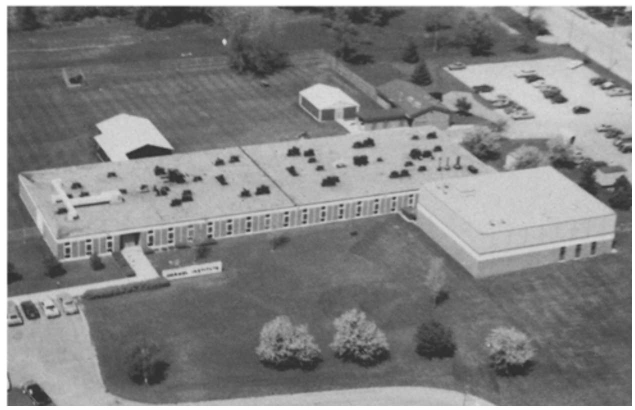
Hormel Institute spans four decades



(Editor's note: The Hormel Institute, in Austin, Minnesota, is known worldwide as one of the leading lipids research laboratories. The following article is based on a report written by Hormel Institute Executive Director Ralph T. Holman for the institute's 1982 report to mark the 40th anniversary of its founding. Copies of the institute's annual reports and other publications are available on request to: The Hormel Institute, University of Minnesota, Austin, MN 55912, USA.)

Forty years ago, during the most discouraging part of World War II, members of The Hormel Foundation and the administration of the University of Minnesota signed a memorandum of agreement establishing a new research facility of the Graduate School. The Hormel Institute was formed to promote education and research in plant and animal science, disease, nutrition, food technology and in allied branches of science. The Foundation provided funds for the operation of the unit, and the University provided the framework and the personnel. From the outset, fundamental research was the primary activity of the Institute. Its first project was the compilation of available information on the nutritive value of soybeans. Initial experimental work was done at the Medical School in Minneapolis in the laboratories of Professors H. O. Halvorson and George O. Burr, which at that time were concerned with the chemistry of lipids, antioxidants and the biological properties of fatty acids. "Doc" Halvorson was the first Director of The Hormel Institute, Walter O. Lundberg was the Hormel Fellow, and Jacques Chipault and Ralph Holman were graduate students.

In January 1944, Chipault moved to Austin and began setting up laboratories in one corner of the stable on the Hormel family estate at the east edge of Austin. After a few months, Lundberg became Resident Director and moved to Austin to recruit staff and to set up a program. When the war was over, the Institute grew rapidly on the wave of people returning to civilian pursuits, on the increased funding for research available through the newly created National Institutes of Health (NIH) and the Atomic Energy Commission, and on the new possibilities for analysis of lipids generated by the electronics and instrument spin-off from new industrial technology. In 1949 the directorship of the Hormel Institute passed to Walter O. Lundberg, and he held that position until 1974, guiding the Institute through its early development and major period of growth.

The early staff had interests in nutrition, microbiology, disease, genetics and lipid chemistry. Thus, experienced, lipid-oriented people were in place and doing lipid research before it became easy and popular. In time, lipids became

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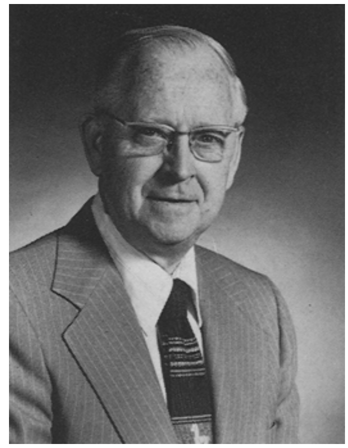
H.O. Halvorson

Walter Lundberg



Ralph Holman

the common theme of its research programs in synthetic organic chemistry, analytical chemistry, phytochemistry, microbiology, biochemistry, nutrition, molecular biology, enzymology, membranes, biophysics and medicine.

Walter O. Lundberg became a leading authority in lipid oxidation. Jacques Chipault worked intensively on absorption of fats, and on the lipids of the eye. Lawrence Carpenter was among the first to test the value of antibiotics in animal rations. George Young made considerable progress in the characterization and control of transmissible gastroenteritis of swine. Arnold Lund made considerable progress in the study of the physiology of bacterial spores. A race of small swine (PIGmeePIG®), was genetically developed to 25% of commercial size and was used widely in biomedical research. Thin layer chromatography was first applied to lipid analysis by Helmut Mangold at the Institute, and it became a universal tool in lipid research.

Orville Privett directed the Fatty Acid Project that made purified lipids for sale at cost to researchers around the world. His major scientific contributions are in developing analytical methods and applying them to the study of biological problems such as lung surfactants and aging. His present work on analytical methods involves the analysis of lipids and related compounds by liquid chromatography employing flame ionization, ultraviolet absorption and fluorescence detectors. One aspect involves analysis by a combination of liquid chromatography and mass spectrometry. Another project involves isolation and analysis of prostaglandins and related compounds. The study includes the influence of dietary fat on biosynthesis of prostaglandins and related compounds involving the isolation of polyunsaturated fatty acids, determination of their structures and the course of their conversion to prostaglandins.

Herman Schlenk's work includes major contributions in the chemistry of inclusion compounds, the metabolism of polyunsaturated acids and the chemistry of the lipids of plants and fish. Study of highly unsaturated fatty acids in fish and microorganisms may contribute to the understanding of their functions in mammals. Schlenk's work with fish focuses on the metabolism of furan fatty acids. His work with microorganisms demonstrated the presence of highly active lipoxygenases in one of the fungi, a little studied area thus far.

Eldon Hill and Ralph Holman concentrate on the metabolism of essential polyunsaturated fatty acids and their quantified requirements. Work includes the study of EFA deficiency, dietary *trans* fatty acids and such physiological conditions as diabetes and hypothyroidism on composition of tissue lipids in animals. The relationship of other dietary nutrients to essential fatty acid phenomena is a new area of concentration. In work on mass spectrometry of lipids, current emphasis is being placed on use of pyrrolidide derivatives for mass spectral elucidation of fatty acid structure. Single and multiple double bonds, triple bonds, methyl branches, hydroxyl groups and keto groups are more readily located in fatty acid structures because the fragmentation of the cyclic amide yields a simpler and readily interpretable spectrum than does the traditional methyl ester. Extension of the use of the pyrrolidides to other types of fatty acid structures is now under study. This group is also working on the influence of nutrition on neuropathy and on topics in chemical taxonomy.

Howard Jenkin applies techniques of lipid analysis to understand the interactions of viruses and intracellular obligate parasites in host cells, using tissue culture methods. A study of lipid changes in macromolecular structures of arbovirus-infected cells and cells under drug treatment is in progress and may aid in understanding mechanisms of virus absorption, maturation, release and pathogenesis in different susceptible cells. These studies include isolation of purified mitochondria, microsomes, plasma membrane, golgi apparatus, endoplasmic reticulum and lysosomes using decavitation and bounce techniques, virus concentrations and purification, ultracentrifugation-density gradient systems, lipid analysis, radiosotopic techniques, NMR and mass spectrometry. In work on carnitine-lipid biochemistry in embryonic heart cells, one major emphasis is the comparison of carnitine metabolism in different heart cells to study possible compartmentalization of cell functions of carnitine and lipids.

Harald H.O. Schmid concentrates on the structure, metabolism and functions of complex lipids in biological membranes, with particular emphasis on the glycerophospholipids. This involves studying phospholipid metabolism in normal cells and the alteration of lipid metabolism in disease. In normal cells, the work includes study of the metabolism of plasmalogens and related other lipids in mammalian heart, brain and sciatic nerve; the role of stimulated inositol phospholipid turnover and its possible regulation by polyphosphoinositide metabolism; the sequential methylation of ethanolamine phospholipids, and the catabolism of ethanolamine phospholipids by *N*-acyltransferase-phosphodiesterase activity. In altered metabolism in disease, current work deals with phospholipase and *N*-actylethanolamines as protective agents against ischemic injury. Work on changes in metabolism that occur in degenerating peripheral nerve is done in collaboration with neurologists at Mayo Medical School.

Wolfgang Baumann studies the functions of diol lipids, lysophospholipids, the involvement of phospholipases in disease such as cancer and neuropathies, and the study of lipid-lipid and lipid-protein interactions by means of nuclear magnetic resonance spectrometry. Current objectives of the lysophospholipid work are (a) to assess the role of lysolecithin as precursor of phosphatidylcholine in lipoprotein synthesis; (b) to elucidate the mode of action of various systemic hypolipidemic drugs that act as inhibitors of lysolecithin; (c) to shed light on the modes of lipoprotein assembly and secretion; (d) to determine the mode of action of lysophospholipid-mediated inhibition of platelet aggregation and of the effect of cholesterol in this phenomenon; (e) to investigate the effects of lysophospholipid and cholesterol in cell proliferation; (f) to define the role of lysophospholipids produced by transient phospholipase A_2 stimulation in the course of virus infection; and (g) to pinpoint the lysophospholipid-myelin protein interactions that induce demyelination.

Howard Brockman is making significant contributions to the understanding of lipid enzymology at interfaces, with relevance to atherosclerosis, using instruments designed and built at the Hormel Institute. Brockman's studies focus on the elucidation of surface structure and on the regulation of enzyme absorption and catalysis. The lab developed and tested a thermodynamic model for predicting the concentration of cholesteryl esters at interfaces. The model seems to be of a general nature and with further theoretical and experimental work should lead to a general understanding of the surface structure of arterial inclusions and lipoproteins. Recent studies of the effects of pancreatic cholesterol esterase on intestinal cholesterol absorption suggest that this esterase activity, which is present in most tissues, may be directly involved in the transmembrance movement of cholesterol.

Douglas Pfeiffer is demonstrating the importance of calcium transport in lipid metabolism using mitochondria and other membrane model systems and he is finding that ion transport is important in the formation of cataracts. In his work, Pfeiffer is studying a class of lipid, *N*-acylethanolamines, that is synthesized by infarcted heart tissue. These compounds inhibit the phospholipase A_2 permeability changes in mitochondria. Also being studied is the ability of arachidonic acids released by the mitochondrial phospholipase A_2 to serve as substrate for prostaglandin biosynthesis and in turn control the blood flow in the nearby microcapillaries. A system of this type may serve to allow mitochondria to regulate their oxygen supply.

Margot P. Cleary, the latest addition to the institute faculty, concentrates on nutrition and metabolism related to obesity. Two primary areas are being investigated: (a) detailed evaluation of the effects of long-term food restriction in the genetically obese Zucker rat; and (b) determination of the mechanism of action of the antiobesity agent, dehydroepiandrosterone (DHEA). DHEA treatment results in decreased food efficiency in that more calories are needed in DHEA-treated animals than in controls to gain an equivalent amount of weight. The mechanism is unknown. DHEA does inhibit the enzyme glucose-6-phosphate dehydrogenase. That relationship is being investigated. One current study is examining the effect of DHEA on energy metabolism in tissues that play a primary role in energy use such as liver, adipose tissue and brown fat.

In 1960, the Institute's activities were expanded by the construction of a new building on the north edge of Austin, using matching funds from The Hormel Foundation and the NIH, and activities continued at the 2 sites for 15 years. A laboratory for mass spectrometry was built in the basement in 1964. In 1968, a wing was built to provide the Microbiology Section with downflow sterile clean-rooms for tissue culture research. Shortly after Ralph T. Holman became Director in 1975, the original facility was abandoned because its inefficiency and cost of operation could no longer justify its use. In 1975 Hormel's orchestra of instruments was expanded by the addition of a nuclear magnetic resonance spectrometer, which is used mainly in the study of membrane structure. In 1976, an external facility for research involving fish and basement rooms for film balance and for plant culture were added.

Hormel acquired its first computer 12 years ago, and now has several, some of which are dedicated to instruments, expanding their efficacy. The electronics group, under the direction of Dale Jarvis, now designs, builds and programs interfaces for instruments. Addition of a machine shop in the basement in 1979 permits Hormel to design and build mechanical instruments as well.

Because of the growing interest in biomedical research, by 1977 all research sections required space for animals. A request to the state for funds for an animal facility was granted. In 1981, a new wing was ready that provides downflow sterile clean-rooms for housing animals and the required ancillary equipment and laboratory facilities. In 1981, Hormel refurbished a laboratory and installed an electron-microscope facility, under the direction of David Stiers. Infrared, ultraviolet, visible and fluorescence spectrophotometers are in use in attempts to probe biochemical reactions at the enzyme, membrane and cellular levels. All the instruments mentioned above are a part of the core facilities provided by a Program Project Grant, now in its 20th year, from the Heart, Lung, and Blood Institute of the NIH.

The administration of the Institute has been modernized by microcomputers. They now provide word processing for the preparation of scientific reports and will soon facilitate the keeping of inventories, making up-to-date budget statements and simplifying other clerical functions. One computer will function as a warning system, monitoring the building and instruments. Another provides a link with a regional library system.

Members of the Hormel faculty have been active in professional organizations. One was president of the Society of Microbiology and two served as president of the American Oil Chemists' Society, a principal forum for lipid research in the United States. The scientific journals, *Progress in Lipid Research* and *Lipids,* have been edited at Hormel since 1951 and 1967, respectively. In addition, the faculty has produced four books, has contributed significantly to many treatises and has a total of 970 publications in the scientific literature. In 1980, Hormel Institute partially sponsored and organized the "Golden Jubilee International Congress on Essential Fatty Acids and Prostaglandins" on the anniversary of the discovery of essential fatty acids at the University of Minneosta by Professor Burr, a discovery that has strongly influenced Hormel research.

The Hormel Institute has grown from 8 people in 1944 to 124 in 1982, and the budget has grown from $15,000 in 1944 to $2,796,753 in 1982. The current budget is provided by The Hormel Foundation (18%), the State of Minnesota (5%) and competitive research grants (70%). In 1955, the institute began hiring technical assistants from among talented students from the local high school, junior college and vocational institute. Thus far Hormel has "graduated" about 200 of these students, and a very high proportion of them are now in the scientific professions. Hormel currently has a training grant that permits postdoctoral fellows to learn by doing lipid research in relationship to heart disease. Over the years Hormel has had 164 postdoctoral fellows who are now pursuing scientific careers in all parts of the world, more than half in academic or clinical institutions. Despite its rural location, the Institute has considerable interaction with the outside scientific world. Members of the faculty attend national scientific meetings to present Institute research and to consult with scientists with similar interests. Seminar speakers come to the Institute to lecture on current topics. For the past six years, Hormel has had a program supporting guest professors, and thus far has been host to nine, including four from abroad.

Since Hormel's earliest years it has had scientific cooperations with members of the Mayo Clinic, permitting Hormel to take part in clinical research. Currently, this is formalized by the inclusion of three of Hormel's sections in the Peripheral Neuropathy Clinical Research Center at the Mayo Clinic. Hormel's associations with the Departments of Biochemistry, Microbiology, Food Science and Nutrition, Chemistry, Pharmacology, Pediatrics and Medicine at the University of Minnesota Twin Cities campuses, and with the Hennepin County Medical Center, Abbott-Northwestern Hospital and the Veterans Administration Hospital have been very fruitful.

In the next few years, Hormel hopes to add other new faculty members to prepare for the transition that will take place by the expected retirements of some of our faculty. Currently, the scientific community appears to be at the perigee of an economic cycle, when the spirits of scientists are at a low point. This is, therefore, the best time to plan for the future. The founders did exactly that forty years ago at the depths of the war, and they created an institution that has made tremendous strides. The present generation can do no less, for research must move forward on the next wave of prosperity in science.