R. Noyori (Nagoya University) discussed his work on nickel(0)–catalyzed rearrangements involving highly strained σ bonds.

J. Halpern (University of Chicago), also active in research on homogeneous catalysis and a participant in the preceding discussion, presented a paper on a different aspect of catalysis—an analysis of the mechanism of catalysis by tris(triphenylphosphine)rhodium chloride. More specific applications of homogeneous catalysis were discussed by J. Kiji (Kyoto University) on diolefin polymerization catalyzed by Ni(0) complexes and acid, G. W. Parshall (DuPont) on activation (for exchange with deuterium gas) of aromatic C–H bonds, and J. Tsuji (Tokyo Institute of Technology) on addition reactions of butadiene catalyzed by palladium(II) complexes.

Two homogeneous catalytic reactions applicable to laboratory synthesis were presented: (i) M. Kumada (Kyoto University) discussed the efficient catalytic coupling of Grignard reagents with aromatic halides by phosphine complexes of nickel and (ii) Iwao Ojima (Sagami Chemicals) discussed the selective reduction of unsaturated ketones by rhodium-catalyzed hydrosilylation. The latter synthesis was also reported to have yielded products of up to 50 percent optical purity from racemic substrate and chiral catalyst.

One most unusual and timely report was that of J. Ibers (Northwestern University), who had observed that cationic rhodium phosphine complexes homogeneously catalyze the conversion of CO and NO to CO_2 and nitrogen.

In addition to the studies of catalytic reactions mentioned above, the kinetics and mechanism of several other reactions were presented. J. Osborn (Harvard) discussed the analysis of the oxidative addition of alkyl halides to Pt(0) and concluded that such reactions generally occur via radical chain pathways. A. Nakamura (Osaka University) examined the mechanism of a molybdenum dihydride complex with various unsaturated compounds, and T. Tanaka discussed his studies on the kinetics of TCNE addition to a cationic rhodium complex. G. Whitesides (Massachusetts Institute of Technology) covered two topics: (i) the decomposition mechanisms of metal alkyls and (ii) some results on synthetically useful Li-Hg-C complexes of unknown structure. Further discussions of metal alkyl complexes were heard. One concerned nuclear magnetic resonance studies of nickel-alkyl phosphine complexes by A. Yamamoto (Tokyo Institute of Technology), and a second the decarboxylation of allyloxycarbonyl platinum(II) complexes by H. Kurosawa (Osaka University).

Two investigators reported specifically on stereochemistry. K. Saito (Tohoku University) concentrated on the asymmetric induction arising upon coordination of an olefin to chloro-L-prolinato platinum(II), while J. Faller (Yale) lectured on the substituents required to prevent palladium-allyl chiral centers from racemizing.

The last session was devoted to biological aspects of organometallic chemistry, dealing chiefly with the metalloporphyrin and metallocorrin systems. J. Collman (Stanford) discussed a synthetic iron(II) porphyrin with a hydrophobic "pocket" in which oxygen could be reversibly absorbed. M. Tsutsui (Texas A & M) presented his work on some novel bimetallic rhenium porphyrins; H. Ogoshi (Kyoto University) also talked about noble metal porphyrins, considering their similarity to vitamin B_{12}. For the final paper, J. Wood (University of Illinois) presented his work on the mechanism of mercury neurotoxicity, which arises from methylmercury ion–catalyzed cleavage of a vinyl ether linkage found only in brain lipids.

The organizers are looking forward to another similar seminar 3 years hence, although a meeting location has not been selected. In comparing the Japanese and American contributions, the only general observation that might be made is that while the Japanese tended to collect more data, the Americans collected less, but analyzed it more thoroughly.

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Polyunsaturated Fatty Acids

The subject of the 1974 Deuel Lipid Conference, which took place at the Highlands Inn, Carmel, California, from 26 February to 2 March 1974, was a consideration of the polyunsaturated fatty acids from biochemical and medical points of view. The first session concerned the control mechanisms in the formation and transformations of the polyunsaturated fatty acids. R. Brenner from the University of La Plata, Argentina, discussed the location, nature, and control of the enzymes involved in fatty acid desaturation. Although all aerobic desaturation occurs in the endoplasmic reticulum and the cofactors are the same, there is good evidence that separate enzymes are responsible for desaturation at the Δ^4, Δ^5, Δ^6, and Δ^9 positions of the fatty acids and that there may be some chain-length specificity as well. Of the various desaturases, the Δ^6 enzyme may be the most important because, since it operates at the slowest rate, it serves as a control point of subsequent elongation and desaturation. Thus, in the important series of reactions leading from linoleic to arachidonic acid, the desaturation of linoleic acid to 6,9,12-octadecatrienoic acid appears to be the control point. The desaturation reaction requires cytochrome b_5 reductase, cytochrome b_5, and a cyanide-sensitive factor, which are intimately bound to the lipid bilayer of the endoplasmic reticulum. Furthermore, it requires a factor loosely bound to this membrane. This factor appears to be a protein, but its structure and function are not yet apparent.

Elongation and desaturation in higher plants was discussed by P. Stumpf of the University of California at Davis. He has found that, although the desaturation pathway leading from stearate through oleate to linoleate follows the usual aerobic desaturation mechanism of the ACP derivatives, the formation of the linolenic acid (a trienoic acid) occurs by desaturation at the C_{12} stage followed by elongation to C_{18} with a series of specific enzymes.

A. Fulco of the University of California, Los Angeles, reviewed his findings on the temperature-dependent regulation of Δ^5 unsaturated fatty acid biosynthesis in bacilli. In *Bacillus megaterium* an increasing rate of inactivation of the Δ^5 desaturase with increasing temperature appears to be the most important factor in determining the degree of Δ^5 desaturation during culture growth at a given constant temperature. In contrast, a sudden downward shift in growth or incubation temperature (for example, from 35° to 20°C) triggers a transitory hyperinduction of the Δ^5 desaturase, a process which is eventually shut off by a repressor and whose synthesis and stability is also governed by temperature. The greater the magnitude of the downward temperature shift, the longer the period of hyperinduction before repression becomes effective. Desaturase hyperinduction can be blocked by protein-synthesis inhibitors added before, or at the time of the temperature shift while repression (but no hyperinduction) is prevented by inhibitors of DNA synthesis added before the shift from 35° to 20°C.

The second session concerned the physiological effects of the essential fatty acids (EFA). R. B. Alfin-Slater of UCLA re-

viewed the symptoms of EFA deficiency in various species and the correlation of structures of polyunsaturated fatty acids with various manifestations of EFA activity. The effect of other substances on such deficiency states was also discussed, for example, exacerbation by saturated fatty acids and cholesterol and potentiation of EFA effects by vitamin E.

O. Privett of the Hormel Institute, Austin, Minnesota, discussed the formation of prostaglandins (PG's) from specific polyunsaturated fatty acids, including the C_{22} analogs of the usual C_{20} precursors, and its inhibition by hypophysectomy and by EFA deficiency.

Of great potential interest was the report by J. Pike of the Upjohn Company that two previously hypothetical intermediates in prostaglandin biosynthesis have now been isolated by B. Samuelsson and coworkers at Karolinska Institute, Stockholm, and are many times more active physiologically than are the final products, PGE and PGF, in certain biological systems. These intermediates both have the endoperoxide structure, but differ in the substituent on carbon-15, PGG being the 15-hydroperoxyendoperoxide and PGH the 15-hydroxy compound.

In a session on EFA deficiency in humans, R. T. Holman of the Hormel Institute reviewed evidence that infants on low-fat proprietary milk substitutes or patients on prolonged fat-free intravenous nourishment regimens show some of the symptoms typical of the deficiency disease and can be cured by administration of linoleic or arachidonic acids.

K. Kingsbury of Amersham, England, reported some results of his long-term study of the polyunsaturated fatty acids of atherosclerotic patients. Analysis of the plasma cholesteryl ester fatty acids revealed that severity of the disease is inversely related to the concentration of linoleate. Moreover, in atherosclerotic patients the arachidonate was also decreased while, concomitantly, oleate, palmitoleate, and eicosatrienoate, symptomatic of EFA deficiency, increased. These results point to some dietary-metabolic abnormality in atherosclerosis.

In a change of general subject matter, W. A. Pryor of Louisiana State University, Baton Rouge, reviewed certain aspects of the chemistry of free radicals, with particular reference to features bearing directly on in vivo lipid autoxidation, this is, initiation modes (via ionizing radiation and atmospheric pollutants) and the modest chain length of the resulting reactions.

Starting from this background, P. B. McCay of the Oklahoma Medical Research Foundation discussed the mechanism of peroxidation of membrane lipids in subcellular particles in vitro and in vivo. In particular, the high susceptibility of the lysosomal membrane to peroxidation, as measured by the release of lytic enzymes, was used to assess the generation of radicals by certain oxido-reductase enzymes. The radicals initiated peroxidation of the lysosomal membrane. Radical scavengers in vitro or feeding α-tocopherol in vivo inhibited the reaction, whereas superoxide dismutase actually enhanced it. This and other evidence suggests that hydroxyl radicals (rather than superoxide) produced by certain types of flavin enzymes cause lysis of the lysosomal membrane. In particular, inhibition by catalase and by excess superoxide dismutase leads to the following suggested reactions producing hydrogen peroxide and hydroxyl radicals:

$$\text{Flavoprotein} + \text{substrate} \rightarrow \text{reduced flavoprotein} + \text{product}$$

$$\text{Reduced flavoprotein} + O_2 \rightarrow \text{flavoprotein} + O_2\cdot$$

$$2\,O_2\cdot^- + 2H^+ \xrightarrow{\text{dismutase}} H_2O_2 + O_2$$

$$H_2O_2 + O_2\cdot^- \rightarrow O_2 + \cdot OH + OH^-$$

$$O_2\cdot^- + ADPFe^{3+} \rightarrow O_2 + ADPFe^{2+}$$

$$ADPFe^{2+} + H_2O_2 \rightarrow ADPFe^{3+} + \cdot OH + OH^-$$

where ADP is adenosine diphosphate.

Measurement of peroxidation in vivo is difficult, but with isolated liver cells and carbon tetrachloride (thought to produce liver damage by forming reactive radicals when acted on by the microsomal drug-metabolizing system), peroxidation of microsomal membrane polyunsaturated fatty acids has been demonstrated by malonaldehyde formation by these cells which increased in hepatocytes from animals pretreated with phenobarbital. Phenobarbital induces the drug-metabolizing system, hence the increased capacity to form reactive radicals.

Stumpf proposed that enzymatic peroxidation may be involved in the α-oxidation process in higher plants and, possibly, in animal tissues as well. Considerable experimental evidence suggests that the first step in the reaction is the formation of D-2-hydroperoxypalmitate via a mixed function oxidase reaction involving an electron source and molecular oxygen in the presence of a cytoplasmic membrane enzyme system. The resulting hydroperoxide may then be either reduced to the D-2-hydroxypalmitate by glutathione peroxidase or decarboxylated directly to CO_2 and pentadecyl aldehyde. Thus, in this scheme neither D- nor L-2-hydroxypalmitate would be expected to function as intermediates in α-oxidation.

The production of lipid peroxides in the phagocytizing leukocyte as a means of killing bacteria was discussed. It has been found that in polygranulocytosis no peroxide is produced and no bacteria are killed.

A. L. Tappel, University of California, Davis, reviewed his work on the identification of the fluorescent pigments produced in aging and antioxidant-deficient conditions. The pigments appear to be the result of lipid peroxidation in cytoplasmic and mitochondrial membranes, largely as a consequence of loss of protection against radicals produced in the normal course of certain enzyme reactions. Malonaldehyde and other aldehydes formed by degradation of peroxides tend to cross-link tissue components (such as phospholipids, proteins, and nucleic acids) bearing free amino groups leading to formation of the characteristic fluorescent chromophore R-N=CH-CH=CH-NH-R, which may thus occur in fat- or water-soluble products or be present in insoluble granules. The polymeric material resulting from these reactions is taken up by the lysosomes; but, being resistant to degradation, it tends to accumulate as insoluble particles within the lysosome. The major protection against lipid peroxidation in membranes is provided by tocopherol, which is effective in limiting the propagation of the chain reaction; and by the selenium-containing enzyme, glutathione peroxidase, which reduces hydroperoxides to alcohols, preventing their transformation into chain initiators.

J. G. Bieri of the National Institutes of Health discussed the structures, sources, and activities of the various analogs of tocopherol, the tocols and tocotrienols. Although γ-tocopherol has a considerably lower activity in vivo, its high concentration in vegetable oils, such as corn and soybean, that form a large part of the American diet, make it a significant fraction of total dietary vitamin E. He pointed out that with all sources of vitamin E taken into consideration there is no evidence that the American diet, in general, is deficient in this regard, or that an increase in extra tocopherol is warranted. Contemporary diets lead to molar ratios of polyunsaturated fatty acids to tocopherol in human tissues varying from about 2000 in liver to about 300 in heart and lung where, presumably, antioxidant is most needed. Whether these tissue concentrations are optimal for prevention of membrane lipid peroxidation has not yet been determined.

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