth of hog firms controlling multiple farms or production units. Each of about 6,600 firms in 1988 controlled more than one "farm" through purchase, lease or contract. Thus the concentration of marketing in farm firms is greater than the concentration shown by the Census data based on farms. A University of Missouri (UMC) survey in 1989 suggests that nearly 70 percent of 1988 market hogs in the United States came from farm firms marketing 1000+ hogs/pigs, Rhodes indicates.

From a regional standpoint, the location of U.S. hog and pig production appears to be more closely tied to grain and protein production areas and thus is not shifting as much regionally as is milk production. Regional shares of pork production have increased slightly in the Northern Plains and Southeast since 1970 and have declined in the Southwest. Within the Southeast region, North Carolina has shown a substantial gain in share of national production--from 2.9 percent in 1970 to 5.4 percent in 1989, primarily because of large contract arrangements with several large meat-packing firms (Table 4).

Table 4. Regional distribution of U.S. hog production [1]

Region	1970	1980	1985	1987	1989
	Percent of U.S. production				
Cornbelt-Lake States					
Eastern [2]	28.6	25.4	27.3	27.1	26.7
Illinois	12.2	11.3	11.2	10.5	10.6
Western [3]	37.2	39.6	41.0	39.9	38.6
Iowa	23.4	24.5	27.1	26.4	25.4
Northern Plains [4]	13.7	13.0	13.0	13.9	14.4
Southeast [5]	14.4	15.8	13.4	13.3	14.9
North Carolina	2.9	3.6	4.4	4.5	5.4
Southwest [6]	2.6	2.0	1.3	1.5	1.5
Other [7]	3.5	4.2	4.0	4.3	3.9

[1] Based on liveweight production.
[2] OH, IL, IN, MI, WI.
[3] MN, IA, MO.
[4] ND, SD, NE, KS.
[5] AK, LA, KY, TN, MS, GA, FL, SC, NC, VA, AL.
[6] TX, OK, NM.
[7] Remaining States.
Source: Futrell, forthcoming; derived from Meat Animals: Production, Disposition, and Income, NASS, USDA (various issues).

Family hog operations are still important in the U.S. According to Futrell's analysis of Census data, two-thirds of the hogs sold were from individual or family operations and one-sixth were from partnerships. Corporations, three-fourths of them family-held, accounted for 15 percent of hog sales in 1987; and less than one percent were from all other sources.

In contrast to the U.S. dairy industry where little contract production takes place, contract production of pork has increased moderately in recent years. Contract production is fairly common in some southeastern states, but is limited in the more traditional midwest production area. According to Futrell, interest in contracting has continued as more firms have offered production contracts and some producers seem to like the low capital requirement and low-risk option provided by some contracts. The 1989 study by Rhodes indicated that around 10 percent of the hogs in the U.S. were produced under contract in 1988. Based on personal communication, both Rhodes and Futrell feel that some further increase in contract production seems likely over the next few years.

Biotechnology in U.S. agriculture: the different classes of growth promotants

A number of different agents influence animal agriculture (Table 5). While some are naturally occurring, others are produced (or refined) outside the animal and then introduced to alter the productivity of the animal. Each class has its own characteristics and often different impacts. An agent may be efficient with one species or sex but not with another. In the United States, livestock hormones are used extensively (Kenney and Fallert, 1989); their use is regulated by the Food and Drug Administration (FDA) and USDA's Food Safety and Inspection Service (FSIS). Under current technology, hormones must be administered by a time-release pellet inserted under the skin of the animal's ear, which is then discarded at slaughter.

Table 5--Anabolic agents can be classified into four categories

Category	Source	Metabolic Action	Anabolic agents
Natural steroids and hormones	Produced in animals and humans	Regulates growth, maturity, and sexual characteristics	Estradiol, testosterone, progesterone
Synthetic sterold hormones	Produced Synthetically	Same molecular structure and action of natural sterold hormones	Melengestrol acetate and trenbolone acetate
Natural xenobiotic hormones	Derived from plants	Although not technically steroids, they have similar effects	Zeranol
Growth promoting compounds	Recombinant DNA technology	Improves feed efficiency through nutrient partitioning	Bovine Somatotropin and porcine Somatotropin

Source: Kenney and Fallert (1989).

Anabolic agent (hormone) use in beef production

Hormones used in beef and veal production are technically known as anabolic agents. These substances affect animal metabolism by improving the use of nutrients absorbed from feed. Nutrients, such as nitrogen, calcium, and phosphorus, are more likely to be channelled for use in muscle (lean meat) growth than for fat. Anabolic agents can be classified as follows:

- *Natural steroid hormones* are normally produced by nearly all animals. The hormones generate sexual characteristics, maintain reproductive functions, stimulate growth, and are essential for regular body functioning.
- *Synthetic steroid hormones* have similar hormonal actions as natural steroid hormones. They are produced in a laboratory and then administered to cattle to enhance the effects of the animals' natural hormones.
- *Natural xenobiotec hormones* are derived from plants and produce effects comparable to those of steroids.
- *Growth-promoting compounds* include substances such as somatotropins, growth-hormone-releasing factors, and somatostatins. Somatotropins, which are also referred to as growth hormones, are naturally occurring animal hormones that regulate growth and metabolic processes. They can be reproduced in the laboratory through recombinant DNA technology. Since they are proteins, they would be broken down by the digestive system if used as a feed additive. Therefore, to be effective, the product must be injected into animals.

Growth-hormone releasing factors and somatostatins regulate an animal's production of somatotropin. These substances are highly species specific. None of them has been approved for commercial meat or milk production in the United States. However, rbST and rpST are currently under review by FDA.

Why Use Hormones? Cattle require more feed per pound of weight gain than hogs or poultry. Anabolic agents are used to improve feed efficiency. These substances also help U.S. producers compensate for the practice of raising steers (castrated males) and heifers rather than bulls. Bulls have better feed efficiency and higher growth rates than steers or heifers because of naturally occurring hormones. They also produce leaner meat and can be fed to heavier weights. But bulls behave aggressively and steers are easier to manage, so U.S. farmers and feedlots generally raise steers instead of bulls. Further, meat from steers is considered more desirable than bull meat, which is usually less tender, less marbled, and a darker red colour, owing to the greater maturity of bulls at slaughter. Castration, however, results in lower internal androgen production. Therefore, androgen implants allow steers to achieve the higher growth rates of bulls.

Scientists at the World Health Organization and FDA have concluded that residues from hormones, when properly administered in both dose and method, pose no threat to human health. Food safety and other issues associated with animal growth promotants have been reviewed extensively (Grueff and Bylenga, 1989; Krissoff, 1989; Kuchler, McClelland, and Offutt, 1989; Norcross et al., 1989; Sachs, 1989; Schams, Kanis, van der Wal, 1989). Some observers maintain, however, that the misinformation and sensationalism surrounding the hormone issue are the main problems. Thus, the real challenge lies in finding ways to educate producers, consumers, and policymakers about the benefits, degree of risk, and other issues associated with hormone use in livestock production.

Bovine Somatotropin (bST) use in milk production

bST is a naturally occurring protein hormone produced in the pituitary gland of cattle that regulates body metabolism and therefore, milk production. Through recent breakthroughs in genetic engineering techniques, the bST gene can be transferred from animals to ordinary bacteria cells. These bacteria can be reproduced on a large scale at relatively low cost, making the purified product available for commercial use. The process is similar to that used to produce human insulin and interferon.

rbST has not yet been approved by the Food and Drug Administration (FDA) for commercial use in the United States. However, it has been approved for research purposes under controlled conditions, and the sale of milk and meat from experimental cows injected with rbST has been approved.

The economic impact of rbST adoption

In October 1987 the Economic Research Service (ERS) of USDA published an in-depth study of the likely effects of rbST on the U.S. dairy industry (Fallert et al., 1987). The focus of the study was the effect of rbST on U.S. milk supplies, commercial use of milk, milk prices, dairy industry structure, the dairy price support program, and the international competitiveness of the U.S. dairy industry. The major findings of that study, which assumed the commercial availability of rbST, were:

- The effects of rbST on the dairy industry would likely be less dramatic than often suggested.
- rbST would reinforce, but not fundamentally change, structural change already underway in the industry.
- Effects of rbST would ultimately depend on the flexibility of the dairy price support program.
- rbST would have little effect on the U.S. position in the international dairy market under 1987 trade policies.

As in any economic study, results are greatly affected by assumptions of the study. The major assumptions of the 1987 study, which were developed from an extensive review of the available literature and personal contacts with university, industry, and pharmaceutical company representatives, were:

- FDA approval is given and the product is available by early 1990.
- rbST will be available as a once-a-month injectable sustained release product.
- rbST will increase daily milk production per cow by 8.4 pounds during the 215 day treatment period.
- There are no size or regional effects on response.
- The cost of rbST is 24 cents per treated cow per day.
- The adoption rate allows most effects of rbST to work through the dairy sector by 1996.
- rbST has minimal effects on long-term animal health and reproduction.
- No adverse consumer reaction to milk and meat from rbST-treated cows.
- There are no constraints on rbST production and availability.

The 1987 study examined an option with January 1, 1990 price supports at $10.10 per cwt, which now is the current support price and, according to the recently proposed farm bill provisions, will be the minimum support price until January 1996. The assumed introduction of rbST in 1990 would lower the cost of producing milk by 50 to 60 cents per cwt by 1990. The number of dairy farms would decline by 3 percent as rbST increases milk production. Commodity Credit Corporation (CCC) purchases by 1996, assuming the milk price support is held at $10.10 per cwt, were estimated to be close to 8 billion pounds (milk equivalent, fat basis) higher with rbST than without.

Another option of the study maintained the price support at the relatively high 1987 level of $11.10 per cwt through 1996 in spite of high government costs. Under the scenario government purchases of dairy products reached 31 billion pounds by 1996. This illustrates the need for a flexible dairy price support program to accommodate cost-reducing and output-enhancing technologies such as rbST. An inflexible program with high supports generates significantly higher returns to producers who adopt the new technology, but government program costs are increased substantially, and consumers do not benefit through reduced dairy product prices.

In May 1989, Senator Patrick Leahy, Chairman of the Senate Committee on Agriculture, Nutrition and Forestry, requested that ERS update and extend the earlier study emphasizing the effects of rbST on small-and medium-sized dairy operations and the potential for exporting additional U.S. milk and dairy products that might result from its adoption. Results of the updated study were published in mid-1990 (Blayney and Fallert, 1990). The findings of the more recent study reconfirmed the general results reported in the 1987 study.

The effects of rbST as it relates to the size of dairy farms have not yet been fully determined. The 1987 USDA study indicated, on the basis of analyzing representative farms, that small farms would be better off with rbST than without it. In general, rbST is considered size neutral because no significant investment in capital and equipment is required to use the product. The additional milk production from rbST use does require more high-quality feed and good management. Revenues generated by the additional milk production more than offset the costs of additional inputs under most market situations.

More recent studies at Texas A.& M. University (Yonkers, Richardson, and Knudsen, 1989) and at the University of Arizona (Angus, 1989) support this conclusion. Overall, the trend toward larger and fewer dairy farms will continue with or without rbST.

Effects of rbST use on international competitiveness of various countries is unclear. A recent study of the costs of producing milk in seven major milk-producing countries (Baker et al., 1990) indicates that milk production costs per cwt in the United States and the Netherlands are quite similar and are in the middle of the range of costs estimated for the seven countries included in this analysis. New Zealand is the lowest-cost milk-producing country in the world, while costs in France and West Germany are substantially higher than in the United States. Costs in Ireland are somewhat lower than in the United States, while milk production costs in Canada are also quite high compared with the United States, but significantly lower than in France or West Germany.

The United States is probably as well positioned as any country to take advantage of rbST to improve its international competitive position because of not having a quota program and

because of having relatively low-cost concentrate feed available. A major factor in the competitiveness issue would be the willingness of importers to accept dairy products produced with milk from rbST-treated cows.

Porcine Somatotropin (rpST) use in pork production

Results from numerous experimental studies (van der Wal et al., 1989; Lemieux and Richardson, 1989) indicate that pork production can be changed through the use of laboratory synthesized compounds normally produced by the hog itself. One of these compounds is rpST which offers the opportunity to produce leaner pork and to substantially increase feed efficiency. By altering the way in which the animal's body utilizes nutrients, rpST reduces feed intake while increasing muscle mass and rate of gain. Although producers can expect cost reductions, increased production could reduce prices to pork producers and thus offset at least some of the net income gain from rpST use. Research indicates that management changes will be required. In contrast to milk production where dairy cows are handled on a daily basis, use of rpST in hogs will depend heavily upon availability of a convenient rpST delivery system. Profitability of rpST use and consumer acceptance of leaner pork produced with the use of a laboratory synthesized growth promotant will also affect rpST adoption rates.

So far as rpST is concerned, much of the public information in the U.S. surrounding this product is being developed and disseminated through the Animal Health Institute's Porcine Somatotropin Public Information Group in response to continued requests for information on the product. One such information document is ***PST: AT A GLANCE*** which briefly presents various issues raised about rpST in scientific forums. It also cites references. An expanded version of this document is under development and should be released shortly.

Consumer demand in the U.S. for various meats is reflected in per capita consumption data over the past 33 years. For example, U.S. combined per capita red meat and poultry consumption at the retail level has increased steadily from 165 pounds in 1955 to 246 pounds in 1988 (Stillman and Weimar, 1990). During this period, per capita pork consumption at retail in the U.S. has fluctuated between 55 and 69 pounds but has shown little growth over time. In contrast, per capita poultry consumption at retail increased dramatically from 27 pounds in 1955 to 81 pounds in 1988. Per capita retail beef consumption increased from 61 pounds in 1955 to a peak of 94 pounds in 1976 when the size of the beef herd reached unprofitable levels and then began a continued downward trend to 72 pounds in 1988. The combined U.S. per capita veal, lamb and mutton consumption declined drastically from about 12 pounds in 1955 to slightly under 3 pounds in 1988.

Much of the decline in pork's share of meat consumption can be traced to two factors (Shagam, 1988). First, pork tends to be less competitive than poultry because, among other factors, hogs require almost twice as much feed per pound of gain as broilers. There also have been substantial increases in productivity in the poultry sector aided by vertical integration and automation that have not been matched in the hog sector. Second, consumers have become far more health conscious and perceive pork as a "fatty" meat that is detrimental to their health, while perceiving poultry as more healthful than beef or pork. To enhance pork's image, packers and retailers are trimming more fat from retail cuts and the industry has begun

a promotional effort to dispel negative perceptions. Although trimming fat improves pork's appeal to consumers, the increased costs are passed on through higher retail prices.

The pork industry, therefore, is faced with a joint task: first, producing a product that appeals more to consumers; and secondly, increasing productivity to make pork more price competitive with other meats and foods. From all indications, producing and marketing lean pork with desirable sensory qualities at a reduced price would be desirable pork industry objectives.

Significant progress has been made in reducing fat and increasing feed efficiency of hogs through selective breeding. However, genetic selection is a time-consuming procedure and based on attempts to breed lean hogs in the early 1960's and 1970's, there appears to be limit as to how far this can be carried to achieve lean muscle production. Although some countries are far ahead of others in genetic selection, the structure of the breeding segment and the pricing and marketing system in the United States has retarded the process of producing pork of a quality most desired by consumers.

One could reason that if the U.S. pork industry is truly several years behind the progressive Danish hog industry in producing the quality of pork desired by consumers (Fleming, 1990), that use of rpST or other growth promotants might be more advantageous to U.S. producers than to producers in some other major pork-producing countries (Steele et al., 1989; Fowler and Kanis, 1989; Fung and Qi, 1989). Given the experience with the EC's reaction to anabolic steroid use in U.S. beef production and the associated restrictions on international beef trade, this issue could become associated with rpST use in pork production as well.

Economic impact of rpST adoption

Several studies have addressed the economic impact of rpST adoption on the livestock industry (Hayenga et al., 1989; Lemieux and Wohlgenant, 1989, Stillman et al., forthcoming). Each of these studies differs in its focus. Hayenga and co-workers address the impacts of rpST adoption on the livestock industry as a unit, addressing cost and demand changes. Lemieux and Wohlgenant, on the other hand, looks at the effects on both the domestic and international markets. Stillman et al. (forthcoming), focus on the impacts on the livestock industry much like the Hayenga study.

In the Stillman et al. study, feed costs were adjusted proportionally to total production costs. Corn costs are reduced by 22 percent, while soybean meal costs are increased by 11 percent. Other costs are adjusted to reflect the reduced number of days on feed, which are reduced by 8 days or 6 percent. rpST costs per hog were set at $2.50 per hog. This level was based on simulating the cost impacts of the rpST over the 1980's and using the average change in returns and a 2-to-1 returns-to-cost ratio for pricing growth promotants.

Demand changes for hogs were assumed to occur at the packer level. rpST results in a higher yielding hog which requires less fat trimming for the retail products. This was assumed to result in a 3.3 percent increase in the value of the live hog in a carcass merit pricing system (Hayenga et al., 1989). Presently, retail pork products are being trimmed to

about 1/4 inch of outside fat. With the adoption of rpST, the reduction of fat would not likely be seen by consumers and, therefore, they would not pay a premium for the product. No changes in consumer demand were assumed in this analysis.

Stillman et al. examines four scenarios relating the effects of rpST adoption on the pork industry from changes in production costs, packer demand for the hog, and varying rpST costs. The impacts of the cost changes due to the adoption of rpST can be explored using ERS costs of production estimates for farrow to finish hog operations and adjusting for the non-adoption of rpST for the breeding herd.

Simulation assumptions

Four basic scenarios were analyzed by Stillman and co-workers over the period 1991 to 2000 assuming the adoption of rpST would start in 1992, using the annual livestock model developed by ERS (Weimar and Stillman, 1989). The results are presented as percent changes from a base solution of the model assuming no impacts from rpST. The first scenario (pst1) only analyzed the impacts of the cost reduction resulting from the adoption of rpST. The second scenario (pst2) analyzed the combined impacts of the cost reduction and the carcass merit price increases realized by producers adopting rpST. The third scenario (pst3) is similar to the second, but the price of rpST is lowered from $2.50 per hog to $1.00 per hog. In the last scenario (pst4), the cost of rpST is increased to $5.00 per hog.

In each of these scenarios, the adoption rate was set at the same level. In the first year, 50 percent of the producers were assumed to adopt rpST. In each year thereafter, a 10 percent increase in the number of producers were assumed to adopt rpST, until the level reached 90 percent. The cost advantage of rpST would force the vast majority of producers to adopt the technology or exit the industry. The feed prices and macro economic assumptions are based on the latest analysis of the 1990 farm bill provisions and remain the same for all scenarios.

Simulation results

Scenario 1 (pst1):

The impacts of the cost reductions due to rpST on the pork industry are increased production and increased returns per head. By the end of the simulation period, pork production was about 1 percent higher than the base solution (Figure 1). Initial reaction of pork producers was to lower production by the removal of gilts from slaughter and to place them in the breeding herd. Returns per hog show a large initial increase due to higher prices from reduced production and lower costs from the rpST adoption (Figure 2). By the end of the period, returns per hog return to near the base levels. The impact on consumers from the adoption of rpST are about 1 percent lower prices and larger levels of consumption. As a result of pork's increased competitiveness, production of other meats decline. Retail prices of pork remain higher than they would have been had only pork production changed (Figure 3).

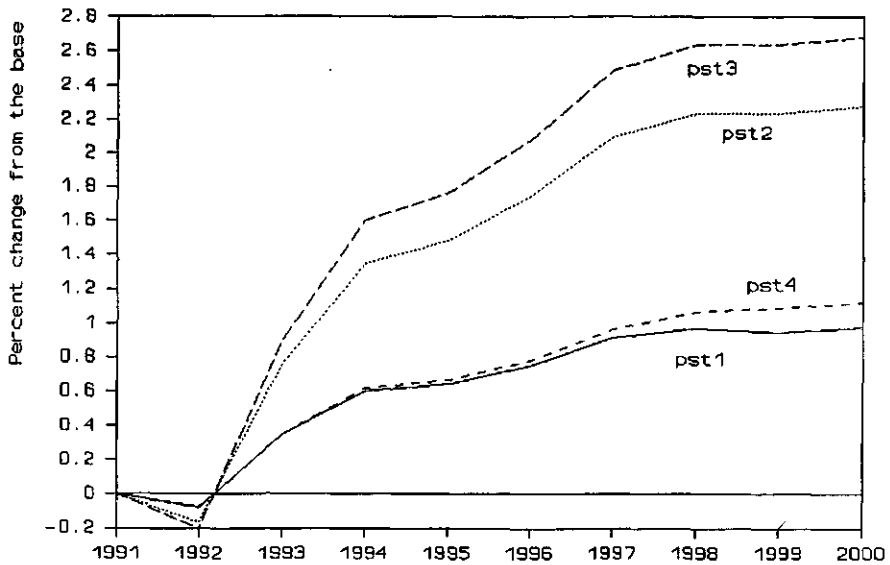

Figure 1. Changes in pork production resulting from pST assumptions

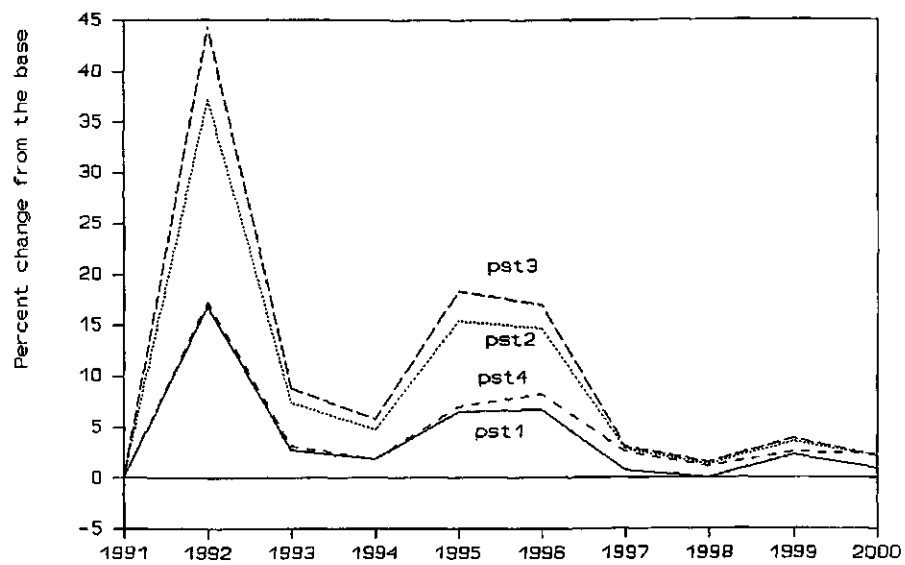

Figure 2. Changes in returns per hog resulting from pST assumptions.

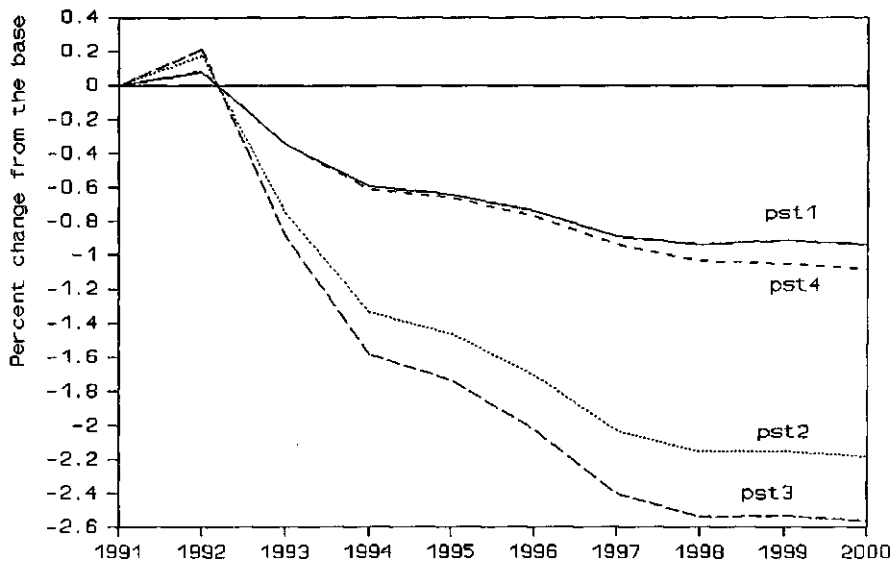

Figure 3. Changes in retail pork prices resulting from pST assumptions

Scenario 2 (pst2):

By combining the impact of increased hog receipts from carcass merit pricing and the reduced cost assumptions from the use of rpST, pork production increased about 2.3 percent above the no-rpST base by the year 2000. The basic time path of adjustment of the pork sector is similar to the first scenario, but the levels are greater. Again, the returns per hog cyclically decline to near the base level as production increases. Retail pork prices decline 2.2 percent by the end of the analysis period.

Scenario 3 (pst3):

The impacts of reducing the cost of rpST to $1.00 per hog results in even larger increases in pork production, about 2.7 percent by the year 2000. Returns per hog approach the base simulation level by the end of the analysis. Retail pork prices are 2.6 percent lower than in the base solution.

Scenario 4 (pst4):

By increasing the cost of rpST to $5.00 per hog, the gains to producers from carcass merit pricing are offset. The results of this scenario are very similar to scenario 1.

Summary of impact of rpST on the livestock industry

Pork producers and consumers are better off with the adoption of rpST from a consumer and producer surplus standpoint. Producers receive the same returns per head by the end of

the analysis and are able to sell more hogs -- thus increasing their total profits. Consumers face larger supplies and lower prices for pork. Although pork producers and consumers benefit from rpST, other meat producers are worse off. Under scenario 2, steer prices are 0.2 percent lower and beef production is 0.03 percent lower. The same impacts can be shown for poultry. However, there is an overall net gain to the livestock industry from rpST availability and use.

Issues in the adoption of recombinant rbST in the dairy industry

In August, 1990, FDA scientists (Juskevich and Guyer, 1990) summarized in the journal *Science* more than 120 studies they say document the safety of milk and meat from dairy cows treated with genetically engineered duplications of the cows' own growth hormone, used to increase milk production. The author-scientists say the studies have led FDA to conclude that the use of recombinant bovine somatotropin (rbST) presents "no increased health risk to consumers."

In their summary report, the authors discuss previously unpublished data from 16 studies supported by manufacturers, who are seeking approval to market the substance, along with publicly available studies. These data demonstrate that:

- "bST is harmless when consumed orally, as in milk or meat, because it is broken down into inactive fragments in the gastrointestinal tract while being digested.
- Even if bST were injected in humans, as it is in treating cows, it would remain inactive because bovine somatotropin is 'species specific.'
- Ninety percent of bST in milk is destroyed upon pasteurization.
- A protein controlled by bST is increased in the milk of bST-treated cows, but data show that concentrations are within the normal physiological range found in human breast milk." The FDA authors go on to state that this protein (an Insulin-like Growth Factor I or IGF-I) is denatured under the conditions used to process milk for infant formulas. Other data demonstrate that oral toxicity studies have shown that IGF-I lacks oral activity in rats at even exaggerated doses.

In addition, the authors concluded that rbST, produced in quantity by recombinant DNA technology, is identical in biological activity to growth hormone made by the cow's pituitary gland. They indicate that milk from cows treated with rbST would have bST residues within the normal range of the naturally occurring substance.

The report underwent extensive and lengthy peer review by a panel of expert scientists selected by the editors of *Science* before it was published. The National Milk Producers Federation (NMPF) had sought this review as part of its ongoing commitment to ensure the public a pure and wholesome milk supply. After the report was published, a memorandum (1990) from Jim Barr, CEO of NMPF stated that "This report, and others like it, will help dispel public concerns about the safety of the milk supply, biotechnology and rbST. As you'll see from the attached peer-reviewed *Science* article of FDA's bST studies, all the extensive scientific research done to date shows rbST poses no health concern to the American public."

Two days prior to the *Science* article, the *Journal of the American Medical Association* (JAMA) also published a review of data showing that "bovine somatotropin causes no

changes in milk composition of any practical importance to consumers..." (Daughaday and Barbano, 1990). The authors reviewed the FDA process of assuring that all new products used by dairy farmers are safe and how bST works. They went on to list the reasons why milk from bST-treated cows is safe for human consumption--and went on to conclude that "Based on scientific evidence, comments from health professionals can play an important role in reassuring the public about the safety of milk and refuting misstatements or misconceptions about bST."

Along this line, it is ironic to observe the different reactions to peer-reviewed scientific articles in these two prestigious journals. Two reactions appeared in print on September 3, 1990--within two weeks of the articles' publication. In the Editorial/Opinion column of *Feedstuffs* magazine the heading read "FDA won in several ways as bST controversy ends." The editorial goes on to state "...The controversy is over because FDA delivered blows to the opposition that cannot be overcome. The critics cannot come up with any worthwhile response to the articles published recently that carefully define the reasons why bST can be called completely safe for humans. The conclusions are irrefutable, because the science is sound and presented completely to the public...." The column heading on the front page of the September 3 issue of *Biotechnology Newswatch* read "Flouting FDA's pro-bST finding, Rifkin says: 'It's war'." The article goes on to say that "Jeremy Rifkin's Foundation for Economic Trends (FET) here revealed plans last week to launch an 'international boycott' of bovine somatotropin (bST), says John C. Stauber, director of the organization's anti-bST educational campaign. They plan to launch their global war against the growth hormone, even before the drug is approved by the U.S. Food and Drug Administration (FDA)."

Partially in response to the latter type of reaction to rbST issues, the National Milk Producers Federation and the National Dairy Promotion and Research Board formed the "Dairy Industry Coalition" which will represent the two organizations with regard to milk safety issues. They state that "...The Dairy Industry Coalition intends to neither endorse nor oppose the use of Bovine Somatotropin (bST) in dairy herds at such time as the Food and Drug Administration approves the product as safe for commercial use. While remaining neutral on bST use by dairy farmers, the Dairy Industry Coalition is committed to communicating the facts concerning the continuing safety and wholesomeness of milk and milk products. The Dairy Industry Coalition is embarking on a public education campaign to communicate its neutrality on the bST issue and its commitment to preserving the integrity of milk." In conjunction with this effort, a *Dairy News and Information Center* was created with a telephone number "1-800-34-DAIRY".

Another review of bST will take place at a National Institute of Health (NIH) Technology Assessment Conference on Bovine Somatotropin to be held on December 5-7, 1990 on the NIH Campus, Bethesda, Maryland. The Conference will take another look at the human health data on bST and FDA's biotechnology approval procedures. This meeting will bring together experts in fields relevant to a thorough discussion of bovine Somatotropin. At this meeting, besides presentations from concerned individuals and organizations, experts speaking from different points of view will present scientific information regarding relevant areas of concern. A panel of experts (non federal government) from several relevant fields with non-advocacy positions and with no financial interests regarding the conference issues will listen to the proceedings and determine points of agreement and areas of inadequate

information regarding the questions. The panel will develop recommendations based on the evidence and discussion.

In the European Community (EC), the evaluation of bST for use in milk production is progressing through both national reviews and the new EC approval procedure for biotech products. To date, the only decision reached has been in the United Kingdom (U.K.), and in that instance, the regulatory authorities have issued a preliminary decision to not allow product licenses for Eli Lilly and Monsanto at this time. Both sponsoring companies are expected to supply additional data and appeal this preliminary ruling. An opinion by the EC Commission on the Eli Lilly and Monsanto applications is expected on November 27, 1990. The EC findings will be advisory in nature and not in the form of a "yes or no" decision. Elsewhere in the world,rbST has been approved for commercial use in the Soviet Union, Czechoslovakia, Mexico, Brazil, Bulgaria, Namibia and South Africa.

Issues in the adoption of recombinant Somatotropin in the meat sector

There has been considerably less debate over somatotropin technology in the meat sector than in the dairy sector. A number of factors could be responsible for this. First,rbST is closer to approval than rpST, hence activists are likely concentrating their efforts and resources on dairy. Perhaps most importantly, both the nature of the food products and the structure of sectors are sufficiently different that some of the issues which dominate the debate in the milk production sector may not spill over into the meat sector.

First and foremost, milk and meat (especially pork) are viewed differently by consumers. Milk is marketed as a "pure, unadulterated, wholesome" product with positive health benefits from consumption. Proponents of rbST argue that its adoption would not change the composition and quality of milk, but that rbST will only improve the efficiency of milk production. Opponents claim that adoption will have a negative impact on the quality of the product and have used this potential detrimental health reasoning to form one of the prongs of the argument against rbST.

Pork, on the other hand, is currently suffering from a negative image as an "unhealthy" product, high in fat and cholesterol. In addition to improved feed efficiency, rpST alters the quality of pork; imparting those attributes perceived by consumers as more "healthful", increased meat muscle area and reduced fat. Thus in the case of rbST, critics claim a "good" product is being made "bad", whereas in rpST it is clearly shown that "bad" attributes are replaced by "good".

Secondly, the structure of the dairy and other livestock sectors differ greatly. While there is considerable intervention by the government in the dairy sector, there is almost no intervention in either the beef or pork sectors (Blayney and Fallert, 1990; Hahn et al., 1990; Shagam, 1990). As a result of government intervention, dairy surpluses have been a chronic problem. Therefore, increased milk production from rbST use and the surpluses which would be generated under the current pricing structure are viewed as a potential burden on the public purse.

Concerns over producer revenue and income impacts from the adoption of rbST have been lessened with the passage of the 1990 Farm Bill. Under the previous Farm Bill, there were automatic reductions in support prices if milk production increased beyond certain targets. This shifted the burden of overproduction from the public treasury to the producer. Under the current Farm Bill, the support price is a floor and the burdens to the producers are minimized. However, all producers will be assessed for inventory management if Government purchases exceed a set level.

No such policies exist for the meat sector. As studies have indicated, adoption of rpST in the pork sector tends to leave producer returns per unit unchanged and total profits increase from larger sales. Since there is no government wedge between production and consumption, consumers reap the benefits of lower prices from increased supplies. Use of somatotropin in the meat sector should have no direct cost to the government.

A final argument, similar for both sectors, would be that there is an impact on the structure of the farm sector and there may be an adverse effect on "family" farms. Studies have indicated the trend towards fewer and larger farms in dairy and hog production. It has been argued that the adoption would speed this trend and therefore, force small, family farms out of business. Since somatotropins require little additional capital investment, this technology should be of benefit to farms of all sizes. There is general agreement, however, that somatotropin technology will be of the greatest benefit to better managers.

This, of course, becomes a political decision, i.e. what should be the structure of the farm sector and what should be the role of government policy in achieving these goals. If the principles of the manufacturing sector are applied, the government's role should be limited to ensuring that there is fair competition and not collusive behaviour. Hence, the marketplace might be a better vehicle for determining the most efficient industry structure based upon increased efficiency and economies of size and scale. If there is a political desire to maintain an established social structure, the so-call "fourth hurdle", then perhaps the government should look towards more transparent means of achieving these goals. This could be through direct income transfers or other policies. It is questionable whether these policies should include the suppression of technology to maintain a status quo.

Conclusions

Each side in the fight over recombinant technology is undoubtedly a "true believer" in the righteousness of their particular stance. Thus, while one side claims that, based on scientific evidence, "the war is over", the other claims the "battle has just begun". Emotion and sensationalism cloud the basic issues, screaming headlines tend to garner more attention than reasoned arguments; as a result, both sides have at times exaggerated their claims.

What is often lost is that in many cases the two sides are talking everywhere but to each other. A common ground must be achieved and each argument must be examined for both its relevance and strength. Some of the questions are only peripherally related to the issue of the safety of recombinant technology and should be addressed outside that context.

However, all relevant arguments must be examined. Failure to do so will lead to imposing a technology from the top down and risking rejection.

Acceptance of recombinant technology will depend upon the choices of consumers, producers, industry leaders, and policy-makers. Whether these decisions are formed by sound evidence or manipulated perceptions will depend upon the efforts of "sensible centrists."

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