FAT METABOLISM

A Symposium on the Clinical and Biochemical Aspects of Fat Utilization in Health and Disease

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A Symposium on Fat Metabolism

1. Clinical and Biochemical Features of Fat Metabolism: An Introduction

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THE PROBLEM OF OBESITY and fat metabolism has been the concern of the medical clinician and the medical biochemist for quite some time. Interest in fat metabolism until a few years ago was merely an offspring of a wider interest focused on carbohydrate metabolism. This perhaps is the natural course of events, inasmuch as carbohydrates generally contribute over 50 per cent of the caloric intake and obesity is therefore due largely to the conversion and deposition of excess carbohydrates in the fat stores. Moreover, diabetes, the disease par excellence of sugar metabolism, is often associated with increased output of ketone bodies which are products of incomplete fatty acid oxidation. Recently, the successful search for the 2-carbon fragment at the last stages of glycolysis, as elucidated by Lipmann, has renewed interest in fat metabolism by opening the way for an understanding of fat synthesis and breakdown at the enzyme level.

Obesity as a clinical entity is ill-defined and obscure. This is mainly due to the lack of understanding of the many factors that give rise to the obese individual. There are instances where an endocrine disturbance can cause excessive deposition of fat such as one encounters in cases of adrenocortical hyperfunction due to adrenocortical tumors or

hyperplasia as exemplified by Cushing's syndrome. Cortisone remains the only physiological compound that can cause obesity when administered in excess of body needs. This type of obesity is indistinguishable from that of Cushing's syndrome. Other than these instances, the causes of obesity abide, for the present at least, in the realm of uncertainty. There are *psychic, environmental, traumatic* and *genetic* factors that may be involved in its etiology. These are necessarily complex causes and require the assistance of factors more intimately concerned with metabolism and the balance between caloric intake and expenditure of energy. Thus a child who is psychologically disturbed and finds refuge in overeating may not gain weight if his redoubt includes overactivity. Similarly, another child with the same disturbance can materially augment his adipose tissue if his refuge is limited to inactivity and sluggishness without affecting his food intake. Postencephalitic obesity is in many cases due to restriction of activity with no concomitant diminution of caloric intake. While there is little doubt that some forms of obesity run in families, it is nevertheless difficult in such instances to separate the genetic and environmetal factors that might be involved. Hereditary types of obesity, however, have been described and studied in animals.

Whether food is conserved in fat depots or fully metabolized depends on the caloric intake as well as on the demand for metabolism. Food intake is governed by the appetite as well as by a host of undefined conditions, physiological, psychological, and pathological. Freed from these shackles, food intake may be regulated by a "glucostatic mechanism." "Gluco-receptors" present in the hypothalamus are sensitive to arteriovenous differences in glucose level. When the difference between the arterial and venous glucose levels approaches zero, contractions of the stomach are stimulated and hunger sensations are felt. A difference

of over 10 mg. per cent is not associated with hunger contractions. Obese individuals in general show a magnitude of arteriovenous difference that is generally greater than normal.

The ingested fat is hydrolyzed by the lipases of the gastro-intestinal tract before absorption by the mucosa. A reconstitution of fat by esterification of the fatty acids occurs in the intestinal mucosa prior to final entry into the blood stream where it is transported mainly as lipoproteins in small droplets of less than 1 μ in diameter called chylomicrons. When lipase activity is diminished such as in celiac disease or pancreatic disease, particularly cystic fibrosis of the pancreas, a good deal of the fat fails to be absorbed and consequently is excreted in the stools.

Fat is not only transported as tiny chylomicrons but also as phospholipids and cholesterol esters. The lipoproteins are of various molecular weights. In these differing physical and chemical states fat is transported to the body tissues.

Here again there may be derangement in this mechanism where, for some reason as yet unknown, fat accumulates in the blood and is not taken up by the tissues. One type of abnormal lipemia shows an accumulation mainly of neutral fats resulting in creamy serum, xanthomatous deposits, enlargement of the liver and spleen. Such cases suffer occasional and unexplained attacks of sudden abdominal pain with all the manifestations of an acute inflammatory process. This is followed by a rapid fall in blood fat with a simultaneous increase in the size of the liver and spleen.

The physical and chemical nature of serum fat has attracted wide attention during the last few years after the discovery of a factor present in serum that is responsible for causing decreased turbidity of lipemic sera. The so-called *clearing factor* effects a hydrolysis of the triglycerides yielding glycerol and free fatty acids. With this lipase-like action, there is a simultaneous decrease in the β lipoprotein of low

density and an increase in the β lipoprotein of higher density. One of the most interesting features of the *clearing factor* is that it is activated by heparin. This can be demonstrated *in vivo* by the injection of heparin which results in rapid clearing of lipemic sera as well as causing a diminution or disappearance of low density lipoproteins. Anaphylactogenic agents also cause an increase in the activity of the serum clearing factor, presumably due to release of heparin.

Another type of derangement that manifests itself in serum is the occurrence of high cholesterol levels in the nephrotic syndrome, hypothyroidism and particularly in idiopathic familial hypercholesterolemia. In all such instances xanthomatous deposits appear in various tissues. Where hypercholesterolemia is prominent, as in the idiopathic familial syndrome, early atheromatous patches may occur similar to those encountered in arteriosclerosis.

Atherosclerosis is indeed a disease peculiar to the human species and intimately associated with cholesterol metabolism. The disease can be produced in animals by excessive feeding of cholesterol. Thus there is a definite relationship between cholesterol and arteriosclerosis even though the disease in humans is not generally associated with high blood cholesterol. Cholesterol transport is associated with the low-density lipoproteins. These are elevated in cases of atherosclerosis and appear in rabbit sera only following cholesterol feeding.

The lipid component of an atheromatous lesion is composed mainly of cholesterol and its esters. In this manner the lesions are similar in composition to those observed in the xanthomatous areas of Hand-Schuller-Christian's disease. Cholesterol is not only a constant companion of lipids in the form of cholesterol esters, but its metabolism is closely linked to lipid metabolism. The reason is not far to seek since cholesterol is built from the same elementary 2 carbon frag-

ment active acetate (-acetyl *CoA*) that forms the smallest building block of fatty acids. Acetate labeled in both carbons is incorporated into the cholesterol molecule as a unit. Squalene has lately been shown to be an intermediate in cholesterol synthesis. Since both fatty acids and cholesterol use acetate as an essential building block, both must necessarily compete for the available active acetate. When fatty acid synthesis is suppressed, cholesterol synthesis is thereby accelerated. In diabetes not only is the synthesis of fat from acetate impaired but there is also an increased fatty acid oxidation and breakdown to yield excessive amounts of active acetate, thereby augmenting still further the synthesis of cholesterol.

The impairment of fatty acid synthesis in diabetes is not limited to synthesis from acetate. The conversion of glucose to fat is also depressed. The injection of insulin corrects this deficiency. *In vitro* studies, using liver slices from diabetic depancreatized animals, also show the same defect in fatty acid synthesis. On the other hand, synthesis is not impaired following the removal of both the pancreas and the pituitary or the pancreas and adrenals. Further evidence of hormonal effects on fatty acid metabolism is the impairment of acetate incorporation by liver slices of normal animals treated with cortisone. Impaired lipogenesis in diabetes is not due to lack of active acetate, as that is formed in excessive amounts, nor is it due to a defect in the Krebs cycle. The cause apparently lies in some deficiency in the glycolytic process. Thus impaired lipogenesis in extracts of livers from diabetic animals can be corrected by the addition of glycogen or the phosphorylated intermediates of glycolysis. However, fructose but not glucose produces the same effect. It now appears that fats are synthesized and not burned in the flames of carbohydrates since, as we have noted above, fatty acid oxidation and breakdown are accelerated in diabetes while

fat synthesis is impaired. It is the latter defect that is abolished by correcting the deficiency in the glycolytic mechanism.

Fatty acid oxidation to carbon dioxide and water occurs in all tissues. However, the liver, of all organs, has a limited ability to oxidize ketones which are the products of incomplete fatty acid oxidation. These products normally are transported by the blood to other organs where they are completely oxidized. In diabetes, however, the acceleration of fatty acid oxidation produces large quantities of ketone bodies which accumulate in the blood and urine.

The steps in the complete breakdown and oxidation of fatty acids have been elucidated recently. One can picture a long chain fatty acid molecule as composed of 2-carbon units much like glycogen is composed of glucose units. Furthermore, coenzyme A (*CoA*), discovered by Lipmann, is necessary for the activation of the fatty acid molecule in much the same manner that phosphate is necessary for the activation of the glucose molecule. One further analogy is that the 2-carbon unit of a long chain fatty acid molecule splits off as the *CoA* ester, acetyl-*CoA*, much like the glucose unit of glycogen splits off as the phosphate ester, glucose-1-phosphate. The first step then in the breakdown of the long chain fatty acid molecule is the formation of the *CoA* ester. This is followed by the removal of two hydrogens (oxidation) between carbons 2 (α) and 3 (β) ($R–CH_2–CH_2CO–CoA \rightleftharpoons RCH=CHCO–CoA$) to form an unsaturated bond. The next step involves adding water at that bond to yield the β hydroxy acid ester ($R–CHOH–CH_2CO–CoA$). A dehydrogenation step again follows to produce the β keto acid ester ($R–CO–CH_2–CO–CoA$). This keto ester reacts with a free *CoA* molecule to form acetyl-*CoA* and a fatty acid *CoA* ester with two carbons less ($R–CO–CH_2CO–CoA + CoA \rightleftharpoons R–CO–CoA + CH_3CO–CoA$). All these steps are rever-

sible towards synthesis and catalyzed by specific enzymes. The acetyl-*CoA* then condenses with a molecule of oxalacetate to form citrate, thereby entering the Krebs cycle where oxidation to CO_2 and water occurs.

Acetyl-*CoA* also reacts with a like molecule to form acetoacetyl-*CoA* and free *CoA*. The acetoacetyl-*CoA*, a short chain β keto acid ester, may by reversal of the above reactions become butyryl *CoA*, a short chain saturated fatty acid ester. A 2-carbon fragment can then be added onto the butyryl *CoA* by reacting with acetyl-*CoA* and again forming a β keto acid ester which by the reverse reactions forms correspondingly a saturated 6-carbon fatty acid ester. The successive addition of two such carbons yields a fatty acid molecule of the desired length. Such is the role of the active acetate, acetyl-*CoA*, in fatty acid synthesis. The first step in the synthesis being the formation of the acetoacetyl-*CoA*. This latter may, however, suffer another fate. In the liver there is an enzyme that splits the ester bond to form acetoacetate and free *CoA*. Acetoacetate can either be reduced to form β hydroxybutyrate or decarboxylated to form acetone, thus completing the assortment of the known ketone bodies. In diabetes, where the breakdown of fatty acids is accelerated, there is presumably a large accumulation of acetyl-*CoA* which forms a considerable amount of acetoacetyl-*CoA*. This cannot go toward synthesis as noted above, because in this disease fatty acid synthesis is impaired. Failing that, the excess acetoacetyl-*CoA* is then deacylated to yield excess free β keto acid and subsequently the other ketone bodies which appear in large quantities in blood and urine. These reactions occur and would seem adequate enough to explain such relevant biochemical manifestations of diabetes, nevertheless the process may be more complicated than pictured above.

The esterification of long chain fatty acids not only

activates the molecules to render it available for breakdown and subsequent oxidation to carbon dioxide and water, but also to make it available for neutral fat formation by incorporation into glycerol to form triglycerides. In like manner incorporation into α glycerophosphate forms the diglyceride phosphatidic acid. The latter with the appropriate nitrogen base gives rise to the various phospholipids.

The foregoing has been a simplified introduction to the material discussed in this book. It is mainly aimed at the clinical investigator. A special effort was made to express biochemical events in simple terms with due emphasis on the main overall reactions. For details the reader is referred to the pertinent papers herein. It is hoped that this volume on *fat metabolism*, like its predecessor the volume on *carbohydrate metabolism*, will serve well its function of bringing to the clinical investigator the pertinent newer aspects of biochemistry and to the biochemist the clinical problems that have long furnished the stimulus to fundamental research.

2. Obesity in Childhood— Some Clinical Aspects

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IN A CLINICAL summary of customary excellence, Henry B. Richardson (1) writes: ". . . obesity can be regarded as a component of a neurosis, the physical expression of which is the accumulation of fat. By the latter term, I mean the bodily processes which are concerned in the obesity, including the over-all exchange of energy, and the formation, transport, storage, mobilization and oxidation of fat." He then properly poses the question as to whether these physical processes are peculiar for the obese person as compared to the person of normal nutrition. The papers to be presented in this symposium contain discussions of various facets of fat metabolism some of which may have bearing on the clinical problem.

The decision to bring the subject of obesity before you was taken by Dr. Najjar with some hesitancy. Some of his doubts must have stemmed from these considerations: (a) the concept of an endocrine etiology of obesity had been entombed with more difficulty for children than for adults, partly because obesity in childhood is frequently associated with puberty and its endocrine adjustments (2), partly because interpretation of the basal metabolic rates in obese children had been confused by choice of unsatisfactory standards of reference (3), (b) interpretable differences, in

laboratory observations such as glucose tolerance, serum cholesterol, specific dynamic action as well as basal metabolism have not been demonstrated (4) possibly because of lack of studies made in the dynamic or progressive (5) rather than static phases of the syndrome. When one adds our usually fruitless therapeutic results to this essentially " negative result " metabolic literature, pediatricians are left facing their patients in a position of discomfort, one to which we are not accustomed either by temperament or experience. In spite of these intellectual and emotional considerations, the frequency of the syndrome and its continuing knottiness make it appear worthy of discussion.

It is my purpose to consider with you some clinical aspects of obesity as seen in general pediatric hospital practice, and in the pediatric endocrine and metabolism clinic of the New York Hospital where, at least during the period from 1932 to 1942, it represented the most common single cause of referral. I will not discuss some of the rarer forms such as obesity associated with:

(1) adrenocortical tumors (6)
(2) injury to the brain, e. g. encephalitis (7)
(3) a heredo-familial degenerative syndrome which may include retinitis pigmentosa, mental retardation, polydactyly and hypogenitalism (8).

In early infancy obesity develops usually without too much concern on the part of either the parents or the physician. Lack of worry stems from the recognition that good appetite and good weight are valid signs of health in babies. The hitch comes in changing opinions of what constitutes good. The earlier introduction of solids into the diets of young infants, the greater reliance on their ability to regulate the intake of artificially prepared and concentrated feeding mixtures, lead not infrequently to obesity, particularly when

interpretations of hunger are made by inexperienced or compulsive mothers. Infants who ordinarily would have tripled their birth weights by the age of a year do so by age six months and this with no obviously harmful effects. One may find oneself objecting on grounds that young and skeptical pediatricians refuse to accept. Possible delay in sitting, crawling and walking do not seem important considerations. One cannot easily prove that fat infants are poorer risks when they develop croup or pneumonia or dehydration, and the fact that antibiotics control so many infections makes the house officer less concerned about the infant's obesity than he used to be when it interfered with intravenous therapy. Surgeons still would rather operate on a thin than a fat subject, but this consideration obviously should not be raised with the parents of a well baby. Parents are vicariously thrilled because they interpret the infant's ability to ingest large amounts of solids and fluids as a sign of high intelligence, not only high, but what is more important, as high as or higher than that of a neighbor's or relative's infant. It is true that most obese babies do not remain obese—their appetites and rates of gain slow down for they must remain in the human species. A certain number however remain obese and when brought to the physician later in childhood, the parent's version of early feeding habits—" he has always eaten like a pig "—constitutes quite a shift in attitude. If one has watched newly born infants, some of them premature, make sucking movements even while asleep, one recognizes the existence of early differences in orality or whatever you want to call it, if this term is unacceptable. On the other hand, the early emphasis on overeating as a pattern of gratification may contribute to the type of symptom later manifest in the neurosis of which obesity is the prominent physical sign. Although no proof for this suggestion is at hand, its possibility is suggested by the occa-

sional recurrence of a reflex such as the whooping paroxysm in children who develop bronchitis some months after complete recovery from whooping cough.

It has seemed proper to discuss the problem of obesity with parents even during the first six months of an infant's life, not in terms of actuarial tables, but rather as a basis for inculcating the view that bigger is not better. One tries to cast at least some doubt on the benefits of conforming to mass standards either in eating habits or rates of gain and hopes it will carry over into other areas. This is actually the only basis of approach since the parents rarely complain about the infant's obesity. Pediatricians with particular experience in the field of allergy have learned to take preventive dietary steps for infants with family background of allergy (9); similar steps may be indicated for obese infants with family background of obesity.

We come now to the problem as it is seen in early, or later childhood. Parents may bring their son to the physician because they have noted that he cannot keep up with his playmates in physical activities, or because obesity makes his genitalia, which are within normal prepubertal limits, appear abnormally small. Daughters are brought by thin or fat mothers because of concern about social implications. Not infrequently obesity is found on physical examination of a child brought for some minor illness; as one takes a complete history one turns up a background in which the need for help is real, but made more complex by the fact that it is unfelt. The circumstances of development of the obesity are varied. As already stated, in many children it has been continuously present since early infancy; in some the patient was obese during the first year, thinned out for a variable period during pre-school years and then began to gain weight rapidly, occasionally after a trying experience. This is frequently a hospitalization, and the most common

single cause of the latter is tonsillectomy. A child whose appetite has been poor because of chronic tonsillar infection has his tonsils removed. On return to his home he reacts to the experience with anxiety which depends on his emotional status (10) and on the success of attempts to "humanize" the hospital experience (11). This anxiety may take the form of night terrors, resumption of bed wetting, orneriness or polyphagia. To parents who have for some time been worried by their child's anorexia, the increased food intake and weight gain are most welcome. But the child who previously had in some way regulated his food intake to permit moderately acceptable increments of gain in height and weight now keeps on eating to become roly-poly, with secondary psychological and physical problems which stem from his overweight. In some children, hospitalization may require prolonged confinement, and diminished activity contributes to the positive energy balance. In others the onset of rapid weight gain is at age ten or twelve or fourteen and one sees the normally increased food intake of the adolescent converted into big spurts in height and weight, with the spurt in the latter sometimes so large as to change the subject into an obese boy or girl.

Now how does one treat these patients? Acceptance of the applicability of the law of conservation of energy (12), and of the importance of economic, cultural and psychologic factors (13) in overeating are necessary first steps in our attempts to understand these patients. Conversion of these concepts into therapeutic successes has not been easy, witness the fact that I can remember successes in detail because they have been so few in number. The histories of two recent patients illustrate some of the complexities.

The first patient, an eleven-year-old boy, was brought to the pediatric out-patient department of Sinai Hospital for evaluation of a possible cerebral birth injury. He had origi-