the E-deficiency changes the fatty acid compositions of the membranes considerably, with decreased quantities of 18:1 and 18:2 in both lung and liver. In the severely E-deficient animals, the cholesterol content as also found to be lower in the lung, but not in the liver. The CCl_4 administration apparently causes no immediate further modification in either fatty acid composition or cholesterol content. The CCl_4 poisoning, however, increased the formation of peroxidation products, especially from cholesterol. These cholesterol oxidation products obtained from the tissue were very similar in nature to the products from the autoxidation of mixed liposomes–dipalmitoylphosphatidyl choline and cholesterol. To a much smaller extent, some peroxidation products derived from 20:4 were also found from these treated animals.

159

POSSIBLE MECHANISM UNDERLYING INTER-INDIVIDUAL VARIABILITY IN THE SERUM CHOLESTEROL RESPONSE TO DIETARY CHOLESTEROL. A.C. Beynen and L.F.M. Van Zutphen, Department of Laboratory Animal Science, University of Utrecht, P.O. Box 80.166, 3508 TD Utrecht, and M.B. Katan, Department of Human Nutrition, Agricultural University, 6703 BC Wageningen, The Netherlands.

Differences in the response of serum cholesterol to dietary cholesterol in rabbits and rats have a genetic basis. In inbred rabbits, a 5-fold greater response was found in two hyperresponsive strains than in two hyporesponsive strains. Similar differences in serum cholesterol response between inbred strains of rats were also observed. Human hypo- and hyperresponders to dietary cholesterol also exist. We have investigated whether differences in responsiveness are caused by differences in endogenous cholesterol synthesis. In rats on a low cholesterol diet, whole body synthesis, measured as fecal excretion minus uptake, was 17 μmol/day in a hyperresponsive strain as opposed to 32 μmol/day in a hyporesponsive strain. In man, synthesis on a low-cholesterol diet, measured as fecal bile acid and steroid output minus cholesterol consumption, was associated negatively with the subsequent response to dietary cholesterol ($r = -0.44$, $n = 32$, $p < 0.05$). Thus hyperresponsive subjects may have less room for down regulation of cholesterol synthesis after cholesterol loading. Suggestive evidence for this thesis came from another experiment, where we measured serum concentrations of lanosterol, a precursor of cholesterol and a possible indicator of cholesterol biosynthetic activity. Serum lanosterol on a low-cholesterol diet was found to be 3- to 4-fold higher in 4 hyporesponders than in 2 hyperresponders. Furthermore, serum lanosterol was found to decrease after inclusion of extra cholesterol in the diet in 4 human hyporesponders but not in 2 hyperresponders.

160

COMPARISON OF NUTRITIONAL TRENDS IN TAIWAN VERSUS THE UNITED STATES. Lung-Bin Hau, Graduate Institute of Food Science & Technology, National Taiwan University, Taipei, Taiwan, Republic of China, and W.W. Nawar, Department of Food Science & Nutrition, University of Massachusetts, Amherst, MA 01003.

A comparison is made between Taiwan and United States with respect to dietary trends and general health statistics. The average daily intake of dietary fat in Taiwan is approximately 74 g/person, less than half that in the United States (160 g/person). This accounts for ca. 32% of the caloric intake (43% in the U.S.A.). Although the present trend in Taiwan has been towards a decrease in total caloric intake, the percentage of calories from fat has been increasing. During the last 30 years, energy intake from rice has decreased dramatically, whereas that from legumes, cooking oils and animal foods has significantly increased. Composition of the diet consumed in Taiwanese cities will be contrasted with that of rural areas. Since 1967, vascular lesions affecting the central nervous system constituted the major cause of death in Taiwan; while cancer was the second. As of 1982, the situation has been reversed; cancer became the first, and cerebrovascular disease the second leading cause of death. Statistical data will be given regarding trends in blood pressure and serum lipoproteins, both in the general population and for certain aborigine tribes. The trends observed in health and disease cannot be attributed solely to the changes in dietary fat intake. Several other dietary and non-dietary factors (e.g. total calories, sodium intake, atmospheric pollution, life style, etc.) are involved.

SESSION Y Biological Activities of Oxidized Sterols Tuesday afternoon

161

BIOLOGICAL ACTIVITIES OF SOME OXYGENATED STEROLS. Nobuo Ikekawa, Department of Chemistry, Tokyo Institute of Technology, Meguro-ku, Tokyo 152, Japan.

Recent observations of the biological activities of some oxygenated derivatives of cholesterol in our laboratory will be discussed. (I) Inhibition of enzymatic convertion of dihydrolanosterol into cholesterol by oxygenated sterols. Seven oxygenated sterols were tested for their effect on cholesterol biosynthesis from 24,25-dihydrolanosterol by rat hepatic subcellular $10^4 \times g$ supernatant fraction. The sterols (40 μM) exhibited considerable inhibitory effects on the synthesis of cholesterol from [24,25-^{3}H]-24,25-dihydrolanosterol (18 μM). 5-Cholest-8(14)-en-3β-ol-15-one had the greatest effect (64% inhibition). (II) Quick modulation of platelet aggregation by oxygenated sterols in plasma. We have investigated the effect of oxygenated sterols on platelet aggregation induced by thrombin and ADP. All the oxygenated sterols with a hydroxyl group on their side chains enhanced thrombin-induced aggregation at 25 μM. In the case of ADP-induced aggregation, however, only 22S-hydroxycholesterol enhanced the aggregation and 22R-, 24S- and 25-hydroxycholesterols inhibited the aggregation. (III) Lysis of platelets and erythrocytes by the incorporation of 22R-hydroxycholesterol. We have found that 22R-hydroxycholesterol lyses not only platelets but also erythrocytes in dose-dependent manner. Elevated temperature was required for the lysis, probably to redistribute the sterol in the lipid biolayers in the plasma membranes.

162

CYTOTOXICITY AND ATHEROGENICITY OF OXIDIZED CHOLESTEROL. C. Bruce Taylor, Albany Medical College of Union University, New Scotland Avenue, Albany, NY 12208, and Shi-Kaung Peng, Department of Pathology, Harbor-UCLA Medical Center, Torrence, CA 90509.

Cholesterol feeding is commonly used for the induction of experimental arteriosclerosis, and ingestion of cholesterol-containing foods has been widely considered a risk factor in human arteriosclerosis. However, it also has been known that cholesterol is unstable and easily oxidized when stored in air at room temperature. The most frequently occurring spontaneous oxidation products of cholesterol, which have been identified in U.S.P. grade cholesterol and a number of commonly consumed foods, are 25-hydroxycholesterol, cholestane-3β, 5α, 6β-triol, 7-ketocholesterol, 7α- and 7β-hydroxycholesterol. Concentrates of these oxidation products of cholesterol, when given by gastric gavage at 250 mg/kg to rabbits, significantly increased the number of dead aortic smooth muscle cells within a period of 24 hr. Similar necrogenic effects have been found in cultured aortic smooth muscle cells, in which 25-hydroxycholesterol and cholestane-3β, 5α, 6β-triol are shown to be most toxic at levels of less than 10 μg/ml in the culture medium. Interestingly, purified cholesterol has no effect on the smooth muscle cells. Using scanning electron microscopy, both compounds, when given intravenously, produced balloon- and crater-like defects on the intimal surface followed by adhesion of platelets and leukocytes and formed microthrombi on arterial walls. Further studies using non-human primates demonstrated 25-hydroxycholesterol was 30% absorbed as measured by the dual-isotope plasma ratio technique; also, a high concentration of its radioactivity in plasma was found in VLDL and LDL and very little in HDL. This finding strongly implicates oxidized cholesterol in atherogenesis.

163

COMPARATIVE ATHEROGENIC EFFECTS OF CHOLESTEROL AND CHOLESTEROL OXIDES. N.A. Higley, J.T. Beery and S.L.