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Etiology of adult obesity

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THE ETIOLOGY OF ADULT OBESITY

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INTRODUCTION

It is the purpose of this paper to discuss the etiology of adult obesity. No attempt will be made to include childhood forms of obesity, as these are worthy of separate discussion, and time and space do no so permit.

It will become evident in the course of this presentation that no single factor is the cause for all cases of adult obesity. True, the energy balance must be positive for a person to gain weight, but it is the author's opinion that other, often less apparent, factors so modify this balance as to make it secondary.

In brief, the opinions extant as to the cause of obesity are these: that it is purely exogenous; that it is endogenous; and that it is heredity. Few workers, it seems, have tried to "strike a happy medium" between all these views. The author feels that this basic interrelationship exists, and that it can be expressed as follows: obesity is primarily hereditary, being transmitted as a mendelian characteristic; and these transmissible characters, acting secondarily upon both exogenous and endogenous factors, account for most cases of obesity. Admittedly, such a proposition does not encompass all cases of adiposity, no more than does

any other generalization which has dependence upon a human factor. When dealing with individuals one must, of necessity, be individualistic. One would not hold that all glycosuria is diabetes, nor that all albuminuria is Bright's disease. The same argument is true as regards the above-described cause for obesity. The author does not maintain that it is the underlying cause for all obesity, but he does maintain that it is the cause for most obesity.

As the discussion progressed, it became increasingly clear to the author that considerable overlap existed between the several main headings, so that it became a purely arbitrary matter to decide where to place certain topics. The reader is asked to keep this point in mind, and to bear with the author's attempts at subject separation.

METABOLISM

THE CHEMISTRY AND NORMAL METABOLISM OF FATS

1. CHEMISTRY OF FATS.

The following classification of fats, or "lipids" as they now are rather generally called, has been advanced by Bloor (7);

Lipids. Substances having the following characteristics:

a. Insolubility in water and solubility in the fat solvents, such as ether, chloroform, benzene.

b. Relationship to the fatty acids as esters, either actual or potential.

c. Utilization by living organisms.

Simple lipids. Esters of the fatty acids with various alcohols.

1. Fats--esters of the fatty acids with glycerol.

2. Waxes--esters of the fatty acids with alcohols other than glycerol.

Compound lipids. Esters of the fatty acids containing groups in addition to an alcohol and fatty acid.

1. Phospholipids--substituted fats containing phosphoric acid and nitrogen: lecithin, cephalin, sphingomyelin.

2. Glycolipids--compounds of the fatty acids with a carbohydrate and containing nitrogen but no phosphoric acid: phrenosim, kerasin. These are also called cere-

brosides.

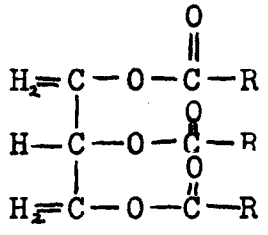
3. Aminolipids, sulfolipids, etc.--groups which are at present not sufficiently well characterized for classification.

Derived Lipids. Substances derived from the above groups by hydrolysis.

1. Fatty acids of various series.

2. Sterols--mostly alcohols of high molecular weight, found in nature combined with fatty acids, and soluble in fat solvents: cholesterol ($C_{27}H_{46}OH$), myricyl alcohol ($C_{30}H_{61}OH$), cetyl alcohol ($C_{16}H_{33}OH$), etc.

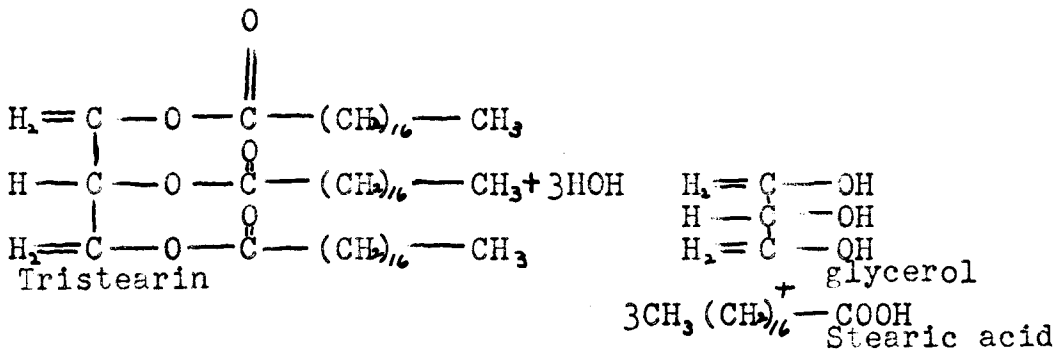
Constitution of the Fat Molecule. The molecular structure of a fat may be represented by the formula:



in which R represents a fatty acid chain.

Fats are hydrolyzed by the action of acids, alkalies, fat-splitting enzymes (lipases), and superheated steam. Three molecules of fatty acid and one of glycerol are formed as a result.

These reactions may be graphically described thus:



2. THE NORMAL METABOLISM OF FATS.

There is no fat-splitting enzyme in the salivary secretion, and there remains some doubt as to the origin of the so-called gastric lipase, one view being that is is secreted with the other enzymes in the stomach, while according to another view it is derived from regurgitated pancreatic and intestinal juice. The hydrogen-ion concentration in the stomach is usually unfavorable both for the emulsification of fat and for the action of lipase, so that the amount of gastric fat digestion is ordinarily slight, being limited to the partial hydrolysis of the highly emulsified fats and the more soluble glycerides of the lower fatty acids, such as are present in egg yolk, butter, and milk. For all practical purposes, then, the fat content of food enters the small intestine relatively unchanged.

Pancreatic lipase (Steapsin). The fat-splitting enzyme of the pancreas, steapsin, is relatively inactive in the form in which it is secreted. However, in the presence of certain substances, such bile, bile

salts, egg albumin, calcium salts, and calcium soaps, the enzyme seems to be activated. This type of activation is obviously non-specific. These activating agents exert their effect on pancreatic lipase by providing a specially favorable adsorption condition for the contact of the water-soluble enzyme with its insoluble substrate, fat. Glick and King (34) obtained a definite correlation between activating effect and the property of reducing surface tension in a study of the activation of lipase by various organic compounds.

Intestinal lipase. Closely associated with the pancreatic juice in the digestive processes that occur in the intestine is the intestinal juice, or succus entericus. It contains the intestinal lipase, which, acting upon its substrate, completes the breakdown of the fat molecules.

No discussion of intestinal digestion would be complete without mention of the important functions of the bile. The bile is a good emulsifying agent; it also promotes the solution of fats, fatty acids, and other lipids, and may exert a direct effect in activating and accelerating lipases. By its power of emulsification, the bile provides a greater surface area upon which the lipase may act. The importance of this action in aiding fat absorption is well illustrated by cases of biliary

duct obstruction in which the well-known steatorrhea needs no emphasis.

Fat absorption. Fat absorption begins in the duodenum but proceeds more rapidly in the jejunum. This process goes on also in the ileum and under normal conditions is practically complete when the terminal ileum is reached (5).

Most of the fat absorbed from the small intestine may be considered to pass through the intestinal wall in the form of fatty acids and glycerol. Since the contents of the duodenum are neutral or acid in reaction, the older view (76) that fat is absorbed as soap no longer is held. The so-called hydrotropic property of bile salts of the phospholipids greatly increases the solubility of the fatty acids in the intestinal fluids (99). The possibility of the passage of unsplit fat across the intestinal wall cannot be overlooked entirely, but as Bloor has pointed out (6), there is every reason to believe a fat is completely hydrolyzed before it passes from the intestine (90).

Absorption of fatty acids is greatly facilitated by the presence of bile. Whereas the higher fatty acids are quite insoluble in water, they readily dissolve in an aqueous solution of bile acids. The property of the bile acids in bringing the otherwise

insoluble fatty acids into solution in water has been described as an example of hydrotropism. The effect seems to be due largely to the formation of bile acid-fatty acid complexes which are characterized by their diffusibility through membranes and by their stability in slightly acid solution. The bile acids, moreover, lower surface tension, as has been described, thereby increasing the permeability of the epithelial cells and in this way probably promote the absorption of other substances as well.

The work of Sinclair (91) suggests that the phospholipids may play an important part in the transfer of fat across the intestinal membrane. He found that the component fatty acids of the phospholipids of the intestinal wall could be changed by feeding different types of fat. These results suggest that the fatty acids of the food displace the fatty acids combined with the phospholipids and pass through the intestinal wall in this form which is of course much more soluble in body fluid than the fatty acids. Just how much of the absorbed fat can pass through this process is at the moment quite undecided. While the leucocytes may also facilitate the passage of fat into the lacteals, the other processes are probably of much greater importance.

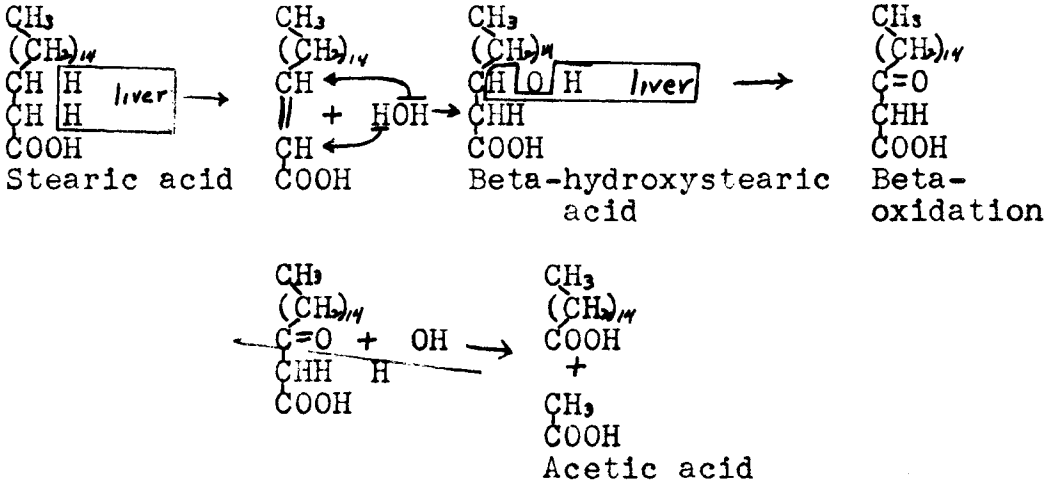
Within the cell, the bile acid-fatty acid complex is dissociated and the fatty acid released (8). Resynthesis of neutral fat occurs immediately and maybe demonstrated histologically. The mode of transportation of fat from the lining cells of the intestine remains somewhat obscure. Only about 60 percent of the absorbed fat can be accounted for in the chyle. D'Errico (22) reported a greater content of portal than jugular vein blood during fat absorption but many subsequent workers did not confirm his findings. However, Cantoni (12) reinvestigated this question, and he presents convincing evidence in support of D'Errico. Eckstein (26) has studied the question of fat absorption through channels other than the left thoracic duct. While his results are admittedly not altogether consistent, they show, nevertheless, that when all the thoracic lymph is diverted from the blood stream, an appreciable, though small, augmentation of the fatty-acid content of the blood follows the absorption of neutral fat from the duodenum. It has been suggested, likewise, that a portion of the fat that is unaccounted for maybe stored somewhere along the path of transport to the blood, or that it may be catabolized in the tissues before reaching the blood (8). In the blood, the fat is

transported as neutral fat, fatty acid, and lecithin, and in the form of cholesterol esters.

The storage of fat may occur in many regions of the body, but especially in the superficial fascia under the skin where it is present as a layer an inch or more in thickness. This layer of fat is called the panniculus adiposus. Large amounts of fat are also deposited around the viscera. It has been shown by Eckstein (27) that, although the fat in the adipose tissue of any given species is normally characteristic of that species, the deposition of a fat foreign to an animal may occur under certain conditions.

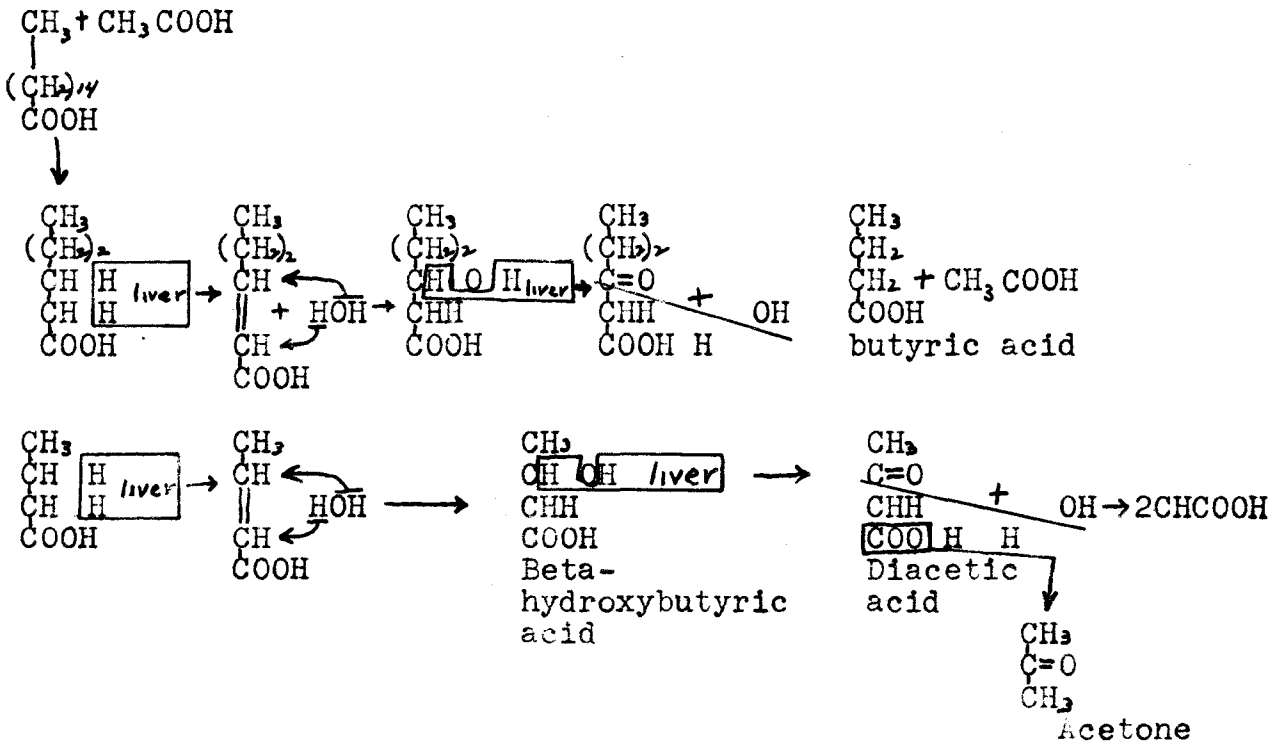
Oxidation of fats. Although very resistant to ordinary chemical oxidizing agents, the fatty acids are broken down completely to carbon dioxide and water in the body with the utmost facility. Although many theories have been advanced, our knowledge of fatty acid oxidation still depends largely on the classical investigations of Knoop (53). On feeding phenylpropionic acid, he found hippuric acid in the urine, showing that two carbon atoms of the side-chain had been removed by oxidation. Phenylbutyric acid yielded phenaceturic acid, and phenylvaleric acid gave rise in the body to benzoic acid, which was in turn converted into hippuric acid and excreted. Knoop (53) therefore concluded that

the oxidation of the fatty acid chain occurs at the beta carbon atom. The exact nature of the chemical reactions which occur are unknown, but it is likely that the liver is concerned (13,43,48,70), and that the following series of reactions (97) may demonstrate what takes place in the body as regards the breakdown of a fatty acid such as stearic acid ($C_{17}H_{35}COOH$):



This demonstrates the formation of acetic acid which is one of the five so-called "ketone" bodies. The other four such bodies are beta-hydroxybutyric acid, butyric acid, diacetic (aceto-acetic) acid, and acetone. Their formation can be shown by a similar series of reactions (97). It can be seen above that the number of carbon atoms of the original fatty acid has been reduced by two, and that from these two carbon atoms acetic acid was formed. We can assume, therefore, that such reactions continue to split off carbon atoms two

at a time, until we reach a six carbon chain. From this point, the reaction can be represented as proceeding as follows:



These reactions, as previously noted, continue in the normal individual until the original fatty acid is completely broken down into carbon dioxide and water. But the aphorism "fat burns in the flame of carbohydrate" is as true as it is picturesque. This is the reason why diabetics, who cannot handle their carbohydrate stores, cannot completely metabolize fats and thus produce ketone bodies, giving rise to ketosis. Anti-ketogenic substances in normal persons are obviously, therefore, carbohydrates, the sugar-forming amino-acids, and

glycerol. In clinical work, it is customary to assume that if the ratio of ketogenic substances to anti-ketogenic substances does not exceed 2, ketone bodies do not accumulate.

Omega-oxidation. There is no doubt of the fact that oxidation of the terminal methyl group of the saturated fatty acids with 8,9,10,11 carbon atoms does occur (90), with the resulting excretion of the corresponding dicarboxylic acids in the urine. It has also been shown (90) that beta-oxidation of the resultant dicarboxylic acids occurs.

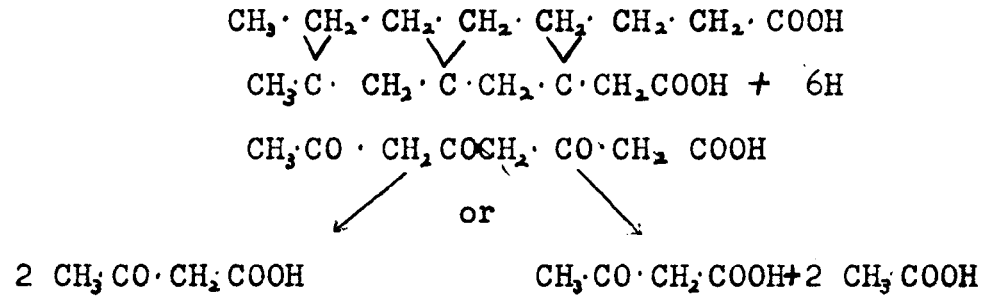
The question remains, however, as to what extent omega-oxidation is to be considered as a major pathway through which the oxidation of all fatty acids proceeds in the body. Some (98) believe that all fatty acids, at least all the saturated fatty acids, may indeed undergo primary omega-oxidation. The reason that dicarboxylic acids are excreted only when C_{8-11} saturated fatty acids are fed is thought to be due to the greater resistance to oxidation of the C_{8-11} dicarboxylic acids than those with longer chains. This interpretation would seem to be borne out by the finding (90) that, when given in equivalent doses to dogs, 45 percent of suberic, 33 percent of sebacic, 17 percent of undecandoic acid, scarcely detectable amounts of brassylic, and no

hexadecandoic acid were excreted in the urine. By omega oxidation of the saturated fatty acids with subsequent two-sided beta-oxidation, succinic acid will result. Since succinic acid can be converted to carbohydrate, it is suggested that this may be the long-disputed key to the question of the conversion of fat to carbohydrate (98). On the other hand, omega-oxidation as a primary pathway leaves no explanation for the formation of ketone bodies. Some (29,30,31) regard omega-oxidation as a special or auxiliary mechanism for the combustion of fatty acids which comes into play only when the carboxyl group is esterified or the beta-carbon is blocked. The free carboxyl group thus formed makes possible a progressive beta-oxidation. Under these circumstances, omega-oxidation certainly does occur (90).

Multiple alternate oxidation. By progressive beta-oxidation of the even-chain saturated fatty acids, it can be seen from the reactions previously described that only one molecule of aceto-acetic (diacetic) acid can be formed from each molecule of fatty acid, regardless of its length. Recent investigations, however, have determined that butyric acid yields less aceto-acetic acid than certain higher fatty acids, such caprylic, capric, and lauric acids.

This result was first obtained by Jowett and Quastel (51) in experiments in which oxidation of the fatty acids was brought about by liver slices, and has been confirmed in metabolic studies on the intact animal (11,23).

To explain the greater production of ketone bodies from acids of 8 or more carbons than from hexanoic and butyric acids, it has been suggested (23,51) that there is a simultaneous oxidation of every alternate carbon atom with subsequent hydration and splitting, not only between the alpha- and beta-carbons to form acetic acid as called for by the theory of beta-oxidation, but also between the gamma and delta-carbons to form two molecules of aceto-acetic acid. This principle of multiple oxidation may be illustrated by the following scheme for n-octanoic acid:



STUDIES ON THE DIGESTION AND ABSORPTION OF FAT IN OBESITY INCLUDING THE NATURE OF FAT DEPOTS

The belief is rather widespread, particularly among the laity but certainly not restricted to them, that obese persons derive more value from the food they eat than do thin persons. That this is not the case was well demonstrated by the work of Neuenschwander-Lemmer (71) who determined the caloric values of the feces and their content of nitrogen and of fat for 3 obese and for 3 control subjects who were of normal weight. The intake of calories purposely was held somewhat below the calculated requirements, and rest in bed was maintained. Under these circumstances the percentage of utilization by the obese persons averaged 87 for calories, 84 for nitrogen, and 83 for fat. The corresponding figures for the controls were 88, 85.5, and 85.5 percent, respectively. The figures for absorption for both groups were somewhat below those obtained by a similar study (103). For normal men these figures were 88.3 to 97.4 percent for calories, 88.3 to 96.2 percent for nitrogen, and 87.3 to 98.3 percent for fat.

There is also some experimental evidence concerning the controling of the mobilization and deposition of fat by hormonal-nervous factors. Coope and Chamber-

lain (18) found that pituitrin causes an accumulation of fat in the liver. Raab (80), experimenting with dogs, came to the conclusion that the hypothalamus contains the fat regulating center. Distruction of the tuber cinereum or severance of the nerve pathways between the hypothalamus and the liver in dogs results in a marked increase in the circulating neutral fat which ordinarily is absorbed and metabolized by the liver. Raab (80) also showed the dependence of the fat-regulating center in the hypothalamus upon a normal supply of pituitrin. The subcutaneous injection of several cubic centimeters of pituitrin caused the complete disappearance of the neutral fat from the blood. One-tenth of the subcutaneous dose of pituitrin if injected into the brain ventricles produced the same effect. If, however, the tuber cinereum is mechanically destroyed or if the nerve pathways between the tuber cinereum and the liver are severed, the injection of pituitrin has no effect upon the reduction of the circulating neutral fat.

Raab (80) concluded that "pituitrin promotes the absorption and destruction of circulating fat by the liver through nervous pathways, starting in the tuber cinereum and running through the cervical spinal cord and the abdominal splanchnic to the liver. Any disturbance of the cooperative pituitary-mesencephalic

system would lead to a retention of excess fat amounts in the body and thus lead to obesity." This experimental work explains, at least in part, the development of obesity in patients having lesions associated with decrease in function or hypofunctional disorders of the posterior pituitary.

Wertheimer (102) found that the accumulation of fat in the liver observed in phloridzin poisoning does not occur if the spinal cord is severed above the seventh dorsal segment; he also found that insulin inhibits the formation of fat liver in phloridzin poisoning, and promotes the disappearance of fat from an already fatty phloridzin-liver. Rony and Ching (83) have shown that the passage of ingested fat from the blood into the tissues is greatly promoted both by insulin and by administration of carbohydrates, and conclude that the fat transport depends on the state of carbohydrate metabolism going on in the tissues, especially in the liver.

These general observations indicate that a delicate and sensitive mechanism regulating the fat content of the body must be working in normal persons, that this mechanism is capable of automatically controlling the impulses for caloric intake and the factors of the caloric output, and that the operation of this

regulating mechanism is governed by the existing fat content of the body-----a mechanism that might be compared to the body heat or water volume mechanism. In the healthy person this body fat controlling mechanism automatically tends to maintain a normal weight. The normal fat content of the body represents the zero point, the normal level, or threshold of the mechanism controlling fat deposition. Factors disturbing fat deposition set the regulatory mechanism to work, resulting in change of appetite or in muscular activity--and possibly other factors concerned with the caloric intake and output--and these changes will restore the normal fat content if not interfered with. This mechanism is probably set at a certain level genetically (hereditary obesity or leanness or normal weight), which may influence or change hormonal (endocrine obesity or leanness), nervous (lipodystrophia, Dercum's disease, etc.), or exogenous factors.

In obesity the level of the fat content regulating mechanism is abnormally high. The operation of the regulatory mechanism in obesity is no less efficient than in normal persons; it is adjusted only at a different level. Incidental or artificial changes brought to bear on the mechanism on obesity will call forth just as efficient operation of the mechanism as

occurs in normal persons, so that it is as difficult to permanently influence the body weight of the obese subject as it is the body weight of the normal subject.(82)

Lipomas are notably resistanc to removal of their fat content, and will remain practically unchanged in size even when the organism as a whole is starving. Long-standing fatty deposits are also more resistant to removal than recent deposits, because, according to Fancher (28), they acquire a lessened blood supply and become more or less walled off by connective tissue.

McCallum (63) has described the changes in the tissues in obesity. There is deposition of fat in the subcutaneous and intramuscular tissues, mesentery, omentum, retroperitoneal tissue, bone marrow, epicardium, kidney, and orbit. In very fat persons it infiltrates the heart muscle and appears underneath the endocardium. That there is an independent, local, predestined tissue disposition to obesity is proved by those cases (1) recorded where an autogenous tissue transplant from the abdominal wall to the back of the hand had been made. It is known that the back of the hand rarely becomes fat, yet in these cases a distinct, local, unilateral obesity occured at the site of the transplant. This indicates that the transplanted abdominal wall, separated from its previous nerve and blood supply,

retained its lipophilia, that is, its irrestible tendency to accumulate fat. Hetenyi (46) advanced the following evidence in support of the theory that tissues of obses persons possess an increased lipophilia, to wit:

Eighteen persons, 10 of them normal in weight and the others obese, were placed for eight days on a subnutrition diet consisting of 800 Gm. of milk and ten crackers. The lipid level of the blood of the subjects of normal weight was unchanged in general, whereas that of the obese subjects fell 18 to 43 percent. Also, 30 subjects, 13 of them obese and the others normal in weight, were given in the morning, without other food, 200 Gm. of cream, representing approximately 60 Gm. of fat. For the obese subjects the lipid level of the blood, determined after two, three, four, and five hours, increased significantly less than did that for the subjects of normal weight. Also, artificial fever was produced in 12 subjects, 5 of them normal and 7 obese. The content of fat in the blood was increased thereby 15 to 36 percent for the normal subjects and up to 11 percent for the obese subjects. Fihally, 50 c.c. of olive oil was injected subcutaneously into each of 11 subjects, 6 of them obese, and the level of blood lipid was determined at the second, fourth, and sixth hours. It increased at one time or another 10 to 48

percent for the normal subjects and only 1 to 8 percent for the obese. Among the patients who were given injections of oil were 2 with lipodystrophy. When the oil was injected into an upper extremity in these cases absorption proceeded as in the normal subjects; when it was given into a fatty lower extremity the absorption was similar to that in the obese subjects.

These observations seem to indicate that mobilization of fat from fat depots is resisted in obesity and that deposition is accelerated. Such a tendency in the obese would account for their delayed sense of satiation following meals, and for their desire to consume carbohydrates in large amounts. According to Wilder and Wilbur (103), this theory also will explain the unequal distribution of fat and the undoubted influence on this distribution of the endocrinopathies, thus harmonizing the point of view of those who have insisted on the primacy of the dynamic features of the problem with the point of view of those who stress its endocrinologic and constitutional features.

It is well-known that, under natural conditions, the depot fat of an animal is characteristic for the species. Certain inherent factors must exist which govern the nature of the depot fat (90). What these factors are, and especially how they operate, are still

quite vague but the following would seem to be involved:

(a) The position in the scale of evolution (47)

(b) Environmental conditions. These would include temperature and possibly salinity or at least marine conditions (58).

(c) Diet. It is a time-honored fact that the feeding of distinctive fats results in the deposition of large amounts of these food fats in the animal stores. However, the extent to which the various ingested fats are deposited is influenced by other factors in addition to their concentration in the food. (92)

(d) Saturation and desaturation of food fat (87). There is evidence that highly unstaurated food fatty acids are saturated to some extent before (or soon after) being stored (59). It must be emphasized, however, that both selective combustion and deposition of certain of the fatty acids in a mixture may account for differences in the composition of stored fat and of that in the food (90).

SUGAR AND FAT TOLERANCE

Rony and Levy (84) observed the response to sugar and fat in obesity. The sugar tolerance of 70 obese persons was examined. Each received 120 Gm. of glucose in 500 c.c. water in the morning on an empty stomach. The blood sugar was determined before and at hourly intervals after the glucose meal for three hours; simultaneously samples of urine were collected and tested for sugar. It was found that 44 of the 70 showed a normal sugar tolerance, 16 exhibited an abnormally low, prediabetic, sugar tolerance, and the remaining 10 showed a definitely high sugar tolerance. The "fat tolerance" of 18 obese and 8 normal weight healthy persons was tested by studying the effect on the blood plasma lipids of the administration of a pint of 20 percent cream. The total fatty acid content was increased in the normal subjects and a fairly uniform curve resulted, a maximum content being reached from three to five hours after the meal of cream. Seven of the obese subjects gave a normal response, 5 showed a high fat tolerance, the fatty acid content of the blood decreasing after the meal, and 6 showed a low fat tolerance, the increase of the fatty acids in the blood being higher than the highest in the normal cases. The subjects showing high fat tolerance had high sugar

tolerance also, and those showing low fat tolerance had low sugar tolerance also. According to these results obesity is not infrequently associated with an abnormally fast removal from the blood of ingested sugar and fat. This phenomenon may also be one of the numerous factors the body fat regulating mechanism employs to promote fat deposition. But that it is not a causal factor is indicated by the fact that in many obese cases the rate of transfer of sugar and fat from the blood into the tissues was found normal and in others even abnormally slow.

Hoffman and Wertheimer (49) showed that there is in the fat cells of the omentum and subcutaneous tissue of experimental animals within two hours after the intake of carbohydrates, an accumulation of up to 6 percent of glycogen which disappears but gradually either by transformation into fat or by release into the circulation in the form of glucose. The storage and gradual release of glycogen in the fat tissue is particularily significant in respect to the alimentary hyperglycemia which is so often met with in the obese and diagnosed as diabetes. In reality, however, it seems to express the inability of the overcrowded fat tissue to fulfill its function as a reservoir of carbohydrates (35).

LUXUSKONSUMPTION

In 1911 and several times thereafter, Grafe and his associates (40) conceived and stated the idea that if the B.M.R. fell during the course of a period of starvation, then conversely the B.M.R. rose during a period of food luxury or, as they called it, "luxuskonsumption." This tendency, if present, would work towards the weight stability which is seen in the normal individual. But, they reasoned, if this rise in B.M.R. associated with increased food intake was not present in certain individuals, they would of necessity tend to gain weight and become obese.

It had already been clearly demonstrated by several investigators (88,108) that the heat production in the basal state falls as much as 30 percent due to prolonged starvation. Much later, F. G. Benedict (3) fed a group of men, who were habitually ingesting 3,200 to 3,600 calories, a diet containing 1,400 calories. After three weeks the average weight of the subjects had declined 12 percent and their basal metabolism had fallen 18 percent. They were now able to maintain this new low weight on 1,950 calories, and the basal metabolism remained low. It is true then that the organism can reduce its rate of oxidation in response to underfeeding and, if the latter is not too extreme, weight

may be maintained after an initial loss. This is clearly an adaptation capable of prolonging the life of the organism in the face of famine. On the other hand, it is not easy to picture any advantage obtainable through the ability to dispose of an over abundance of food rather than store it so that it would be available in time of need. Grafe (40) however tried to prove that the normal mammalian organism did automatically dispose of excessive food through the mechanism of an increased metabolic rate.

Wiley and Newburgh (104) believe that his data do not support his hypothesis, for when the fasting, resting metabolic rate of his dogs obtained during a period of over nutrition is compared with this rate obtained when the dog was apparently normal, no significant increase is found. He obtained an apparent increase by first pushing the rate down by means of a long period of starvation. He thus obtained a metabolic rate 26 percent lower than the normal but, nevertheless, he accepted this value as a proper basis for comparison. The same criticism applies to the study of the patient whose rate was 22 percent below normal when he was emaciated and in whom very marked "luxuskonsumption" permitted the rate to return to the usual level for such an individual in health.

Wiley and Newburgh (104) studied a subject who belonged to the group of persons alleged to be pathologically lean because, accepting the dictum of Grafe, they oxidize all of the food taken into the body without regard to quantity. Their work was carefully carried out in what amounted to a "metabolism cage" in which only one person was observed at a time and in which all factors of food intake and energy output were measurable. The slight increase observed in both the basal and total metabolism on a super-maintainance diet was found to entirely attributable to the increase in surface area plus the extreme specific dynamic effect of the greater diet. It was equally clear that this subject was quite capable of gaining weight when he took food in excess of his habitual desire. A scrutiny of his life brought out the important fact that he had always been indifferent in regard to food and that he had consequently eaten sparingly. However, during a short period of his life he had food set before him which was so attractive that it overcame his usual indifference and he gained a large amouht of weight during this interval. A recognition of the fact that he habitually ate less than the usual amount of food for his group is sufficient reason for his leanness. According to this scientific work, therefore, there is no reason for accepting the attractive theory of luxuskonsumption.

SPECIFIC DYNAMIC ACTION

Plaut (77), Grafe (38), Strouse (94), and Bernhardt (4) claim that the specific dynamic effect of foods is usually abnormally low in obesity. Kestner (52) and the Hamburg school have also emphasized the importance of the specific dynamic action of the food stuffs in the etiology of obesity. Thus they hold that a saving in oxydizable body material results which must lead in time to considerable fat deposition. It is only necessary to point out that in those conditions in which there is an almost complete abolition of the specific dynamic action, as in Simmonds' disease, cachexia, rather than obesity, is the rule. Then, too, these changes noted by Kestner, etc., in obesity may well be the result of the obesity rather than its cause. It is obvious that if there is a tendency to deposit food stuffs rather than to burn them the oxygen consumption and the specific dynamic action will be decreased.

On the other hand, in a large number of normal persons Benedict and Carpenter (2) found the specific dynamic effect as low in several instances as 3 percent, and as high as 33 percent, and Lauter's (55) careful tests on obese persons resulted in the finding that the specific dynamic effect of foods varies just as widely in the obese as in the normal. The question as

to whether the specific dynamic effect of foods is abnormally low in most cases of obesity is therefore not yet settled. Furthermore, even in cases where it is definitely low, the question remains as to its etiologic importance.

EVALUATING THE BASAL METABOLIC RATE

In 1910, von Noorden (95) demonstrated that the heat production per kilogram of body weight was definitely lower in obese than in normal persons. He took this fact to mean that the adiposity was caused by some serious abnormality of the metabolism. However, in so doing, he completely ignored the law of surface area, discovered by Rubner (85), who, with his pupils, showed that the basal metabolism for all mammals is proportional to the area of the surface of the body. It is a simple matter to prove by recalculation of the older data and by means of a series of subsequent observations (74), including the work of Boothby (10), that the basal metabolism of obese persons per square meter of their body surface is also normal.

Today, the concensus of opinion, reenforced by fact, is that the basal metabolism of obese adults is not inherently changed except in the group with hypothyroidism. Of the 21 patients whose basal metabolic rates were determined by Werner and Weir (101), ten patients were between 0 and plus 10 percent, four were between plus 11 and plus 14 percent, and seven were between 0 and minus 10 percent. It can be seen that all were within the standard limits of normal (minus 10 to plus 10 percent) except four who were slightly above

the plus normal.

Rony (82) agrees that the variation of the basal metabolic rate lies between plus and minus 10 percent in the large majority of obese persons. He feels, however, that the ordinary methods of determining the basal metabolic rate do not hold true for the obese. In order to obtain direct information or a comparison between the obese and lean and the normal weight individual the author (82) believes that the 24-hour basal caloric production of obese subjects should be compared with that of normal average weight persons of the same sex, age, and height. When this is done, a marked difference is found, obviously. For example, an obese patient weighing 349 pounds has a total 24-hour basal metabolism of 2,264 calories with a basal metabolic rate of plus 4.5; but if this patient were of normal average weight--129 pounds--the normal total basal metabolism would be only 1,405 calories. The extra weight with increase in body surface has caused an increase in total metabolism of 859 calories, or an increase amounting to plus 61.5 percent. Rony (82) suggests that the percent increase or decrease in the 24-hour basal metabolism of an obese or lean subject over or under that which would be presumably manifested if the subject were of normal weight be called the basal

metabolic ratio.

The metabolic ratios of 50 unselected cases of obesity were observed by Rony (82). It was noted that the metabolic ratios varyed widely, however, from plus 3 percent to plus 111 percent, the average increase for 100 pounds over weight being plus 30 percent. This compares well with Lauter's (55) data obtained by a similar calculation.

Regarding the question of why obese persons have a higher basal metabolism relatively, the following considerations are suggested. Some part of the excess basal metabolism of the obese may be accounted for as the metabolism in the excess of fat tissue; but this part can account for but a fraction of the basal metabolic ratio. Also, if we consider an obese person as composed of excess fat tissue and basic tissues, and if the fat tissue augments the basal metabolic ratio but little, then we must conclude that the larger portion of the excess metabolism originates from the basic tissues as an actual increase in their normal metabolic activity. All or only some parts of the basic tissue mass may be involved. Thus the work of the heart is evidently increased in the obese, even at complete rest. And the respiratory movements of the heavier chest require additional energy production in

the respiratory muscles; furthermore, obese persons are frequently dyspneic, which necessitates increased work of the respiratory muscles, even at complete rest, and some may even be orthopneic. This extra activity of the heart and the respiratory muscles can easily account for from five to ten percent in the basal metabolic ratio of the obese.

In other cases the high basal metabolic ratio may be due to increased metabolism in all of the protoplasmic structures because of over-activity of the thyroid gland. Obesity and hyperthyroidism are by no means incompatible.

It is a widely held and fairly well supported belief that a low basal metabolic rate is synonymous with hypothyroidism. According to fairly recent research, the thyroid gland is only one of the factors which maintain the basal metabolism at a physiological level. The pituitary gland produces two different factors which, each separately, stimulate oxygen consumption even in the absence of the thyroid gland (Riddle et al(81), O'Donovan and Collip (75)); a third factor, the thyrotropic hormone acts upon metabolism by maintaining the function of the thyroid gland. The inadequate production of calorigenic hormones in pituitary disease accounts for the low basal metabolism

of these patients, even in the absence of all clinical signs of hypothyroidism.

GENERAL DISCUSSION OF OBESITY

Obesity is a disease which has been known to man since time immemorial, but it has not been until the past twenty or thirty years that a proper realization of the importance of the disease has been reached. The meaning of the word itself, which first appeared in the English language in the early seventeenth century, is not without interest. It takes its origin from the word "obesus", which is the past participle of the Latin word "obedere". The meaning of "obesus" passed through several stages in Roman times and signified, in turn, "that which has eaten itself away," "that which has eaten itself fat," and finally it was occasionally used to indicate fatness, laziness, or slothfulness. It can be deduced that overeating, fatness, and laziness have been associated together from Roman times. The word obesity was rarely used in any writings before the nineteenth century. During the present century, however, the public have taken the keenest interest in the subject and this has helped to stimulate the medical profession to give the disease the most careful consideration.

Christie (14) has stated that as far as he knows, the first man to teach the world that obesity is a curable affliction lived in Paddington, England. His name

was Banting, and he was employed by St. Mary's Hospital as an undertaker. So little was obesity considered a medical disease in those days that this undertaker took it on himself to address to the people "an open letter on corpulence", in which he extoled the method by which he himself had lost "2.5 stone", and had been converted, from a man who could not tie his own shoes or walk down the stairs other than backwards, into a comfortable, elderly gentleman.

The body weight of obese persons is usually considerably above the normal average but overweight is neither a necessary nor a pathognomonic characteristic in obesity. There are obese persons who are not overweight, and there are overweight persons who are not obese. The first group might be called "masked obesity" and comprise persons who maintain a normal or slightly over-normal weight by artificial means, that is, by living on a restricted diet and forced exercise, resisting constantly their natural eating and exercising impulses. These persons, in spite of their normal weight must be classified as masked or larvaceous obesity for the same reason as diabetics who have no glycosuria on a low carbohydrate diet are classified as diabetics. As soon as the voluntary or artificial restrictions as to diet and exercise are re-

moved these normal weight obese persons immediately gain weight, thereby demonstrating the presence of the anomaly. The second group might be referred to as "pseudo-obesity" and comprises persons who have become overweight because of forced overeating and limited exercise. That they are normal persons is manifested by the fact that as soon as they live again according to their instinctive habits they lose their excess weight in a short time. These persons may manifest all the clinical symptoms of obesity, but, from the pathologic point of view must be distinguished from essential obesity. To classify such normal persons in the stage of overweight as obese, would be as incorrect as to classify the polyuria of the beer drinker as diabetes insipidus, or the high temperature caused by a frequency current as fever.

It is a common view that obese persons tend to gain weight. This statement needs an important correction. Even the weight gains of the very obese tend to reach plateau and there remain. When this particular weight is gained by the subject, a phase is entered in which the high body weight is maintained practically automatically. There is a period in which the tendency to gain weight is very marked--Rony (82) refers to this as the dynamic phase of obesity--and there is a period in which there is no tendency to gain weight, which

Rony (82) calls the static phase of obesity. It is frequently observed that obese persons who find themselves unable to prevent further gain at say 180 pounds maintain with ease their body weight at 220 pounds. No tendency to gain is present at this time and at this weight. But if the weight of the person is reduced by diet, etc., the tendency to gain immediately reappears. It seems, then, that the tendency to gain weight is not a characteristic of obesity in general, but only of one of its phases, the dynamic phase (82).

There is no doubt that obese patients will lose weight on a low caloric diet exactly according to the caloric deficit. The peculiar feature of obesity is only that symptoms of caloric underfeeding, e.g., hunger, weakness, dizziness, restlessness, headaches, and insomnia, may appear at a stage when their body fat content is still way above the average normal. Apparently the obese is just as sensitive to reduction in his abnormally high body fat content as the normal is to reduction in his normal body fat content.

DEFINITION OF OBESITY

Obesity is a relative term. Defined (32) as "an excessive accumulation of fat in the body; corpulence; fatness," the vagueness of this definition leads to misunderstanding. Fancher (28) proposes that a better definition might be; "a disproportion of body fat, either local or general, with or without abnormal weight." This definition would embrace not only those cases with unusual fat deposits, but also those persons who, by virtue of rigid adherence to diet, have reduced their body weight to within the standards accepted as normal. Coombs (17) states that it is not an easy matter to give a rigid definition of obesity. He feels that while gross forms of the disease are easily recognized, mild degrees are less readily appreciated.

Indeed it is a matter of some difficulty to acertain the ideal weight of any individual. We are all familiar with the average tables of weight, but there is some considerable difference between the figures given by the various authorities. A woman of 20 who is 65 inches in height should have a weight of 125 pounds according to Wood (106), 127 pounds by the tables given by Lawrence (56), and 129 pounds by the tables of the Metropolitan Life Insurance Company.

A small reserve of fat seems to protect the indi-

vidual against the infectious diseases such as tuberculosis, pneumonia, etc., which are the chief causes of death in the first decades of life. After taking various factors into consideration the Life Extension Institute (106) has issued tables by which the woman mentioned above should have an ideal weight of 134 pounds. Even with the above large variations only the sex, age, and height have been taken into account. No allowance is made for any difference in the size of the bony skeleton from individual to individual, whereas it is a matter of every day experience that two men of the same age and height may vary by 15 pounds in weight and both be perfect specimens. To overcome these difficulties various calculations to give ideal weights have been suggested which are based on several measurements of the body, but the involved nature of the measurements and calculations has limited their use.

In practice the assessment of optium weights, like so many other problems, should really be an individual matter and should rest on the clinical experience of the medical advisor (17). A complete physical examination should be undertaken in which particular attention should be paid to the amount of abdominal and other adipose tissue and also the size of the bony frame. This examination, together with a consideration

of average tables, will serve as a basis of judgement for determining the ideal weight, but the advantage of slight overweight in youth, and the marked advantage of a weight less than average after middle life when infectious diseases give way to degenerative diseases as the primary cause of death, should be carefully borne in mind.

CLASSIFICATION OF OBESITY

Many classifications of obesity have been suggested by various authors (Freed(32), Fancher(28), Coombs(17), McLester(66), and Clasen and Ginsberg(15)). Yet, when one attempts to classify many cases of obesity, either on an etiologic or on a clinical basis, confusion and uncertainty remain. As early as 1910 Lyon (61) indicated this difficulty, and Jarlov (50), in his exaustive work, well illustrated the disagreement and difficulties in classification, even when the etiology was entirely disregarded. If etiology is considered, there is even more confusion. It would appear, however, that no one cause by itself explains obesity and that obesity is usually the resultant of several factors. For these reasons the following classification is offered, not certainly, that any startling revisions are contained in it, but merely in the hope that it will serve as a basis for classifying the commoner types of adult obesity, which are the types herein to be considered.

Classification of Obesity

A. Exogenous

B. Endogenous

Thyroid

Pituitary

Gonadal

Pancreatic

Hypothalamic and other Cerebral forms

Adrenal

C. Mixed, including Hereditary or Constitutional forms.

D. Localized fat accumulations

It may be mentioned that the above classification, like all others, is not very satisfactory. The vast majority of cases fall within groups A, B, and C, but it is often difficult to place any individual strictly within one group or another. Moreover, even within group B it is often impossible to say to what extent the different glands are responsible for the obesity. These uncertainties are due to the many factors involved in the production of obesity.

EXOGENOUS OBESITY

The importance of the exogenous factors in the production of obesity are accepted by the vast majority of both clinical and experimental workers. In other words, the sole avenue to obesity is through the mouth, and there is no excape from the fundamental law that obesity can only be caused by the ingestion of food in excess of the individual's needs. The nucleus of the argument, then, would seem to be whether the exogenous factor is primary, or whether it is secondary to some deeper-seated tendency lodged in the endocrine glands and/or transmitted directly as an hereditary characteristic. These points will be elaborated in the further course of the discussion.

Newburgh (72), in attempting to refute the argument that adiposity is caused by endocrine disease in those patients who do not lose the expected amount of weight when they are put on reduction diets, states that "it is first necessary to determine accurately how much weight should be lost under the circumstances. In order to do this it is essential (a) to know how much energy the subject receives in the diet; (b) to have absolute assurance that the subject adheres strictly to the diet; and (c) to obtain the transformation of energy for the whole period. The problem has not

been studied with sufficient care in the past. Usually the report did not contain any guarantee that the subject did not obtain food in addition to the diet, but even more important was the lack of any satisfactory method for determining the total amount of energy transformed by the subject. This figure was inaccurately approximated by adding to the basal heat production a value that was thought to account for the specific dynamic action of the food and the activity throughout the twenty-four hours.

"My associates and I have conducted our studies of obesity in such a way that we have been able to deal satisfactorily with each of these three problems. We have made observations on only one subject at a time, while he was confined in what is essentially a metabolism cage, so that he received only the food that we cared to give him. The special diet prepared for him was analyzed in our laboratory so that we knew precisely what he was receiving. Finally, it was necessary to measure the total heat production of the subject. We found that this information could be obtained by calculation from the insensible loss of weight (74).

"With such data at hand, it is a simple matter to calculate how much body tissue is being destroyed and to plot the loss of weight that is caused by the

oxidation of this tissue. When now the course of the body weight of an obese subject who is being undernourished is compared with the loss due to destruction of body tissue, one may find that the two do not coincide. The actual weight may not decrease, even though tissue is certainly being destroyed. The subject may actually gain weight, even though being severely underfed. But this apparent paradox is by no means characteristic of any type of obesity, since it occurs under similar circumstances when entirely normal subjects are observed. We have found that this phenomenon may be regularly produced by underfeeding anyone in such a way that a rapid destruction of the liver glycogen is brought about.

"If now the water exchange (105) is also recorded during such a period, it is found that there is a progressive retention of water by the body and that the weight added in this way conceals the loss of weight caused by the destruction of tissue. Such observations made it clear that the course of a subject's weight cannot be used as a measure of the metabolism, as has been done in the past. A gain of weight may occur while body tissue is being consumed, solely because water is being added to the body; and weight may dininish in the face of overfeeding because a depletion of water

is also taking place. It should be emphasized that this shifting back and forth of body water is merely a response of normal protoplasm to conditions that may be set up as desired by the investigator." Accordingly, Newburgh (72) feels that the main support for the hypothesis that obesity is caused by internal disease vanishes.

However, the author feels that elaborate experiments are not needed to prove that obese persons are in a positive energy balance. Their being obese is proof enough of that. What is needed are studies to prove why these people constantly exceed their metabolic needs, not to prove the fact that they do.

Greene (42), in a clinical study of 250 cases of obesity, concludes that the high percentage of his patients who gave a history of diminished activity while they were gaining weight indicates, to him, that many cases of endogenous obesity would be eliminated by a more detailed history. Illness or convalesence diminished the activity in most instances and corpulence very likely could have been prevented in these cases. He states that it is just as important to prevent obesity as it is to relieve it, yet this phase of the subject has been emphasized comparatively little. The development of obesity with pregnancies in 20 percent of his (42)

cases demonstrated the value of the practice of prevention of excess gain in body weight with pregnancy which has long been stressed. Corpulence could have been prevented in many of the 131 patients who became obese with pregnancies or with illness and convalesence (42). Adequate nutrition during a long illness or convalesence does not signify, however, that the patient must become obese.

Rynearson and Sprague (86) state that there is no evidence to indicate that any obese patient will not lose weight if he follows a diet which is planned to furnish less calories than are necessary for his normal caloric requirements.

When one realizes that a two-ounce bar of chocolate, one pint of beer, the most polite of afternoon teas--a buttered scone, a piece of cake, and a cup of tea--have a caloric value of approximately 300 and that the daily requirement of the average person is only 2,500 calories, it needs very few "snippets" to yield an excessive intake of food. Too, patients have little idea of food values and if they miss what they call a square meal, they frequently take a sandwich or cakes in place of the said meal, the caloric value of the latter often being much greater than that of a square meal. For example, one-half pint of beer and an ordinary

meat sandwich have a greater caloric value than a meal composed of a reasonable helping of roast beef, greens, potatoes, a cup of coffee, a biscuit, and a small piece of cheese. An occasional "drink" may effect the degree of weight loss. McCullogh (65), in discussing the role of alcohol in the induction of obesity, emphasizes that alcohol itself yields 7 calories per gram, although the question remains unsettled as to whether it is utilized as food.

Such a discussion could be endless. Can anyone deny the truth of the statement that the only source of fat is food. It is impossible to disregard the important observations of workers in the field of metabolism such as Liberson (57), Du Bois (25), Grafe (39), von Noorden (96), and Means (67,68). Careful evaluation of the work done by these men gives added weight to the concept that obesity is due to an increased intake of food and that man must follow the laws of energy exchange.

It is merely of interest to mention the name of Gigon (33) who denies the existence of an exogenous obesity.

ENDOGENOUS OBESITY

Seligman (89) and Gusman (45) believe that the endocrine factor in obesity far outweighs any other. Seligman (89) states that the insufficient daily increment associated with tremendous alimentary ingestion and a definite weight plateau established by most individuals shows that there is an intrinsic regulatory mechanism. Thus with a normal functioning mechanism, Gusman (45) believes that we are able to maintain a more or less stationary weight for years at a time, even though our food intake varies in amount from day to day. This normal mechanism even permits us to overeat occasionally without materially changing our weight. However, if this overeating becomes more frequent, obesity may result, at first of an exogenous nature and purely due to too much food, but with persistent over indulgence and repeated insult to the endocrine mechanism, this simple exogenous obesity may be converted into a more complex endocrine or endogenous obesity (45).

Silver and Bauer (1) agree that Newburgh (73) has shown that in obese patients the energy expenditure is less than the caloric intake and that the patients are on a positive energy balance. They further admit that Newburgh (73) has also shown definitely that if the energy intake be reduced below the output these patients

lose weight. However, it is pointed out (1), he has not explained why it is that these obese patients consume more food than they need to maintain normal weight or why their energy expenditure on a given caloric intake is less than that of normal people.

The concept of the endogenous nature of ordinary obesity, then, does not deny the principle of the conservation of energy, as some of its opponents seem to believe. It accepts as obvious the fact that obesity is due to an intake of food that exceeds the energy output. However, it goes further and attempts to explain the mechanism of this disturbance.

Obesity must be considered as a failure of the mechanism that normally keeps the weight of adults constant. It is quite remarkable that this mechanism is so perfect in the normal adult that he goes on from year to year always altering either his energy expenditure or his food intake, and yet the regulatory processes proceed at the same rate so that his weight remains constant. If the food intake be voluntarily increased then an increased output of energy occurs, or if on the other hand, changes in activity take place, then corresponding changes in appetite occur. As a result the normal person, paying no attention to either the extent of his activity or the intake of food, arrives

at a perfect balance between the two.

What then, is the mechanism that allows obese patients to remain for a long period of time in a positive energy balance? Why do they continuously exceed their caloric necessity? The understanding of the problem of obesity requires an answer to these questions rather than experiments to prove the obvious fact that obese patients eat more than they expend. We must, then, center out attention upon perversions of the normal relationship between appetite and energy expenditure. When the regulation is perfect the individual is in equilibrum and there can be no question of obesity. It is only when the mechanism fails and the appetite exceeds the energy requirements that obesity appears. This failure of the regulatory mechanism, this tendency toward obesity, it is contended by the author, is passed from generation to generation by hereditary means. Although it may reveal itself as being of the pituitary, gonadal, or other types, the fundamental cause remains hereditary.

HYPOTHYROIDISM

The thyroid gland has been considered the cause of innumerable cases of obesity. Actually, it is seldom the offender (32). It is true that hypothyroidism may result in increase in weight, but this consists of an accumulation of water, albumin, and salt in the tissues rather than adipose tissue. When these are lost, the patient may actually be underweight.

The distribution of fat is typical in the hypothyroid, there being a general diffuse, subdermal infiltration along with localized pads of fat, the cervical, nuchal, anklet, and bracelet pads. Dermal changes are present, the skin being dry, thick, and rough. The hair is dry, brittle, coarse, wirey, and often falls out rapidly. The teeth show a tendency to decay and loosening. Congenitally absent teeth are the rule in typical hypothyroid cases, as well as early decay. The palate may be high and narrow. The tongue at times is large and thick.

When hypothyroidism is marked, a myxedema may appear which is an exaggeration of the above description along with other definite changes. The myxedematous face is expressionless, the appearance puffy and mask-like, the color waxy with apple-blossom cheeks, the eye-lids are puffed, the lower lids baggy. There are

supraclavicular pads and frequently the seventh cervical padding is very pronounced. Padding of the hands and feet is characteristically on the posterior surfaces. The obesity is, as described above, a diffuse, subdermal infiltration, affecting the entire body and is characterized by a non-pitting edema. The lower legs have a doughy puffiness. Due to the markedly lowered metabolism characteristic in these cases there is a profuse lowering of all vital processes resulting in such changes as bradycardia, constipation, lethargy, mental sluggishness, subnormal temperature with resulting sensitivity to cold and tolerance to hot weather. The speech is slow and monotonous, the voice may change to a coarser tone. Mental efforts meet with increased difficulty there being a progressive loss of memory and concentration. Physical exertions are reduced to a minimum because of lack of interest and also because of fatigue that results from even slight activity. In the female, menstrual changes are noted, menorrhagia being the rule, and amenorrhea present at times. Libido may be diminished or absent. This describes briefly cases of hypothyroidism from the mild to the extreme degree. In this group, an extreme degree of obesity is not reached.

THE PITUITARY

The pituitary gland, which is called the "master gland" by Cushing,(19) and the "leader of the orchestra of glands" by Langdon-Brown (54), plays an especially important part in the management of metabolism. This is borne out by the demonstration of directly calorigenic hormones in the interior lobe (75,81) besides the trophic influence on the thyroid and by the secretion of a fat metabolism or ketogenic hormone. The latter is demonstrably decreased in pituitary disease, as was described by Goldzieher, Sherman, and Alperstein (37). The inadequate production of calorigenic hormones in pituitary disease accounts for the low basal metabolism of these patients even in the absence of all clinical signs of hypothyroidism (35).

Pituitary obesity or adiposogenital dystrophy, or Froelich's syndrome refers to the characteristic girdle obesity complicated with functional disturbances of sex of varying degrees, and hypertrichosis. The true etiology remains indefinite; however, the syndrome points to a concomitant involvement of the pituitary gland and of the tuber cinereum. In regard to the cause of the adiposity of Froelich's disease, Mazer (62) makes the following remarks, "It does not follow extirpation of the animal pituitary gland nor is it present in Simmonds'

disease wherein the function of the gland is partly destroyed by organic lesions. It can, however, be produced by trauma or chromic acid injections into the suprasellar area. Moreover, it is present in some cases of suprasellar tumors of the human. These observations point to an associated functional derangement of the hypothalamic area as the cause of the obesity of Froelich's disease. This assumption is also supported by the well-known fact that low-dosage irradiation, which frequently improves pituitary function, resulting in the reestablishment of menstruation, does not influence the associated obesity." Diabetes insipidus may be associated with Froelich's syndrome expecially when tumors are present in the region of the diencephalon.

In pituitary obesity we have a classical pelvic girldle obesity from the navel downward to the junction of the middle and lower third of the thigh; mammary adiposity, also adiposity of the deltoid or shoulder and around the malleoli and buttocks. In addition, there is much fat folding about the lower part of the thorax. In the adult male there is much subcutaneous fat--the feminine type with hypertrophy of the breasts. The external genitalia, penis, scrotum, testes, are poorly developed and testes are often undecended. In the female there are secondary sex characteristics,

such as paucity of hair about the mons veneris, the beard and axillae, hypotrophy of the breasts and often a tendency to masculinism. There is a disposition to amenorrhea, dysmenorrhea and sterility. If it comes late in life, sex characteristics are not so pronounced. The fat is solid, compact and firm with no tendency toward water retention (15). The skin is smooth, the hair is scanty, the incisor teeth are poorly developed and the fingers are long and gracile. The carbohydrate tolerance is increased.

Adiposis dolorosa is a syndrome of symptoms associated with fat metabolism. It is characterized by localized adiposity, pain and tenderness of the fatty tissues, asthenia and psychic disturbances (61). It was first described by Dercum in 1792, and is frequently referred to as Dercum's disease. Since dysfunction of the thyroid gland was found to be such a frequent concomitant, this gland was originally incriminated. The pituitary also has been considered of etiologic importance, hence the inclusion of the disease at this point, but there is no agreement on the issue. It may be a polyglandular dyskinesia. There is a strong familial tendency.

Cushing (20) has described a characteristic syndrome associated with a pituitary basophilic adenoma

in most cases. It occurs as a rule in relatively young adults. It is a rapidly acquired adiposity confined to the face, neck, thorax and abdomen, the extremities showing no involvement. The face is round and florid, the breasts large and the abdomen protuberant and often pendulous. The shoulders have a tendency to become rounded. This has been referred to as a "buffalo" type of obesity. Usually, the female patient is short in stature. If the disease occurs before puberty, sexual development is apt to be precocious, but functional impotence and amenorrhea develop in adult females. They have extreme fatigability, generalized pains with osteoporosis of the bones which is similar to hyperparathyroidism (89).

Water Retention. The factors concerned with obesity and water retention are best considered at this point, since they are so intimately bound up with the pituitary as to make a separate discussion illogical.

There is a type of pituitary obesity which is due to water retention (100). These patients give a history of a rapid gain in weight and present characteristics of pituitary adiposity. It is thought that this condition may be the result of a hyperactivity of the water hormone, one of the constituent hormones of the posterior lobe. If this is true, then this condition is a direct

contrast to diabetes insipidus, the latter resulting from a dificiency of this hormone.

It has long been known that the posterior pituitary exercises an influence on water balance in the tissues. Two active principles of the posterior pituitary have been isolated and these are named pitressin and pitocin. Among other effects of pitressin it prevents excessive loss of water from the body tissues.

It has been shown (101) that the flow of water through the kidneys is controlled by an antidiuretic hormone formed in the neural division of the hypophysis (posterior pituitary). This part of the hypophysis is innervated by a tract of nerve fibers which reaches it from the hypothalamus. Interruption of this tract from the hypothalamus causes atrophy of the neural division of the hypopothis and absence of the antidiuretic hormone. Diabetes insipidus results from this sequence of events and also results when the neural division of the pituitary is removed leaving the anterior pituitary intact. In man, diabetes insipidus develops when the tract, going to the hypophyshis, is interrupted in its course close to the base of the brain by traumatic injury or inflammatory lesions and when tumors selectively destroy the neural division of the hypophythsis (101)

Retention of water in the form of edema based on

cardiac or renal disease is much better understood than the invisible water retention due to metabolic disorders. The retained water may remain partly in the circulation and account for an increased blood volume, usually accompanied by increased blood pressure. Often, however, the retained water remains entirely within the tissues and especially within the cells. Greater hydration of cellular protoplasm is the result of colloid chemical changes, the mechanism of which is still unknown; only a few factors are understood (35) which make for intracellular accumulation of water. One of these is the retention of sodium chloride and, probably, other sodium compounds which may or may not be accompanied by the increase of sodium chloride in the circulating fluids. Another contributing factor is the deposit of glycogen, the formation of which from glucose is predicated upon water retention.

GONADAL OBESITY

Werner and Weir (101) state that gonadal obesity always arises from hypofunction or afunction of the ovaries in the female or the testes in the male. The clinical observation that obesity frequently follows castration, childbearing, and the menopause (89) has led many observers to conclude that lack of ovarian function leads to physical inactivity with the subsequent deposition of fat. Freed (32) feels that these cases are rare, and that the gonads have little direct effect on obesity. However, most writers, particularily the endocrinologists, believe in the existence of a hypogonadal obesity which is more or less characteristic. A notable feature of this type of obesity is its late development, the adiposity occuring after the age of thirty. The earlier stage of this condition is characterized by a trochanteric adiposity without any other localized or general adiposity. This trochanteric adiposity is an accumulation of fatty tissue localized over the greater trochanter. If this accumulation becomes very great it may include the upper thigh. Later there is a generalized subdermal infiltration, especially involving the breasts and mons as well as the trochanteric region. The accumulation of fat over the mons may in time become so marked as to form an

apron-like fold overlapping the vagina. In the male, the mammary development is marked and there is a definite girdle and trochanteric adiposity. Of these three locations, greatest consideration and diagnostic dependability must be placed on the trochanteric deposit (101). While mons veneris and mammary fat deposits are found in most instances when a gonad obesity develops, they also occur together with almost any other type of obesity. The hair distribution is feminine in type and secondary sex characters are almost or entirely absent. The physical characteristics of eunichoidism are readily detected, as for example, the long tapering fingers and toes and the increased length of the long bones.

HYPERINSULINISM AND THE PANCREAS

Fancher (28) states that excess of pancreatic secretion, of hyperinsulinism, eventually may be found to be the cause of all endogenous obesity. Poulton (78) discussed the hyperinsulinism theory of obesity and stated that the following were reasons in its favor:

(a) Obesity not uncommonly overtakes diabetic patients who are treated with insulin.

(b) Insulin and carbohydrate have been used in fattening lean people.

(c) The frequency with which diabetes occurs in obesity is compatible with the wearing out of an over-active function.

(d) The sugar tolerance of obesity is increased in some cases, which is compatible with an increased output of insulin.

(e) It has been shown by many observers that repeated ingestion or injection of glucose stimulates the pancreas to secrete insulin, as indicated by the fact that the blood sugar does not rise so high after the second administration.

Bonilla (9) states that hyperinsulinism is constant in obesity. Sometimes it is due to a greater production of insulin, and at others to a lack of antagonistic hormones, which correspond to the thyroid, pituitary, and

genital obesities, but it is always the insulin which produces the obesity.

The suggestion that the exogenous type of obesity may be the result of pancreatic stimulation following the ingestion of too much carbohydrates is attractive; for this stimulation may well lead to some hypertrophy of the islet tissue which will cause the blood sugar content to fall and produce feelings of hunger which must be satisfied by more food. Thus a vicious circle may be established.

Against this theory it may be stated thatcase reports of patients suffering from hyperinsulinism as the result of tumors of the islets of Langerhans show that obesity was not a pronounced feature. Further, in these cases (64) of hyperinsulinism with hypoglycemia and extreme hunger periods, obesity was not noted although the patients were fed large amounts of carbohydrates to combat the hypoglycemia. This does not lend support to the suggestion that obesity has as its basis an increased appetite conditioned by hyperactivity of the insular apparatus.

CEREBRAL OBESITY

While the nervous centers and tracks of temperature regulation have been known for some time, experimental evidences of a central regulating mechanism for metabolic processes were not available until fairly recent times. Grafe and Gruenthal (41) found that injury to certain parts of the hypothalamus in the dog is invariably followed by a marked drop of the basal metabolism. Bernhard and Zondek (4) noticed that the basal metabolism of certain cases of obesity was markedly lower after a lumbar puncture and removal of spinal fluid. Others (17, 32, 42, 89) have described cases of cerebral obesity in which brain tumor or encephalitis or other brain pathology was found in connection with a rapidly growing obesity. Zondek (107) described the so-called hypophyseal-cerebral-peripheral type of obesity.

Freed (32) states that "there is little doubt that certain lesions of the brain may result in severe adiposity. The condition has been produced experimentally by injuring the hypothalamus or infundibulum . It has been observed clinically in patients with tumors near the pituitary, where there is pressure on the nerve tissue, following attacks of encephalitis, chorea, or other forms of brain injury. The exact mechanism is not known, but the evidence at hand warrants the conclusion

that there may be a nervous control of the fat mobilization mechanism."

Greene (42) believes that encephalitic lesions of the hypothalamus play a minor role, if any, in the production of obesity. He states, "the development of obesity in five cases and its disappearance in five other patients after the onset of chronic encephalitis might be attributed to a different distribution and intensity of the brain lesions. A history of diminished activity with a good appetite was obtained, however, from three of the patients who became obese after the encephalitis developed, and two cases in which encephalitis antedated the obesity were known to have followed low caloric diets and lost weight satisfactorily." Such observations, however, do not deny that encephalitic patients may, because of their lesion, become physically inactive, develop a polyphagia, and secondarily gain weight.

It is further stated by Greene (42) that, "lesions of the hypothalamus apparently were not important factors in the production of adiposity in our cases of coexisting obesity and diabetes insipidis or suprasellar tumors. It is difficult to detect any difference in the obesity which develops in association with long inactivity due to a fractured leg and that which develops with a

long illness due to pituitary tumor, suprasellar tumor, chronic encephalitis, or myxedema. One has to admit, however, that not all patients with fractured leg, etc., become obese but neither do all cases of myxedema, pituitary tumor, and chronic encephalitis."

Nevertheless, the weight of the evidence is in favor of a cerebral type of adiposity. However, there is no evidence to prove that the increased appetite is not the result of a tendency to obesity occasioned by the lesion rather than that the appetite disturbance is primary. The distinction whether a nervous lesion causes a primary polyphagia or whether the polyphagia is merely the sequal of a newly instituted tendency to obesity cannot be settled easily. The relationship between growth (or obesity) and appetite is well shown in the experimental work of Putnam, Benedict, and Teel (79). In their studies in the experimental production of acromegaly in dogs by the injection of hypophyseal extracts, they noted rapid growth and enormous increase in appetite. One would scarcely say that the anterior lobe of the pituitary gland stimulates the appetite in the sense that bitters do. One would not say that these dogs grew because they ate more. They ate more as an inescapable result of a newly instituted tendency to growth which is a specific action of the anterior

pituitary lobe. The dogs did not grow because they ate more, but they ate more because they were growing. The increase in appetite is a result, not a cause.

ADRENAL OBESITY

Obesity of adrenal origin is not common (35), not withstanding the fact that the adrenal cortex plays a considerable role in the maintenance of body weight by virtue of its effects upon the resorption of ingested food from the intestines, the fixation of fat and cholesterol in the tissues, and the physiological control of water and electrolyte metabolism.

Hyperfunction of the adrenal cortex results in obesity in the female. It has no effect on the male after puberty, but causes precociousness before that time. In suspected cases an attempt should be made to visualize the adrenals by perirenal insufflation (69). The clinical manifestations of adrenal obesity include the peculiar distribution of the fat which leaves the extremities free and accumulates about the trunk, neck and head, in addition to other signs of adrenal cortical hyperactivity.

Goldzieher (36), by prolonged injection of cortical hormone in rabbits, demonstrated a tendency to obesity and a drop in blood cholesterol, the latter, he felt, being due to the action of the endothelial cells. Why obesity develops with adrenal cortical hyperplasia is not definitely settled. There may be some connection with the pituitary and/or the gonads. The evidence is inconclusive.

HEREDITY IN OBESITY

That heredity is an important factor in obesity is recognized by most workers in this field. However, it is questionable whether it has received sufficient emphasis in medical discussions. The findings of Davenport (21) seem definitely to indicate that body build follows the mendelian laws of inheritance. By studying the progeny of parents of similar and dissimilar builds, he concluded that there are three gametic factors, of which one may correspond to dystrophy of the thyroid, and one to dystrophy of the pituitary, and the third may be a metabolic factor that effects the actual metabolism of the cells themselves. If this hereditary factor is accepted, the onset of obesity in one person as opposed to that in another who is subject to the same environmental influences and is even receiving the same diet may be more readily understood. In this connection, Rynearson and Sprague (86) quote Danforth as reporting a strain of yellow mice in which the tendency to obesity was transmitted as a unit character.

The work of Gurney (44) is outstanding. Seventy-five stout women were studied with these points in mind: (1) the factors associated with the onset of obesity as compared with the same factors occuring in

a nonstout control group; (2) the incidence of obesity in the parents of the stout group as opposed to that in the parents of the nonstout control group; (3) the body build of the progeny of different matings with special reference to mendelian inheritance of build.

Fifty-five women who were definitely not stout were chosen at ramdom as controls. Patients with any debilitating illness were not included. The control patients came from approximately the same age group and had approximately the same incidence of operations and pregnancies--the two most common factors apparently associated with the onset of obesity.

Eighty-three percent of the stout group were between 21 and 50 years of age, which includes the period of childbearing and the menopause. Eighty-six percent of the nonstout group were in this same age period. Sixty-one percent of the stout group and 50 percent of the control group had had one or more pregnancies. Thirty-six percent of the stout group and 47 percent of the nonstout had had operations. Thus the two groups may be compared, being from approximately the same age period and having had approximately the same number of pregnancies and operations.

Sixty-three women in the stout group gave a reliable history as to the onset of obesity. Of the forty-one of

these who bore children, or 65 percent, 29, or 71 percent, stated a direct association between pregancy and the onset of obesity. Of the 24 who had major operations, or 38 percent, 7, or 29 percent stated a direct association between the operation and the onset of obesity. Of the remaining 27 patients, 4 associated the onset of obesity with puberty and 2 with the menopause, 8 maintained they were "always stout," and 13 apparently had no determinable factor associated with the onset of obesity. Thus, in 67 percent of the stout group, the onset of obesity was apparently associated with some physiologic or physical episode. However, in another group of women of approximately the same age period and subject to the same physiologic and physical episodes, obesity did not occur.

When one studies the builds of the parents of the stout and of the control group a very different and real difference in the incidence of obesity is apparent. Of the 61 stout women whose family history seemed unquestionably reliable, 26, or 43 percent, had a stout mother; 9, or 15 percent, had a stout father, and 15, or 25 percent, had both a stout mother and a stout father, making a total of 50, or 82 percent, having either one or both parents stout. In contrast to this, of the 47 nonstout patients with an equally reliable family history,

14, or 30 percent, had a stout mother; 1, or 2 percent, had a stout father, and 3, or 6 percent, had both a stout mother and a stout father, making a total of 18, or 38 percent, with either one or both parents stout, as opposed to 82 percent in the stout group.

If build is inherited, as it seems to be from these figures, this inheritance must be along mendelian lines, as there is probably no other kind of inheritance, (16). A study of inheritance in human beings is, of course, exceedingly difficult because so few generations are available for observation. However, if segregation, which is the indispensable condition of the mendelian theory, can be shown, it follows inescapably that mendelian inheritance is present. Segregation is the dissociation of two unit characters from each other in the course of the formation of the germ cells. Thus, evidence for segregation in human inheritance is a difference in variablity of the progeny of different matings, (21).

A study of the progeny of different matings in this group shows a definite difference in variability. There were 89 offspring from matings of stout persons, 65, or 73 percent, of whom were stout, and 24, or 27 percent, of whom were not stout. Of the 170 offspring of matings of a stout and a nonstout person, 70, or 41

percent, were stout, and 100, or 59 percent, were not stout--a marked variability. Of the 176 offspring of matings of nonstout persons, only 16, or 9 percent, were stout, in contrast to the 160, or 91 percent, who were not stout. Thus, there is present a marked difference in variability in the progeny of different matings, with the offspring of a stout and a nonstout parent the most variable and the offspring of nonstout parents the least variable. The fact that the offspring of stout parents are more variable than those of nonstout parents suggests, as pointed out by Davenport (21), that stout persons carry gametes for slenderness whereas nonstout persons rarely carry gametes for stoutness. As a corollary to this, regression to a more normal build as a result of these gametes for slenderness can be seen in the offspring of stout parents to a considerably degree than in the offspring of slender parents.

There appears to be no definite dominance in the series, which, of course, is not essential in mendelian inheritance.

May we not regard these findings as significant in the origin of obesity? Eating from a common table or following a common table tradition alone cannot explain these figures. These people become obese even if they eat exclusively outside their homes. Also, it is

a common observation that the most severe grades of obesity and emaciation can be seen in the same family among people who live from a common table. Apparently, there may be a defect in the congenital factor that determines and regulates weight, and this defect may manifest itself in the exhibition of obesity or its direct opposite.

There is an inclination to attribute the frequency of stoutness in the children of obese parents to habits acquired from eating with the parents rather than to heredity. Certainly, stout persons appreciate good food more than do nonstout persons, and their children are thus "exposed" to better food. However, it would appear that something more than habit is involved and that this something, which is acquired by inheritance, gives the stout man a better as well as a more discriminating appetite.

These views are nicely summed up by Silver and Bauer (1) who state that the constitutional concept of obesity considers this exaggerated tendency to store fat, and possibly water and salts, as the primary factor in the causation of the obese state. It regards this tendency as congenital and hereditary, although, like many other congenital factors, it may not become evident for many years after birth.

If we locate the genesis of obesity in a constitutional destiny of the tissues of certain people to store fat, then we can understand a disturbed balance between energy intake and expenditure as a necessary sequal of this almost irresistible tendency. We can also understand those cases of obesity, common in the experience of everyone, where in spite of rigorous diet and exercise, we are unable to reduce the fat from the areas where it is most obvious. Patients may suffer from a severe grade of inanition and even emaciation without any effect on the fat deposits that we would most like to influence.

The concept of constitutional obesity regards the lipophilia of the tissues as the basis and cause of the metabolic disturbance. It does not deny that obese patients are on a positive energy balance, nor that an endocrine imbalance is present. It explains this perversion of metabolism as the result of a congenital factor, already present in the fertilized ovum, that destines the organism to accumulate fat. Obesity is not the result of overeating, but overeating may be an inescapable consequence of an inborn tendency to obesity.

SUMMARY

The factors in metabolism, and the arguments for the three main causes of obesity, viz., exogenous, endogenous, and hereditary, have been presented.

(a) The digestion and absorption of fats has been shown to be not characteristically different in the obese than in the normal person. Some patients demonstrate a more rapid removal of blood lipids after fatty meals, and also show a lower blood lipid level. This factor may be of importance in accounting for a delayed sense of satiety, and may be of an inheritable nature. There is no evidence to show that obese persons derive more value from their food than do normal or lean persons. Absorption of nutritive material from ingested food remains remarkably constant except in the presence of vomiting or diarrhea.

(b) The increased lipophilia of certain tissues may be hereditary.

(c) There is no proof for the theory of luxuskonsumption.

(d) The relationship of the specific dynamic action of foods to obesity remains the source of contention. Depending on the point of view of the authors, the lowered specific dynamic effect can be

proved to lead to obesity, or cachexia, or to be of no importance at all.

(e) The basal metabolism of the obese, as arrived at by the usual calculations, is not changed except in the cases of hypothyroidisms. This maintence of the metabolic rate by the thyroid gland is enhanced by the production of two calorigenic hormones from the pituitary gland. If the metabolic rate of an obese person is compared to that of a normal weight person of the same sex, age, and height, a figure is obtained which may be called the basal metabolic ratio. The average increase of this basal metabolic ratio in the obese is plus 33 percent for every 100 pounds overweight.

(f) It is freely admitted that the patient must be in a positive energy balance if obesity is to occur. The question, then, is why these people constantly exceed their caloric requirements.

(g) The "endogenists" believe that obesity results secondarily to an endocrine disturbance.

(h) The "mendelianists" believe that obesity is the result of an hereditary transmission of characteristics.

(i) After a review of the literature, the author is of the opinion that all of these arguments can best

be used collectively to explain the etiology of adult obesity in the vast majority of cases. It is the writer's conviction that obesity is essentially hereditary in nature, and that heredity, acting through and on both exogenous and endgenous variants, accounts for the mill-run of cases of adiposity.

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