PATHOPHYSIOLOGY OF OBESITY

A. W. PENNINGTON, M. D., Wilmington, Del.

THE WIDELY prevailing opinion that energy exchange studies have proved the absence of any metabolic defect in obesity has, for many years, relegated biochemical details of this condition to a position of minor importance. Analysis of energy exchange studies has proved the absence of any metabolic defect in obesity has, for many years, relegated biochemical details of this condition to a position of minor importance. Analysis of energy exchange experiments on the basis of their evidence for or against a passive dependence of the adipose deposits on the caloric balance, however, indicates that many cases of obesity must be attributed to a metabolic defect involving the storage of body fat. Details of fat metabolism, therefore, can no longer be considered inconsequential. Instead, it appears that they form the necessary basis for an understanding of the pathogenesis of obesity and its rational treatment.

The Newer Knowledge of Fat Metabolism

Studies of fat metabolism during the past two decades have necessitated a startling revision of older concepts concerning the role played by fat in the body economy. Older concepts characterized the adipose deposits as a lifeless mass, accumulating from the residue of the food intake after energy needs have been met, and remaining functionally segregated from the metabolic activities of the body until called on in time of necessity. Carbohydrate was assigned a supreme position as the supplier of energy for ordinary metabolic needs, the liver being thought in some miraculous way capable of storing enough glycogen for most of the energy needs between meals. It was believed that fat could be burned in moderate amounts if assisted by the simultaneous oxidation of carbohydrate but that if care was not taken, the precarious ability of the body to burn fat would give rise to harmful products of incomplete combustion.

If some of these ideas are still current it may very well be the result of indifference concerning biochemical details that oversimplified concepts of the energy metabolism have fostered; with body weight as the criterion of the adequacy of the energy supply to the organism, the intermediate steps between caloric intake and outgo have probably seemed to matter very little.

It has been found that the adipose tissues constitute an essential functional link in the regular, daily metabolic activities of the body. They act as an energy buffer: much of the food of all types taken at meals is rapidly converted to fat and deposited in them, and deposit fat is gradually released for energy between meals. The fat released, furthermore, is not converted to carbohydrate before it is utilized. It is burned readily by the general tissues and by the liver, without the necessity for any simultaneous oxidation of carbohydrate. The liver manufactures ketones as part of the normal process of fat breakdown, and the general tissues readily oxidize these for energy. Ten times as much of the carbohydrate ordinarily eaten may be converted to fat as is synthesized to glycogen; and in the post-absorptive state fat furnishes the body with 60 per cent of its energy requirements. Carbohydrate, far from occupying a supreme position, serves largely as a precursor of the fat that is needed by the body for its ordinary metabolic needs from day to day.

These details concerning the metabolism of fat have a definite bearing on the problem of obesity, for they are all intimately involved in the physiology of fat storage. Since body fat is not converted to carbohydrate, it is clear that once fat has been introduced into the body or has been formed from ingested carbohydrate or protein, it must be accounted for, almost entirely, by fat storage and fat oxidation. The storage of fat in the body must, therefore, amount quanti-
tatively to the difference between fat available from food and fat oxidized. The essential relationships can be expressed in the following equation:

\[ \text{fat available} = \text{fat storage} + \text{fat utilized}. \]

In this equation fat storage may be positive or negative, or may be zero. The three terms of the equation represent the rates, equated to calories per unit of time, of the processes involved. If the body were as simple as a storage tank there would be little left to consider in connection with the matter; but the body is endowed with physiological mechanisms that exert regulatory control over each of the three processes: fat available, fat storage and fat utilized.

**Physiological Regulations**

The fat available from the diet depends, first of all, on the caloric intake, which is ordinarily adjusted to the energy needs through the mechanisms of appetite (17). Fat can be eliminated from the diet, but since fat is formed from the other foodstuffs ingested (12) fat is made available to the organism as long as any kind of food is taken.

The storage of fat in the body was formerly considered a purely passive matter of balance between fat available from food ingested and fat utilized. Knowing that the blood lipid level tends to remain constant, it seemed that an easily reversible reaction in the adipose tissues must cause fat to be deposited or mobilized, depending on a high or low blood lipid level (13). While fat storage is undoubtedly influenced in this way it is, however, regulated by active physiological mechanisms. Wertheimer has shown that active neutral and hormonal mechanisms adjust the rates at which fat is deposited in the adipose tissues and mobilized from them (3). Two sets of opposing forces form a dynamic equilibrium that appears to strike a balance at a particular level of body weight, causing the organism to resist change from an established weight level and operating to restore the level when it has been changed by unusual circumstances. These forces, through their control over fat storage, exert a powerful and, at times, a dominating influence on the balance between the caloric intake and output of the individual. Thus, the body tends to conserve energy during caloric restriction and it restores its reserves through the establishment of a positive caloric balance after weight has been lost through severe illness or starvation (11).

The utilization of fat, ordinarily, appears to be chiefly by oxidation of fatty acids, but some ketones are continually formed in the liver and oxidized by the general tissues (5). The rates at which the body oxidizes fatty acids (14) and ketones (15) are influenced by the concentrations of these substances in the blood, just as the rate at which the body oxidizes glucose is influenced by the blood glucose level (16). The extent to which the body depends on fat or carbohydrate for energy is influenced by the relative proportions of these substances in the diet (17), but considerable fat is utilized, regardless of the constituents of the diet, for if it is not supplied as food the body manufactures it from carbohydrate and protein.

The physiological mechanisms that regulate the energy balance and those that regulate energy storage are integrated in such a way that, ordinarily, the caloric intake is adjusted to the caloric output at an established level of body weight. Each of the two sets of mechanisms influences the other and also displays a certain degree of flexibility, so that either the caloric balance or the level of storage can be altered in the service of the body economy as a whole. A third set of mechanisms is also integrated with these two. It makes possible an adjustment of the organism to deal with diets in which either carbohydrate or fat is predominant.

**Adjustments to Carbohydrate and Fat Diets**

If much carbohydrate is eaten, the pancreas is stimulated to secrete insulin (18); this furthers the conversion of carbohydrate to fat and the deposition of fat in the adipose tissues (19). If much fat is eaten, the anterior pituitary is stimulated to secrete its ketogenic principle (20). This acts on the liver (21), furthering the breakdown of fat to ketones; and the resulting ketonemia is followed by mobilization of fat from adipose deposits (22). The adrenal cortex appears to cooperate with the pituitary, for it inhibits the formation of new fat (23). The hormonal responses to the ingestion of foodstuffs appear to balance the effects on fat storage of the markedly different blood lipid levels that follow the ingestion of carbohydrate or fat predominantly. On either type of diet an appropriate amount of fat is stored.

Oxidation of carbohydrate and fat, though subject to the concentrations of these substances in the blood, is also subject to hormonal influences similar to those affecting fat storage (24). In addition, they are profoundly affected by certain intermediary products that are formed during the breakdown of the foodstuffs themselves. Wertheimer has called these substances “metabolic regulators” (25). One of them, which appears to have particular importance in connection with obesity, is pyruvic acid.

Pyruvic acid is the product of the first, or glycolytic, phase of carbohydrate breakdown in the tissues of the body; when carbohydrate is oxidized it is actually the pyruvic acid that is oxidized, for pyruvic acid must first be formed. Lactic acid has received much attention in the past, but this is merely a hydrogenated form of pyruvic acid that can only be reconverted to pyruvic acid. When much carbohydrate is eaten much pyruvic acid is formed. The general tissues proceed to oxidize this, but an unoxidized residue remains, and some of this diffuses out of the cells into the blood in the form of both lactic and pyruvic acids. These are carried to the liver (26, 27). Pyruvic acid appears to be a powerful metabolic regulator. It inhibits the conversion of fatty acids to ketones in the liver (28), so that if much carbohydrate is eaten very little fat is burned in the form of ketones. This limits the total amount of energy that the body can derive from fat (5). On the other hand, if fat is predominant in the diet and carbohydrate is greatly limited, little pyruvic acid is formed. The liver then forms ketones abundantly; these are readily oxidized by the general tissues, increasing greatly the amount of energy that the body obtains from fat (5).

It can be seen that the body is abundantly supplied with regulatory mechanisms that adjust the organism to varying conditions of diet. As a consequence, most people are able to operate on either a "carbohydrate
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There appears reason to believe that a common cause of obesity is an impaired ability of the tissues to oxidize pyruvic acid. The evidence for this consists in experimental work indicating that pyruvic acid tends to accumulate excessively in the tissues of the obese.

The tissues normally are unable to oxidize all of the pyruvic acid that is formed in them from the first phase of carbohydrate breakdown (26, 27). In certain physiological circumstances such as in strenuous physical exercise, a factor limiting the oxidation of pyruvic acid is the supply of oxygen. Some of the pyruvic acid formed in the tissues then diffuses into the blood and is carried to the liver, where it is synthesized to glycogen or fat. Much of the pyruvic acid is first reduced to lactic acid, and it diffuses into the blood in this less toxic form. The blood levels of pyruvic and lactic acids both reflect the degree to which the tissues fail to oxidize the pyruvic acid formed in them from the first phase of carbohydrate breakdown. The failure to oxidize pyruvic acid can be due either to lack of oxygen or to the limitations of the tissue enzyme systems.

Evidence for an excessive accumulation of pyruvic acid in the tissues of the obese is derived chiefly from determinations of the blood lactic acid. Lichtwitz found that light muscular exercise caused an abnormal increase in the blood lactic acid of the obese, and this was confirmed by Kugelmann (29). Prodger and Dennig obtained the same results in experiments that took into account the greater energy expenditure of the obese on a given task (30). They also determined arteriovenous oxygen differences and ruled out any circulatory insufficiency that would diminish the supply of oxygen. They reported, "The high lactic acid values which we obtained, therefore, may be considered as due to disturbed intermediary metabolism, with no relationship to circulatory insufficiency." Mayer has found an excessive accumulation of pyruvic acid in the hereditary obesity of mice (32). Horwitt has found that in human diabetes the blood level of pyruvic acid is abnormally elevated after mild muscular exercise (32); and, since insulin does not prevent the rise in pyruvic acid, this finding suggests that the often suspected common denominator between obesity and diabetes is an impaired oxidation of pyruvic acid, which precedes the development of diabetes and leads only to obesity as long as the production of insulin by the pancreas remains sufficient. It seems to have become well established that a major action of insulin is to facilitate the conversion of carbohydrate to fat (10).

An abnormally increased concentration of pyruvic acid checks not only the conversion of fatty acids to ketones in the liver, but also the oxidation of fatty acids in the general tissues (14) and the oxidation of acetate (33), a late product in the breakdown of fat. Block and Kramer found that, in the concentrations they used, pyruvic acid not only inhibited the oxidation of fat but actually stimulated the formation of fat from smaller elements (34).

Pyruvic acid, a product in the breakdown of carbohydrate, and a metabolic regulator, is also an intermediary substance in the conversion of carbohydrate to fat (35). It would seem that the person who becomes obese has, first, an impairment in the capacity of the enzyme systems for oxidizing pyruvic acid. Much of the carbohydrate he eats, therefore, instead of proceeding to complete oxidation, is converted to fat. From the equation,

fat available = fat storage + fat utilization,

it can be seen that an abnormal proportion of the food-stuffs ingested would be diverted to storage as excess fat instead of being oxidized for energy. The appetite, then, regulated as it is to supply the energy needs of the body, would dictate the intake of an increased amount of food to make up for the amount diverted to storage. Thus, excessive fat storage, or obesity, would be the cause of an increased appetite, rather than the result of it.

The supply of sufficient energy to the organism appears, with good reason, to be a primary biological task for which mechanisms of regulation and adjustment are abundantly provided. The intake of energy is assured by the forces that adjust the appetite to the energy needs, and steadiness in the supply of energy to the organism is made possible by the forces that regulate energy storage. In the obese these two sets of mechanisms appear to be intact; but the third set of mechanisms, which adjusts the metabolism to deal with a predominantly fat or carbohydrate type of diet, appears to have become impaired, with the result that the task of securing sufficient energy from a predominantly carbohydrate diet can be accomplished only at the expense of an abnormal increase in the storage of body fat. The development of the obese state, in fact, appears to be an adjustment of the handicapped organism, making possible a sufficient energy supply on a highly carbohydrate type of diet. This adjustment appears to progress until the excessive size of the fat deposits, through the development of forces that they bring to bear upon the biochemical equilibria, achieve compensation by making possible the utilization of more fat for energy (36). The individual, then, maintains constant though excessive weight.

The oxidation of pyruvic acid in the tissues proceeds through a number of steps, by way of an intricate enzyme system. The details of this, as they become more fully known will, it seems, make possible the isolation of the precise point at which the metabolic fault in obesity occurs. According to a recent review by Slater (37), there are several metabolic steps, involving 2-carbon molecules, that must be traversed before pyruvic acid is converted to acetyl coenzyme A, which enters...
the tricarboxylic acid cycle for the final oxidation to carbon dioxide. The essential metabolic fault in obesity would seem to involve, not the first, but a succeeding one of these steps. This would be compatible with Mayer's findings in obese mice (31). Two-carbon elements would pile up in the tissues causing, in turn, a piling up of pyruvic acid with its inhibiting effect on the oxidation of fat and acetate.

The Cause of Obesity

An impaired oxidation of pyruvic acid can arise from a number of causes. Many genetic studies indicate that obesity is often inherited (38); and these studies have been attacked with only the weakest of logical weapons. Davenport concluded from his studies that an inherited metabolic defect in obesity would often not reveal itself till age 20 or later (30). An inherited weakness of the enzyme systems might, therefore, be a cause. It might even be inferred that the human race, which subsisted for thousands of years on a diet consisting predominantly of protein and fat (40), has not completely adjusted itself to a diet containing considerable amounts of carbohydrate.

It seems possible that toxic influences can cause obesity by interfering with the enzymatic oxidation of pyruvic acid. It is of interest that arsenic, formerly used to build up the weight of undernourished individuals, has as one of its primary actions a blocking of the oxidative pathway of pyruvic acid (41). Any substance that can combine with a sulfhydryl group can inhibit the oxidation of pyruvic acid (42). This appears to include gold and other metals (41). In the days when it was customary to give series of treatments with mercury, it was known that obesity often ensued (43). Another possibility is that a low protein or even a low calorie diet, by failing to support the tissue enzyme systems, can cause impairment in them: semi-starvation has been followed by excessive weight gain in the period of rehabilitation (44). Another possibility is suggested by the finding that lipoic acid, which has been isolated from the liver, is involved in the breakdown of pyruvic acid (37); it is not known, however, just how it participates or if it is insufficient in obesity. Studies by Kriss and Smith indicate that excess salt may impair the oxidation of carbohydrate (45) to a degree that reduces the caloric expenditure of the body (46). Dehydration of the tissues, from an insufficient drinking of water, also reduces the caloric expenditure (47). Lack of physical exercise has usually been implicated in obesity on the basis of the reduced number of calories expended, but it seems possible that lack of exercise might also cause, in some cases, an alteration in the intermediary metabolism, especially at some particularly vulnerable step. There is much in connection with the oxidation of pyruvic acid that remains for future investigation. Evidence that alcohol checks carbohydrate oxidation in the liver seems to give this substance a more important role in the development of obesity than that usually assigned on the basis of its caloric content (48).

Physiological Principles of Treatment

Treatment of obesity, for many years, has been simple in theory but difficult in practice. It has been believed that caloric restriction causes the body to "draw on" its fat deposits in amounts sufficient to maintain a normal energy supply to the organism. Difficulties arising from hunger, weakness and mental depression, have been given psychiatric explanations. Analysis of energy balance studies (1) however, indicates that while theory has triumphed the patient has starved.

Part of the difficulty encountered with low caloric diets arises from the fact that while fat is being mobilized from the adipose deposits new fat is, at the same time, being formed and deposited in them; and it appears that as the weight falls below its customary level there is an increase in the rate at which new fat is formed from carbohydrate (49). The rationale on which current treatment of obesity is based has maintained an exquisite simplicity, it seems, by regarding the powerful physiological mechanisms that regulate and adjust the organism to varying conditions. As a result, the law of conservation of energy has been applied to storage-tank concepts of physiology and has even been raised as a warning banner against further thought or investigation.

If, as there seems ground for believing, obesity develops as an adjustment that enables an impaired organism to obtain the energy it needs on a highly carbohydrate type of diet, little can be gained by opposing the physiological forces that have brought this adjustment about. Instead, it seems that efforts should be directed toward overcoming the impairment. Lacking any specific means of restoring the ability of the tissues to oxidize pyruvic acid it seems reasonable, first of all, to avoid circumstances that may impair further the enzyme systems involved. This would mean the avoidance of food from which it is difficult to remove the arsenic used in spraying, the avoidance of salt, the avoidance of alcohol, and the avoidance of either a low protein or a low calorie diet.

The chief means available in treating obesity seems to be provided by the ability of the body to operate on a "fat economy" when its ability to operate on a "carbohydrate economy" is impaired. This appears to make possible the regulation of weight to normal on a calorically unrestricted intake of protein and fat, provided carbohydrate is sufficiently limited. Carbohydrate must be limited to a degree that will remove the inhibiting influence of pyruvic acid on ketogenesis, so that sufficient fat can be utilized for energy. The possibility of weight reduction on a calorically unrestricted diet seems to depend entirely on securing a sufficient utilization of fat; this can be aided, also, by exercise in the post-absorptive state (5).

Application of these principles appears to provide a method of treatment that makes use of the still-intact physiological mechanisms that regulate fat storage and the caloric balance. By making use of these mechanisms, instead of opposing them as is done in treatment by caloric restriction, it appears possible to treat obesity effectively without detriment to the energy supply of the organism (50).

Summary

The human body appears to be endowed with physiological mechanisms that regulate fat storage and the caloric balance. By making use of these mechanisms, instead of opposing them as is done in treatment by caloric restriction, it appears possible to treat obesity effectively without detriment to the energy supply of the organism (50).

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the third is impaired. Obesity appears to develop as an adjustment of the impaired organism, making possible a sufficient energy supply on a high carbohydrate diet. The metabolic defect appears to involve the oxidative pathway of pyruvic acid. Limitation of dietary carbohydrate, specifically, as the chief source of pyruvic acid, makes possible a treatment of obesity without restriction of the total caloric intake.

REFERENCES