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Symposium on

The Mode of Action of Lipotropic Factors in Nutrition*

THE GRADUATE School of Public Health of the University of Pittsburgh takes pleasure in welcoming all of the participants in this *Symposium on The Mode of Action* of Lipotropic Factors in Nutrition to our campus and to our city. As most of you know, we are indebted to The National Vitamin Foundation for joint sponsorship of this Symposium, that 51 per cent of sponsorship in fact, which has provided the wherewithal to permit us to gather here today to take stock of our knowledge in this important field. I'm sure that all of you join me in paying my compliments to Dr. Robert S. Goodhart, the Scientific Director of The National Vitamin Foundation, who has been instrumental in the organization of at least two such Symposia per year for the past several years. These Symposia have provided a meeting place for the basic scientist and the clinician working in various fields of nutrition to appraise current research and exchange views. Experimental and clinical nutrition are fields in which the workers not only profit from better communication between their respective groups but also gain enrichment from intimate contact with the respective basic and clinical disciplines which underlie them. This cross fertilization is one of the dividends which has emerged from these Symposia in the past and I am hopeful that such dividends may be forthcoming from this Symposium as well.

With regard to the subject under discussion, *the mode of action of lipotropic factors*, we might recall that the field was opened by the discovery of Allan *et al.*[1] that depancreatized dogs maintained with insulin developed fatty livers. Subsequently, Best and Hershey[2] showed that raw pancreas supplements to the diet of depancreatized dogs protected against fatty liver and that the active principle was lecithin. The production of "dietary fatty liver" in the rat by Best and Huntsman[3] and the demonstration that choline was the active lipotropic agent in lecithin, opened the way for hundreds of productive investigations of the role of specific dietary nutrients in the control of fat content of the liver in this species. It is somewhat ironic that although the replacement of pancreas in the diet of the insulin-treated depancreatized dog prevented the fatty liver which ordinarily developed, it did so for a different reason than that of the intact functioning pancreas. As more recent studies have shown,

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the intact pancreas supplied proteolytic enzymes essential for the liberation of *methionine* from dietary protein[4] whereas the dietary pancreatic tissue supplied *choline* which produced the same hepatic effect. An explanation for the sometimes clear,[5] sometimes enigmatic, interrelationship of choline and methionine in influencing liver lipid content, lipid transport, kidney structure and function and even vascular integrity will most certainly be the concern of many of the essayists in this Symposium.

The term lipotropic is derived from the Greek *lipos* meaning "fat" and the Greek *trope* meaning "turning." Literally, it means the "turning of fat." It was first used by Best, Huntsman, and Ridout in one of their early papers.[6] As originally defined "lipotropic" compounds were those substances which "decreased the rate of deposition or accelerated the rate of removal of liver fat." Through common usage, the term has been applied to the action of substances upon histologically visible fat in any tissue which ordinarily does not have visible fat present. I am hopeful that we shall return, in this Symposium, to a more literal use of the term. I suggest that we think in terms of the relationship of this group of nutrients to the "turnover of lipid" in the dynamic sense—considering their role in various processes by which lipid is synthesized, enters, becomes visible, is oxidized or leaves the organ under consideration.

This Symposium was planned to embody a dual progression: from enzymology to physiology—and from animal to man. This morning Dr. Stekol will tell us about the biosynthesis of "labile" methyl groups, transmethylation and the biosynthesis of choline. Dr. Kennedy will next review his important contributions dealing with the enzymatic synthesis of phospholipid from choline. Next, Dr. Artom will review for us the evidence that lipotropic factors play a role in the oxidation of fatty acids and Dr. Zilversmit will present data on the role of lipotropic factors in the turnover of phospholipids.

We shall then turn to animal nutrition for a consideration by Dr. Harper of the dietary factors which influence liver fat deposition in the rat and a discussion by Dr. Wells of the effects in the animal of antimetabolites to the lipotropic factors. Dr. Griffith will review his classical work on the renal lesion in choline deficiency and Dr. Wilgram will define the role of the lipotropic factors in maintaining the integrity of the heart and vascular tree in the rat.

We then plan to take a great leap from the experimental to the clinical situation and consider the information which is available about fatty liver in man. Dr. Frenk will discuss kwashiorkor and marasmus in children and Dr. Gabuzda fatty liver in adults. Next, Dr. Labecki and I shall contemplate the evidence which ascribes a role to these factors in controlling the blood lipids in man.

When the last word is said, it is doubtful that we shall have answered the question posed by this Symposium in entirety. If some questions are answered, if a clearer definition of the problem is obtained, if ideas about new approaches to the problem are sparked from the discussions, then this meeting will be well worth while. Further research is essential to answer many questions, particularly those dealing with the relevance of the results of animal experimentation to man. The etiology and pathogenesis of fatty liver in the human are still not known with certainty. Further, the relationship of liver function in man to the pathogenesis of atherosclerosis in states of under- and overnutrition is a field which demands further thorough and systematic exploration.

At present, however, unprecedented opportunities exist for the study of liver function and metabolism in man. Safe procedures for liver biopsy, micromethods for enzyme assay, access to hepatic venous blood via cardiac catheters, isotopic methods for the study of intermediary metabolism, and knowledge to achieve highly specific dietary control are realities and should provide an exciting challenge to the clinical investigator working in this field.

Finally, since research and teaching go hand in hand in most medical centers, it seems to me that the field of clinical nutrition provides an avenue for the teaching of "comprehensive

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medicine" which is not available in many other fields of medicine. The recent emphasis upon consideration of the "total man" in modern medical schools has meant improved coverage in breadth—i.e., of the social and behavioral aspects of the clinical problem in addition to the conventional study of the medical history, physical examination, and the common laboratory parameters. I should like to suggest that there is another dimension which should be covered in the approach to the "total man" and that is the vertical plane via which one uncovers the processes of cellular physiology which underlie the clinical syndrome. The field of nutrition not only has its behavioral overtones but is undergirded with a wealth of information about the function of the nutrients in cellular physiology and their relation to intermediary metabolism. I hope that the range of subject matter embraced by this Symposium—from the origin of the C_1-fragment to the pathogenesis of fatty liver in the chronic alcoholic will provide a panoramic view of what the field of nutrition has to offer to both the advanced researcher and to the student of medicine.

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