1946

Etiology of obesity

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Senior Thesis Presented to the
College of Medicine, University
of Nebraska, Omaha, 1946.

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In reviewing the literature on the etiology of obesity, it is discovered that almost everything associated with human life has been indicted as a reason why people get fat. There are explanations offered as to why some individuals become obese in spite of the fact that a history is entirely lacking in etiologic material, and there are also explanations offered as to why some individuals never become obese no matter what the extenuating circumstance may be that ordinarily produces obesity. It will be the purpose of this writing to discuss the factors regulating body fat content and to note the most important factors contributing to a derangement of the mechanism involved in this regulation.

DEFINITION

What constitutes "obesity" or, in other words, an abnormally large amount of adipose tissue, is not the easiest thing on which to become agreed. The word "obesity" first appeared in the English language in the early seventeenth century and takes its origin from the word "obesus" which is the past participle of the Latin word "obedere." The meaning 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 occasionally used

to indicate fatness, laziness, or slothfulness.

There have been many suggestions as to the definition of obesity. Behnke, Feen, and Welham (1) concluded that (a) the fundamental biologic characteristic of corporeal density can be accurately measured usually within 0.004 unit by the method of hydrostatic weighing, provided a correction is made for the air in the lungs; (b) values of specific gravity for healthy men ranging in age between twenty and forty fall between 1.021 and 1.097; (c) low values for the specific gravity indicate obesity and conversely, high values denote leanness (on a study of ninety-nine healthy naval men); (d) individual loss in weight through exercise and a restricted diet is associated with an increase in specific gravity; (e) the difference in the circumferential measurements of the chest and abdomen serve as a criterion of obesity and can be correlated with the specific gravity; (f) variation in the percentage of bone in relation to body weight, excluding excess fat, is not expected to produce a deviation of more than 0.013 units in comparable values. In studies on twenty-five exceptional athletes and seventy-five navy men as to specific gravity in relation to height-weight tables, it was decided that the criterion as to the proper weight of an individual is based on a relationship between stature and absolute body weight, mod-

ified by age. Numerous sturdy persons, however, exceeded by fifteen percent the weight values recorded as average for a given height. A more valid basis than standard height-weight tables for an estimate of whether or not an individual is obese is not absolute weight, but rather specific weight, that is, the weight in relation to the unit volume of tissue. Of seventeen rejected "all-American" football players in one study, eleven fell into the group possessing high corporeal specific gravity. So according to these men, these players were in prime physical condition if the absence of excessive fat is a criterion of fitness. The type of physical exertion, moreover, that these men were called on to make is proof of their sturdy physique, estimated in terms of speed, agility and endurance. So, Welham (1) and Behnke (1) propose the classification of men as overweight on the basis of the specific gravity of the body mass, using a tentative dividing line of 1.060 for the elimination of the obese (a value below this indicating obesity). This division is diametrically opposed to a division based on height-weight tables.

And as Barr (2) puts it, standard insurance averages for weight to given height cannot apply accurately to individuals because they do not take into account bone and muscle structure. Such factors are considered in Willoughby's (3) classification. Thus, nonedematous persons who are ten to twenty pounds or more over the average weight for their build, height, and muscular

development are obese.

The following table indicates desirable weights for men and women of ages twenty-five and over and are based on numerous medico-actuarial studies of hundreds of thousands of insured men and women in the Metropolitan Life Insurance Company (4). It takes into account the frame of the individual and is probably as valid an approach to this phase of the problem as one can obtain.

MEN				WOMEN			
Wt. in pounds according to frame (as ordinarily dressed)				Wt. in pounds according to frame (as ordinarily dressed)			
Ht. (with shoes on)		Small frame	Med. frame	Lge. frame	Ht. (with shoes on)	Small frame	Med. frame	Lge. frame
Ft.	In.				Ft. In.			
5	2	116-125	124-133	131-142	4 11	104-111	110-118	117-127
	3	119-128	127-136	133-144	5 0	105-113	112-120	119-129
	4	122-132	130-140	137-149	1	107-115	114-122	121-131
	5	126 136	134-144	141-153	2	110-118	117-125	124-135
	6	129-139	137-147	145-157	3	113-121	120-128	127-135
	7	133-143	141-151	149-162	4	116-125	124-132	131-142
	8	136-147	145-156	153-166	5	119-128	127-135	133-145
	9	140-151	149-160	157-170	6	123-132	130-140	138-150
	10	144-155	153-164	161-175	7	126-136	134-144	142-154
	11	148-159	157-168	165-180	8	129-139	137-147	145-158
6	0	152-164	161-173	169-185	9	133-143	141-151	149-162
	1	157-169	166-178	174-190	10	136-147	145-155	152-166
	2	163-175	171-184	179-196	11	139-150	148-158	155-169
	3	168-180	176-189	184-202				

IMPORTANCE

That this matter of obesity is an important factor in life expectancy is no exaggeration and certainly this subject should

occupy more of our as well as lay attention for that very reason. Fisk (5) has shown that the average weights of persons over thirty are too great as judged by their life expectancy and has found that the average weight at thirty is the most desirable weight for the remainder of life. His experience in life insurance has shown that heavyweights, regardless of type and heredity, show an extra mortality.

Dublin and Lotka (6) analyzed the influence of weight on the duration of the life of 192,304 men aged twenty-one or over when accepted for life insurance. They concluded that "the penalty of overweight is one-fourth to three-fourths excess in mortality." Table I shows deaths per 100,000 men accepted for insurance, (age disregarded):

Table I

Weight	Deaths
Standard	844
Underweight, total	848
Overweight, total	1,111
Underweight, 5-14%	833
Underweight, 15-34%	913
Overweight, 5-14%	1,027
Overweight, 15-24%	1,215
Overweight, 25% or more	1,472

Also, excessive weight carries a much greater risk in persons beyond forty-five years than earlier. Table II shows the influence of weight on mortality as modified by age and deaths per 100,000:

Table II

Weight	Age, Year	
	Under 45	Over 45
Standard	463	1,308
Underweight, total	498	1,274
Overweight, total	527	1,824

The risk is exceedingly great for the years from forty-five to fifty. Table III shows the influence of overweight on mortality in persons aged forty-five to fifty years:

Table III

Pounds Overweight	Increase in death rate over average percentage.
10	8
20	18
30	28
40	45
50	56
60	67
70	81
90	116

Fisk has also stated (5) that "fifty pounds overweight at age forty-five imposes as much extra mortality as valvular heart disease."

PHYSIOLOGY OF FATS AND FAT TISSUE

In a discussion of the etiology of obesity, it is well that we consider some of the physiological aspects of the problem. Our first consideration will have to do with the metabolism of fat.

THE METABOLISM OF FAT

As to the synthesis of fat in the body, we know that there are two possible sources available, namely, proteins and glucose. Carbohydrate is converted into fat, although the problem of intermediary phases of the process are still unsolved. Three main steps are involved in the process: (a) the building up of the even carbon atom number straight chain fatty acid from glucose, (b) the formation of glycerol from glucose, and (c) the union of three fatty acid molecules with glycerol to form a triglyceride.

The transformation of glucose into fat is an endotherm process, the caloric value of fat (9.3) being more than twice that of glucose (4.1), and therefore needs a supply of free energy. This is thought to be obtained by oxidation of additional amounts of glucose which do not take part in the synthesis.

Little is known about the place of fat synthesis in the body. The fact that practically all cells may contain considerable amounts of neutral fat does not prove that all cells may perform

the synthesis of fat from glucose; the fat might have been taken up by the cell from the blood stream either from feed fat or from fat originally synthesized or deposited in other organs or tissues.

Phospholipid formation from neutral fat is known to occur in the intestinal mucosa during fat absorption, and in the liver, kidney, and red blood cells.

It is believed that fat synthesis from glucose normally occurs when carbohydrate intake is abundant and the glycogen steres in the liver and muscles are filled. It appears that insulin promotes the transformation of glucose into glycogen as well as fat, and it depends on prevailing conditions which process actually takes place.

As to oxidation of fat in the body, we know that normally fat is completely oxidized to carbon dioxide and water. The intermediary substances which occur in the process are of a very transitory character and cannot be normally demonstrated in the tissues, blood, or urine. However, it is possible to recognize some steps in the breaking down of the fatty acid molecule in certain experimental and clinical conditions, from which conclusions can be drawn concerning the normal process. Oxidation of the fatty acid chain starts at the beta carbon atom --the one second from the carboxyl group-- with the result that two terminal carbon groups are split off; then the remaining, now shorter, fatty

acid chain again undergoes beta oxidation, with two terminal carbon atoms being again thrown off. This process goes on until the beta-oxidation product of the four carbon chain, beta-hydroxy-butyric acid is formed; this is further oxidized to aceto-acetic acid and acetone.

Normally only traces of the ketone bodies are found in the tissues, blood, and urine; but in starvation, on diets rich in fat and poor in carbohydrates and in severe diabetes, marked ketonemia and ketonuria may develop. It is known that the ketone bodies are produced mainly in the liver.

Under certain conditions, omega-oxidation, that is, initial oxidation at the methyl group on the other end of the fatty acid chain, may occur, but whether this process takes place in the oxidation of the common food fats and depot fats is not definitely known.

The further fate of the two carbon atom groups (split from the fatty acid chain in the process of beta oxidation) and of the ketone bodies is not definitely known. According to one theory, the split- and end-products of beta oxidation are normally directly oxidized to carbon dioxide and water; according to another theory they are normally first transformed into glucose (presumably by reduction to acetaldehyde to glucose) and then the glucose oxidized to carbon dioxide and water, The first is advocated by Graham Lusk (7) and the latter by Geelmuyden (8).

Soskin (9) has presented evidence indicating that the hypo-

physis plays a role in the conversion of fat into glucose. Hypophysectomized animals show marked hypoglycemia in starvation or on an exclusive fat diet; when protein was fed, the blood sugar rose to normal. This would indicate that the hypophysectomized animal is unable to derive sugar from fat in contrast to the normal animal which derives sugar both from protein and fat; consequently, when the carbohydrate stores of the hypophysectomized animal are depleted and exogenous carbohydrate is not available, sugar is produced from body protein alone, and hypoglycemia results because the rate of this process is not rapid enough to maintain normal blood sugar levels.

THE TRANSPORT OF INGESTED FAT

As to digestion and resepption of fat, we know that digestion of fat may start in the stomach by action of the gastric lipase, but that it takes place mainly in the small intestine. The initial step is emulsification, in which bile salts and bile lecithin play an important part. There is evidence that some emulsified fat is resorbed as such; almost all fat, however, is first split into fatty acid and glycerol by the lipases contained in the pancreatic and intestinal juices. How the water-insoluble fatty acids are brought into solution and transported across the intestinal wall, is not definitely known. It has been demonstrated that the bile acids are capable of bringing a considerable amount of fatty acids

into solution in water, and it is probable that the fatty acid is absorbed on the surface of the intestinal mucous membrane as a fatty acid-bile salt complex from which the former enters the epithelial cell while the latter remains absorbed to the surface and conducts new quantities of fatty acid in water soluble form through the surface of the epithelium. These are the observations of Verzar and Laszt (10).

There is evidence that resynthesis of fat in the mucosa is not simply a reversion of the process of previous hydrolysis. It appears that resorbed fatty acids are transformed into phospholipid in the intestinal mucosa, and that fat cannot be absorbed if this transformation does not take place.

Verzar and Laszt (10) found that fat absorption is considerably retarded in adrenalectomized animals, and that it increases in rapidity after injection of a potent cortex extract. They believe a cortex hormone is necessary for the transformation of resorbed fatty acids into phospholipid in the intestinal mucosa, and that fat cannot be absorbed if this transformation does not take place.

Some of the resynthesized fat passes from the epithelial cells into surrounding capillaries and is carried, together with the digestion products of protein and carbohydrate, by the portal vein

to the liver. Most of the resynthesized fat, however, is transported to the central lacteals of the villi and carried in the chyle vessels and thoracic duct into the internal jugular vein. The thoracic duct lymph which is clear in the postabsorptive state and contains about 0.2% total lipids, yields a milky chyle within an hour after a fat meal, the fat content gradually rising to a maximum of 3% to 5% in five or six hours; then gradually declin- to the postabsorptive level in about ten to twelve hours after the meal.

As to the transport of ingested fat in the blood, we know that in the postabsorptive state human blood plasma normally contains about four hundred to seven hundred milligrams percent total lipids with the following composition:

Neutral fat	80 - 200 mgm.%
Phospholipids.....	170- 240
Total cholesterol.....	100 - 200
Free cholesterol	40 - 60
Total fatty acids	250-450

Raab (11) has demonstrated that pituitrin injected hypoder- mically causes a twenty to thirty percent decrease of the petroleum ether extract lipids (neutral fat plus free cholesterol) of the blood plasma, lasting ten to twelve hours.

Thyroxin, epinephrine, and insulin have no definite effect on the postabsorptive lipid level. Adrenalectomy is followed by an increase in blood cholesterol. These conditions will be taken up later.

It is known that the blood cholesterol is a fairly accurate index of pathological changes in blood fat. Decreased blood fat is present in chronic anemias, thyrotoxicosis, and acute infectious fevers. Increased levels are had in acute starvation, the second half of pregnancy, lactation, myxedema. jaundice, narcosis, alcoholism, phosphorus and phlorizin poisoning, nephrosis, diabetes and after repeated bleedings.

Bloor (12) found an increase in the phospholipid and cholesterol content of the red blood cells, following the feeding of fat, and since the increase in the amount of these substances was greater in the red blood cells than in the plasma, suggested that most, if not all, of the neutral fat poured through the thoracic duct into the blood stream is taken up by the red blood cells, transformed to lecithin and cholesterol esters and released later in this form to the tissues.

Abnormal alimentary lipemia curves have been found in destructive liver diseases, the alimentary increase in blood lipids being very little or absent, and in nephrosis where alimentary lipemia is greater than normal, and in some cases of obesity.

The alimentary lipemia curve is a resultant of two processes, the passage of resorbed fat into the blood, and the passage of blood fat into the tissues.

As to the transport of alimentary fat from the blood to the

tissues, it is known that alimentary fat is transported from the blood (a) to the tissue cells for immediate utilization, (b) to the liver to be stored temporarily and to be acted upon chemically, and (c) to the fat depots for lasting storage.

That some of the fat is immediately utilized by tissues is indicated by the fall of the respiratory quotient and the appearance of ketone bodies in the blood and urine following a fat meal. It appears that the anterior pituitary exercises control over this process. This was shown by Burn and Ling (13).

A few investigators have shown the presence of a hormone ("ketogenic principle" of the anterior lobe) in the blood after a fat meal.

That the liver absorbs part of the ingested fat is known from the fact that this organ which normally contains about two to four percent fat, shows higher fat content, as much as twenty percent, a few hours after a meal; when "earmarked" fat is fed the liver fat shows characteristics of the earmarked fat.

THE TRANSPORT OF MOBILIZED FAT

As to the discharge of fat from the depots, we know that in starvation, as much as ninety percent of the energy required for the maintenance of life may be derived from fat. As organs and tissues where this fat is oxidized normally contain but

small amounts of fat, most of it has to be transported to them from the fat depots. In lactation, fat appearing in the milk is brought by the blood to the mammary gland and not produced in the gland.

Little is known about the mechanism of fat mobilization. Certainly, the endocrine and nervous systems are intimately involved and it is reasonable to suppose that the mechanism is more a general cellular function than a function of some specific organ.

As to the transport of mobilized fat in the blood, we know that apparently, in starvation there is a delicate adjustment of the amount of fat removed from the depots to the amount of fat required for energy consumption, the hungry tissues absorbing mobilized fat from the blood at about the same rate as it pours into the blood from the depots.

In certain pathological conditions fat mobilization regularly involves a higher concentration of lipids in the blood as in the case of fasting animals poisoned with phosphorus or phlorizin and rabbits following repeated bleedings. On the other hand, fat mobilization in thyretoxicosis and fever is usually accompanied by a lower than normal blood lipid level.

Fat mobilization may take place at normal or even subnormal blood lipid level and endogenous hyperlipemia may be present

without excessive discharge of fat from the depots.

As to the transport of mobilized fat from the blood to the tissues, we believe that the liver apparently acts as a reservoir for excess blood fat, be it ingested or mobilized fat; it removes fat from hyperlipemic blood, and releases fat into the blood when the blood lipid level tends to drop below normal. During its temporary retention in the liver, the mobilized fat is probably desaturated and phospherylized (transformed to lecithin) in preparation to utilization, as occurs with ingested fat. Agents preventing phosphorylation --indo acetate or adrenelectomy-- prevent fat accumulation in the liver in phosphorus poisoning.

In starvation, either fat goes directly to "hungry" tissues or else the liver is able to dispose of the fat carried to it quickly. In phosphorus and phlorizin poisoning, much fat may accumulate, as much as twenty percent of the weight of the organ. In starvation, a man of average weight secretes daily at least thirteen to fifty grams of lipids into the lumen of the bowel, with a reabsorption of eleven to forty-eight grams into the chyle system, representing about six to twenty percent of the total mobilized fat.

THE FAT DEPOTS

The largest internal fat depots are located in the mesenterium (omentum), in the perirenal, subperiteneal, pericardial

and retrobulbar spaces, around joints, between muscles and in the canine fossa; most of the subcutaneous fat is found in the abdominal wall, lumbar regions and buttocks, but fat is normally present in all other subcutaneous regions except in the eyelids, penis, scrotum, and scalp.

As to the histology of the fat tissue, we know that there are closely packed fat cells with a few scattered small fibroblasts, wandering cells, and mast cells; collagenous fibers and elastic network run in all directions between fat cells; there is a rich network of capillaries and vegetative nerve fibers. The fat tissue is loose, irregularly arranged connective tissue in which fat cells have gradually crowded out most of the other elements.

The fat cells seem to originate through a transformation of the fibroblasts near to the capillary wall. First, a few small fat droplets appear in the protoplasm of the fibroblast; the droplets rapidly grow in size, gradually fuse into a single large drop pushing the nucleus to the periphery, stretching the protoplasm and reducing it to a thin membrane. Maximow (14) states: "It is possible that fat cells arise not from fully differentiated fibroblasts but from undifferentiated mesenchymal cells. This would agree with the fact that new fat cells always appear along the small blood vessels which are known to be accompanied by many cells of undifferentiated mesenchymal nature."

Sympathetic innervation appears to promote mobilization of fat from the depots, parasympathetic innervation would promote deposition of fat into the depots.

As to the chemical constitution of fat tissue, we know that the average fat tissue contains about ninety percent fat and ten percent water. Water content may be as little as seven percent and as high as forty-six percent.

The depot fat of men who have lived on mixed diets contain about five percent stearic acid, fifteen to twenty percent palmitic acid, and sixty-five to eighty percent oleic acid. Other lipids --cholesterol and cholesterol esters (about 0.2%), phospholipids, and free fatty acids or soaps are found in fat depots. Of enzymes, diastase, dehydrogenase, the esterases and true lipase have been demonstrated in fat tissue. The protein content of subcutaneous fat tissue is about 4.4% of the dried tissue.

The tissue fat, that is, the fat contained in tissues other than the fat depots, is largely made of bound fat; the amount and constitution of tissue fat is fairly constant in every organ, with the exception of the liver and muscles, regardless of the nutritional state, and amounts to about five to ten percent of the dry weight of the organ.

As to the metabolism of fat tissue, it was earlier thought that fat tissue takes little part in the production of body heat. Ruska and collaborators (15) however thought that fat tissue con-

sumes two to three cubic millimeters of oxygen per milligram of protein per hour, which amounts to about ninety percent of oxygen consumption of surviving liver tissue per milligram of protein.

There is conclusive evidence that at least one metabolic process, glycogen formation, may extensively occur in the fat cells.

It has been demonstrated that fat tissue which is normally practically free of glycogen, contains large amounts of glycogen --up to seven percent-- a few hours after an excessive carbohydrate meal, especially when the meal was given after a period of fasting. Thus, it can be concluded that after extreme carbohydrate intake, the fat cells take up glucose from the hyperglycemic blood, synthesize it into glycogen, and then transform the glycogen into fat.

Other authors have demonstrated that the fat cell is capable of performing the synthesis of fat from glucose as well as the transformation of fat into glucose. It appears that insulin promotes the accumulation of glycogen in the fat tissues, although the transformation of fat into glucose is unproven.

PATHOGENESIS

ALTERATION OF CALORIC BALANCE

As Coombs (16) has suggested, all authorities agree that there is one fundamental cause for all forms of obesity, namely, that the energy intake is greater than the output. Although several factors may modify the condition, there is no escape from the fundamental law that obesity can only be caused by the ingestion of food in excess of the individual's needs.

It is true that excess calories may be stored to some extent in the form of proteins and carbohydrates, but the capacity of the body to hold these substances is ordinarily limited to a few hundred grams.

INTAKE

In view of the fact that continued positive caloric balance is accompanied by fat deposition, a study of the caloric equilibrium appears to be a logical approach. Accordingly, the obese person differs from the normal in that his caloric intake is higher than his caloric output, while normally intake and output are balanced.

But in studying this thusly, we must consider that (a) obese individuals do not accumulate fat persistently. They gain weight for a time, then they maintain that for a time. The period of

gain in weight has been termed by Rony (17) as the dynamic phase; the periods of maintained weights as the static phase. Caloric balance is said to be positive in the dynamic phase, but is equal in the static phase. The conception that obesity is due to positive caloric balance is useful in explaining how a patient reached excessive weight, but it doesn't inform us as to why he maintains it, why he resists attempts to reduce it to normal, why he tends to regain it after a successful reduction. So, the caloric approach is applicalbe only on the dynamic phase of obesity.

(b) The fact that caloric balance is positive in the dynamic phase of obesity does not necessarily imply that a positive caloric balance is the cause of that phase, for the caloric balance is known to be positive in growing children. Studies of the caloric metabolism in fever revealed how the disturbed mechanism of temperature regulation junctions in fever; but the cause of the disturbance is something different and is not revealed by this approach. (There is a retention of calories in fever.)

A positive caloric balance may be regarded as the cause of fatness when fatness is artificially produced in a normal person by forced excessive feeding or forced rest or both. But obesity ordinarily develops spontaneously; some intrinsic abnormality seems to induce the body to establish a positive caloric balance

leading to fat accumulation. Positive caloric balance would be a result rather than a cause.

In a discussion relating to the intake and output of calories, it is quite necessary that we review rather briefly the physiology of hunger. As many have defined it, hunger is an intermittent or periodic unpleasant sensation of tension or pressure, a hollow or empty feeling in the epigastrium which may be accompanied by more or less headache, weakness, nausea, dizziness, and nervous irritability. Appetite is defined as a pleasant desire for food which depends on a previous acquaintance with the food in question and is accompanied with memory impression of sight, taste, and smell of certain foods which have proved palatable. One can be hungry and have no appetite, as when angered or worried, or the food offered may be distasteful or repulsive. Appetite becomes weaker and finally almost disappears after the first three or four days of continued starvation in spite of sustained hunger pangs. On the other hand, after hunger is satisfied by having eaten enough, appetite may be aroused by some specially favored food.

The fundamental initiation of the hunger contractions is inherent in the gastric neuromuscular apparatus, for it was found that hunger contractions, albeit at longer intervals and with less vigor, occur in stomachs completely isolated from the brain and spinal cord. The afferent impulse of contraction arises by

stimulation of the sensory nerve endings of the vagi in the gastric submucosa or muscularis. The primary hunger center consists of the sensory and motor nuclei of the vagus nerves in the medulla oblongata. From this center stimulating motor impulses pass via motor neurons of the vagi to the gastric muscles; inhibitory motor impulses pass through the splanchnic nerves and visceral sympathetic ganglia. There is a higher hunger center and relay station in the thalamic region of the interbrain, as indicated by the presence of hunger manifestations in decerebrated animals.

Conditioned stimuli undoubtedly play some role in the production of the sensation of hunger and even more in that of appetite. When a hungry individual sees or smells good food, the gastric hunger pangs become more intense although there is no change in the amplitude of the gastric hunger contractions. Carlson (18) states that this is due to a "central reinforcement." Mild hunger contractions do not enter consciousness as pangs of hunger if the individual's attention is diverted. Appetite may also be intensified or weakened by habit and training, that is by artificial conditioning. This is true insofar as selective appetite is concerned, for one can develop an appetite for foods formerly disliked. The general appetite may be somewhat a matter of habit but, as a rule, it is quite resistant to training.

Fullness and satiety is the warning to stop eating. Generally, the hungrier we are, the more food we require to produce

the feeling of satiety. Satiety is a more complex feeling involving besides the sensation of fullness, taste and smell memories of the consumed feed; it is more subject to cerebral influences. Booth and Strang's theory (19) as to the mechanism involved is: (a) the extra heat production represented by the specific dynamic action of the meal leads to an elevation of skin temperature; (b) this causes a sensation of warmth; (c) this gives a warning to cease eating. However there seems to be considerable evidence lacking in the support of this.

Carlson (18) states that "the gastric hunger mechanism is primarily automatic or independent of blood changes as well as of nervous influences, but in the normal individual, chemical changes in the blood as well as nervous impulses augment or decrease this primary automatism in a way to correlate it with the needs of the organism."

Factors influencing the automatic mechanism are: (a) a lessened amount of available sugar for use of the tissues, especially in hyperinsulinism; (b) the appetite may be depressed by deficiencies in the thyroid, adrenals, and pituitary; (c) rapid growth has a stimulating effect on appetite; (d) the vitamin supply available for the body is another factor.

As to the hunger mechanism in obesity, a great deal has been said. Conclusions have been quite varied. Increased appetite and feed intake of obese subjects is at least in part the

result rather than the cause of obesity. It is known that the total resting heat production of obese individuals is usually higher than that of normal persons, in proportion to their greater body surface. This results in a high maintenance energy requirement which is conducive of a high level of appetite; thus, in marked obesity the caloric intake is bound to be high as a sequel of overweight. Especially in the static phases of obesity the increase of caloric intake over the average normal intake may be entirely of this origin.

In many cases (strenuous work, thyrotoxicosis), increase in caloric intake is secondary following a primarily increased caloric output; as such it does not, as a rule, exceed the need that created it, and does not result in obesity. If the increase in appetite is primary in origin, that is, independent from the actual caloric output, it is likely to result in fat deposition. The normal person's ability spontaneously to adjust his caloric output to variations in his caloric intake is limited; therefore, when a primarily increased appetite greatly increases caloric intake, the output may remain at or near to the previous level, which necessarily leads to fat deposition. But, we might ask, what is the origin of the primarily increased appetite? Why does the obese person (in the dynamic phase of obesity) eat independently from his caloric requirement? What is wrong with the

mechanism that normally adjusts appetite to caloric output? What part of this mechanism is disturbed: the peripheral neuregastric hunger apparatus, or its chemical, glandular or cortical control? All these questions come to mind when one attempts a solution of this phase of the problem.

As suggested above, Booth and Strang (19) have a rather attractive theory about this: (a) the primary abnormality consists in a delay (diminished abruptness) of the specific dynamic action of food; (b) this leads to a delay and a lessening of the temperature elevation of the skin following a full meal; (c) this results in a delay and lessening of the general sensation of warmth which normally serves as an important element of the feeling of satiety; (d) the warning to cease eating being delayed, the subject continues to eat until he experiences warmth; (e) in the meantime, he has consumed food in excess of his maintenance requirement which leads to fat deposition and obesity. Many criticisms have been made of this however. In the first place, the theory of normal satiety is a questionable one. And as to the warning warmth offers, it is well to note that patients were required to eat as much as possible. Were the skin temperature so important, one would expect the obese to eat until they showed as high a skin temperature as did normal controls. As it was, the obese patients had stopped eating before reaching a normal elevation of temperature, which indicates that something else furnished the main

warning element. And as to this lack being the fundamental defect, it is well to remember that forty-three percent showed "normal types" of temperature curves, while three out of nineteen (sixteen percent) showed curves of the "obese type." This would indicate that the suggested mechanism does not in itself lead to consumption of food in excess of the maintenance requirement, nor does its absence necessarily prevent consumption of such amounts of food.

Bram (20) has thought so strongly about the deranged hunger mechanism as being the etiologic agent that he has prescribed one to two grains of U. S. P. powdered digitalis leaves three times daily, preferably at meal time with favorable results. This is sufficient to reduce the appetite by producing definite slight nausea but no vomiting, thus curtailing the capacity of the patient to eat.

Conditioned stimuli play some role in this hunger mechanism of obesity. In normal individuals, appetite and satiety are intensified or weakened, to some extent, by habit or training. To what extent this occurs in obese persons is a problem. Is it acquired habits and training or is it some intrinsic, unconditioned stimulus? Johnston and Newburgh (21) are in favor of the former theory, as we shall speak more about later. But as to this theory: (a) most of us know how difficult it is to improve by training the appetite of "the child who won't eat." Removing of any sub-

acute or chronic infection may make good eaters. In two hundred cases, Rony (17) found twenty-eight who were more or less underweight until they were eight to sexteen years of age when their appetite improved and they began to gain weight; (b) sudden increase of appetite and weight in adults is often accompanied by objective findings, as in menstrual disturbances, pregnancy, hypoglycemia, etc.; (c) a "craving for sweets" (carbohydrates) is particualrly resistant to intentional inhibition. There may be some organic change, as the craving of calcium in parathyroidectomized rats; overindulgence in sweets in hyperinsulinism; selective anorexia (aversion to certain foods) often due to a food allergy as propounded by Stroh (22); (d) there are few who "deliberately disregard the warning." Rather they fill up to capacity because they feel no early warning. Therefore it may be more probable that mental make-up and imitation or training are not ordinarily factors of prime importance in appetite and satiety levels in obesity. It follows, according to some authors, that anomalies of the caloric intake in obesity must be inherent in unconditioned factors of the appetite mechanism.

Again, as Harrington (23) has expressed, appetite is not too accurate a guiding post in this "search for truth" since (a) standard diets, so-called, contained 1.5 to 2.0 calories per gram; (b) bulky diets were given, omitting concentrated foods and em-

phasizing fruits and vegetables, in which there wa 1.0 calories per gram and on which all subjects lost weight; and (c) a concentrated diet, including cream, butter, sugar, etc., was given, in which there was 2.5 calories per gram and on which all gained weight.

LUXUSKONSUMPTION

There has been considerable discussion about the veracity of the theory of luxuskonsumption in which the intensity of metabolism is stimulated by generous (excessive) feeding and depressed by meager supplies of food. As Grafe and Koch (24) and Zuntz (25) have reported, it is true that the oxidative (basal) rate is greatly depressed by prolonged severe underfeeding for, as the latter showed, the decrease might amount to as much as thirty percent of the normal value. The organism does them possess a mechanism that retards the destruction of body tissues when it has to contend with starvation. But this phenomenon seems to bear no relation to Grafe's concept that the lean organism is so because it overoxidizes an otherwise adequate supply of food or that adiposity represents underoxidation. Careful studies of Boothby and Sandiford (26) have demonstrated that the basal metabolic rate of an obese person is normal.. Grafe (27) has not presented any data to support his contention that continued superalimentation is capable of causing the oxidations to proceed

at a rate greater than normal. Wiley and Newburgh (28) studied the responses of a thin person by using a method for determining total heat production for any desired length of time and found no evidence that either basal or total metabolism was stimulated by supperalimentation.

OUTPUT

Having discussed alterations in caloric balance from the standpoint of intake, let us now review the material that deals with the output of calories. We know that the twenty-four hour total caloric output is the sum of (a) the resting heat production, (b) the specific dynamic action of food, and (3) the heat production connected with muscular activity.

BASAL METABOLISM

A person lying motionless and relaxed twelve to fourteen hours after the last meal, at ordinary room temperature, is considered to be in the resting state of metabolism. The heat production per square meter of body surface is generally accepted as the measure of the resting heat production of an individual; the hourly basal metabolism at the age of twenty to fifty amounts to about thirty-nine calories per square meter for men and thirty-seven calories per square meter in women.

Although Grafe and Koch (24) claimed that in the normal man

caloric overfeeding is followed by elevation of the resting metabolism above the original level, other workers can't corroborate this. Duel, (29) the Sandifords, and Boothby showed a variation in one of their own metabolisms of from 60.8 to 80.9 calories per hour (a basal metabolic rate of from minus twenty-one to plus nine) with a variation in nitrogen intake of from 0.24 to 36.2 grams. But Kleitman (30) expressed the opinion that the alteration in the rate was a function of both the protein intake and the total caloric value of the diet. Johnston and Maroney (31) showed the expected fall witha lowered intake and a prompt return to normal with an increased intake. An amount of food on which gain in height and weight may be promoted for a period of months may be accompanied by a basal metabolism considerably below the normal. This may then be increased, though but slightly beyond normal, by an increase in protein, the total number of calories being nearly constant. So the latter's conclusion is that caloric over-feeding does not cause an increase of basal metabolism unless it includes protein over-feeding. Also, there is definite lowering of basal heat production evident in subjects on submaintenance diets. As Strang and Evans (32) have pointed out however, the obese do not require the protective depression of the energy exchange to the extent it occurs in the non-obese, because the large stores of fat are so readily available for energy consumption that

he is not in a state of undernutrition.

As fat tissues are metabolically active, according to Rony (17), part of the excess energy is undoubtedly produced by the excess fat tissues of the obese. However, this part probably does not exceed one-tenth of the excess energy, the rest being produced by other tissues of the organism. Since the protoplasmic mass of the other tissues increases little when a person becomes obese, the resting heat production per unit protoplasm mass has to be higher than normal in obese subjects and this was demonstrated in the mouse by Benedict and Lee (33). Whether all tissues participate equally in the excess energy production is not known; probably, much of the energy is produced by the heart and respiratory muscles which work at an increased rate in the obese subject even in the resting state.

There is considerable evidence to point out that obesity is not caused by lessened expenditure of energy in the basal state. Strouse, Wang, and Dye compared basal metabolic rates of normal persons with those of subjects who were underweight and overweight. They found practically no differences per square meter of body surface. The occasionally moderately low basal metabolic rate exhibited by an obese person does not contribute to the understanding of obesity, since equally low rates are encountered as frequently among healthy persons.

Bernhardt (35) made a study of one hundred obese patients and determined that sixty-six percent had basal metabolic rates within the normal, twenty-five percent had rates somewhat elevated, and ten percent had rates somewhat decreased. Of Boothby and Sandiford's ninety-four obese patients (26), ninety-five percent had rates between minus fifteen and plus fifteen. Only four had rates below fifteen percent and only one below twenty percent.

So, it seems that basal metabolism is not abnormal to the extent of playing an important role in the alteration of caloric balance and the development of obesity.

THE SPECIFIC DYNAMIC ACTION OF FOOD

Food intake immediately increases the resting heat production, the increment being termed the specific dynamic action of food. It has been pointed out that the ingestion of proteins results in a rise of oxygen consumption up to forty-six percent. However this protective mechanism against overnutrition is believed to be deficient in certain types of obesity.

As Dock (36) has pointed out, at least eighty percent of the specific dynamic effect is due to increased heat produced by the hepatic cells during protein digestion in rats. If something upsets this metabolism the patient might gain weight except for the fact that the appetite would direct him not to eat so much since he needed less. So it is this author's impression that

lessened specific dynamic effect of food is not the cause of obesity.

Again, the effect of the individual food elements, particularly protein, on the basal metabolism has been discussed by Wang and others (34), and these investigators found no significant change in the basal metabolism when the protein intake was varied from 0.6 to 2.0 grams per kilogram of body weight. Johnston and Maroney (31) suggested that the discrepancy between their results and those of other investigators who had related a rise in the metabolism following an increase in nitrogen intake might be due partly to variations in caloric values, to short periods for adjustment, and to abnormally large quantities of protein ingested. And it is the definite impression of the latter authors that maximal elevation of the basal metabolic rate is a result of a high intake of calories and a high intake of protein, and that the addition to an adequate diet of a high increment of protein was followed by a marked increase in basal metabolism.

Certainly, it is not an economy of food that produces obesity for as Newburgh (28) has pointed out, the utilization of the dietary calories, nitrogen, and fat by the obese persons was 87, 84, and 83 percent respectively. For the controls, the corresponding values were 88, 86 and 89 percent.

CALORIC EXPENDITURE IN CONNECTION WITH MUSCULAR ACTIVITY

As Goldzieher (37) has observed, any expenditure of physical energy is predicated upon the oxidation of food material which otherwise would be converted into fat. The relationship between energy expenditure and metabolism is far from simple, however. It has been shown that the same amount of physical labor requires varying amounts of oxygen in different people and noticeably smaller amounts in the obese, according to this author. Another estimated a saving of energy in the obese to be about twenty-eight percent. But as Newburgh (28) has observed, and I quote: "In no case did we find anything unusual about the total metabolism. These patients certainly did not exhibit any capacity to live at a lesser expenditure of calories than normal persons. In fact, the total expenditure was large and indicated that they produced considerably more heat than persons of the same height, age, and sex whose weight was normal." Moreover, an obese subject requires more energy to perform a given peice of work than does a normal control, according to Lauter (38). Also, DuBois (39) has concluded that the average obese subject is rather less economical in his heat production at work than the average normal person, and that there is no special "negative phase" to compensate for heat losses during work, as others have supposed. And as Bernhardt (35) has stated, obese patients usually show about the

same increase of metabolic rate as do normal people. When doing heavy work, however, they show a higher increase and mostly a longer lasting increase than do normal people.

The question whether the average obese subject generally works less than the average normal person, does not lend itself to experimental study, neither are statistical data available which would serve as a basis for a fair comparison.

In three hundred and fifty cases that Greene (40) studied, inactivity occurred simultaneously with a gain in weight in 67.5% of cases. A history of an increase in food intake, on the other hand, was obtained in only 3.2%. A long illness or convalescence produced the inactivity in 64.3%.

This of course shows that with lessened muscular activity, the caloric intake remaining as before, there is an increase in "caloric retention" within the body, obesity resulting.

WATER BALANCE

It is repeatedly encountered that periods are had during which patients fail to lose weight, even though the calories of the diet are far less than the dissipation of heat. It has been shown that this failure to lose weight when patients are being underfed is due to a retention of water. The greater hydration of cellular protoplasm is the result of colloid chemical changes.

Contributing factors are: the retention of sodium chloride, and the deposit of glycogen, the formation of which from glucose is predicated upon water retention. Certainly, endocrinologic responses lead to the retention of water also, especially where the pituitary gland is involved.

Thus, after a review of the enormous mass of experimental and clinical observations on the total metabolism of the obese, it must be concluded that no qualitative or important quantitative difference between fat and normal individuals has been proved, (that is, as in appetite, basal metabolic rate, specific dynamic action, efficiency of muscular work).

THE ENDOCRINE SYSTEM

In interpreting the coincidence of endocrine disorders and obesity, the following relations should be considered:

(a) The co-existence may be incidental, that is, without any causal or intimate relationship. One is likely to find a certain number of glandular disturbances in any large group of patients, whether obese or not. However, the high incidence in obese patients indicates that, in the majority of cases, some close relationship must exist.

(b) Glandular disturbance might be a sequel of obesity. Kraus (41) asserts that histological pituitary basophilia which he found in a number of cases of "constitutional obesity" is of a compensatory nature, secondary to the "fat metabolism disturbance." Zondek (42) described a type of obesity characterized by signs of increased thyroid activity, the latter representing, in his opinion, a compensatory response to the obesity. He found this condition mostly in middle aged women showing a moderate hypertension, a rapid pulse, slight enlargement of the thyroid, scant menstruation, and shortness of breath; the basal metabolic rate was not elevated. The subjects were usually obese years before these signs appeared, indicating, according to Zondek, "that the body endeavors to counteract the metabolic disturbance that leads to obesity by enhanced activity of the thyroid gland." These

contentions are, of course, entirely hypothetical. On the other hand, it is known that menstrual disturbances, such as amenorrhea or oligomenorrhea, occasionally disappear in connection with the successful dietary treatment of obesity. This suggests that a menstrual disturbance may be a sequel of the obese state in some cases, although the mechanism of this effect is not understood. Another example is in diabetes in which there is the presence of a diabetic predisposition. This may develop in obese subjects as a result of overeating and possibly of fatty infiltration and subsequent atrophy of the pancreatic islets.

(c) The coincidence might be due to the topographical relationship of the structures involved. The hypothalamus in the midbrain which has a close embryological, anatomical, and functional relationship with the hypophysis, may be the site of pathological processes that lead to obesity (hypothalamic). By extention or otherwise, such processes may secondarily involve the hypophysis or vice versa. In this way a glandular disturbance may occur without necessarily being a causative factor in the obesity of the subject.

(d) The coincidence may be due to hereditary linkage of genes transmitting obesity with genes transmitting a glandular disturbance. The association of obesity with glandular disturbances in

the Laurence-Biedl syndrome and in Dercum's disease might conceivably be due to linkage.

(e) Glandular disturbance may be the cause or a causal factor of obesity, by virtue of hormonal effects upon certain of the processes that determine the deposition of fat in the body.

THE THYROID GLAND

It is generally agreed that manifest thyroid deficiency is rare in obesity. In Reny's series (17) of two hundred and fifty consecutive cases of obesity, conclusive signs of hypothyroidism were found in one juvenile and three adults, that is in 1.6%. Some authors have designated cases of obesity with manifest hypothroidism as "thyregenic obesity," meaning that obesity in these patients is due solely or mainly to thyroid deficiency. Other authors have questioned the pathogenetic role of thyroid deficiency even in these cases in view of the fact that patients with severe myxedema may remain lean. Falto (43) has offered the opinion that hypothyroidism merely creates a predisposition to obesity in that it leads to a decrease in caloric output (by lowering the basal metabolism and the impulse to muscle activity); but it depends on another factor, the appetite (which determines caloric intake as we have already seen), as to whether or not actual obesity follows. The appetite, according to Falta (43), depends mainly on the function of the pancreatic islands. Slight rather

than severe thyroid deficiency would be conducive to obesity because "in slight degrees of thyroid gland insufficiency, the balance between the thyroid function and the function of the pancreas is disturbed in favor of the latter, and thus is furnished the impulse for the origin of obesity while with a severe disturbance of the function of the thyroid, often all vegetative functions are highly diminished, and therewith the ingestion of food and the appetite are restricted."

So, evidently the lessened caloric output of hypothyroidism leads to obesity only when the appetite stays at a relatively high level. But the contention that this depends on the pancreas is speculative. Neither is the statement that the appetite suffers relatively more in severe than in mild thyroid deficiency generally true; the fact is that patients with sever myxedema may be markedly obese, and patients with mild thyroid deficiency may lose considerable weight. Whe the appetite mechanism is relatively resistant to the depressive effect of thyroid deficiency in some individuals, and relatively sensitive in others, is not known, but clinical observation indicates that an originally streng appetite is likely to remain relatively unaffected even in marked thyroid deficiency, while an originally poor appetite may be further weakened even in mild thyroid deficiency.

And then too, as Newburgh (28) has pointed out about the basal metabolic rate test itself, a low rate is not so significant

since the standards are probably from five to ten percent too high. He states that some persons who are entirely at home in the metabolic lab have rates year after year that are twenty or even twenty-five percent too low, according to the standards, and still they exhibit the attributes of health and have not become obese of myxedematous. Even a response to treatment does not always establish the diagnosis, for the thyroid hormone stimulates the metabolism of all the cells and their augmented activity may well correct symptoms that were daused by sluggish fundtion for any reason.

Also, it is believed by most men that the organism, ideally at least, obtains the amount of food that well replenish its losses and when the outgo lessens, the appetite diminishes proportionately. MacKay and Sherrill (44), in experimenting with thyroidectomized rats and controls with thyroids intact, whowed that the controls gained more weight over a peroid of time than did the thyroidectomized animals, both being on the same diet, and that much more fat content was in the bodies of the control rats than was in the bodies of the rats deprived of their thyroid. From this study, it seems that athyrea actually seems to cause wasting of adipose tissue.

Plummer (45) studied two hundred myxedematous patients and found that 61.5% were overweight, but that in these, the greatest excess weight corresponded to the least depression of metabolism,

and those patients whose basal metabolic rates were lowest weighed the least.

Again, that a low basal metabolism alone is not productive of obesity is evident from the cachexia in cases of Simmond's Disease, according to Barr (2). In many patients with myxedema, overweight is due to albuminous fluid and some authors have shown that the loss in weight following effective thyroid therapy can be accounted for by the loss of water and nitrogen in the urine.

Thus, it appears that the thyroid gland is not usually the fundamental cause for obesity.

THE HYPOPHYSIS

In a study of the relationship of the pituitary gland to obesity, it is discovered that some authors have taken up positions with one of the following extreme views: that after hypophysectomy or some similar treatment of the pituitary, (a) sequelae observed are due to the removal of the pituitary secretions, or (b) sequelae are due to injury of the hypothalamic nervous centers. As will be subsequently shown, it is probable that neither of these views is entirely tenable.

As early as 1887, several cases of obesity associated with genital underdevelopment --later termed "adiposogenital dystrophy"-- were described in conjunction with pituitary tumors. The report

in 1901 of a case of tumor of the hypophysis without acromegaly seems to have originated in the belief that hypopituitarism is a common cause of obesity, especially among children. However, he sited a number of cases of similar condition proved at autopsy in which poor nutrition was not uncommon. Thus, there is nothing in the original report to indica te that the obesity was anything more than incidental.

The primary seat of the tumor may be anterior, middle, or posterior lobes. Of the anterior lobe, chromophobe, eosinophilic, and basophilic adenomas may be associated with obesity and some form of genital dystrophy. In most patients with basophilic adenoma, obesity and genital dystrophy are elements of a peculiar syndrome which as a clinical entity was first described by Cushing (46). The obesity is the upper body or "buffalo" type; there is amenorrhea and hirsutism in the female, regression of the genitals and impotency in the male. Hypertension, osteoporosis, kyphosis of the lower cervical and upper thoracic spine, large bluish-red striae of the skin of the lower abdomen, pàlycythemia, hyperglydemia, glycosuria, and marked muscular weakness may be additional features. It occurs in both sexes, more in women, usually in adolescents or young adults. Cushing (46) attributed the enlargement of the trunk to excessive deposits of fat and reasonad that a localized adiposity could not arise from overeating but must

be a direct outcome of the disease of the pituitary.

Other conditions besides tumor --traumatic lesions or hypoplasia of the gland or changes in the neighborhood of the gland-- may give rise to this condition. Adiposogenital dystrophy may even be a functional abnormality which spontaneously disappears after puberty, according to some students.

Of 149 cases of adiposogenital dystrophy that came to autopsy (from the literature), one author classified twenty-one as "mainly of pituitary origin," with involvement of the anterior lobe in e eight, the posterior lobe in seven, and the whole gland in six cases. In sixty-three cases, both the hypophysis and the floor of the third ventricle showed pathological changes, while in sixty-five, the hypophysis was "intact or not seriously affected."

Asyndrome similar to Cushing's was found in cases of adrenocortical adenoma. Walter, Wilder, and Kepler (47) examined hypophyses in some cases of adrenocortical adenoma and found a number of basophilic cells in the anterior lobe that were normal. Also, patients with clinical pictures resembling Cushing's Disease were found t be suffering from carcinoma of the thymus, in the absence of basophilic adenoma. And, basophilic hyperplasia or adenoma was found in patients who did not exhibit clinical signs of Cushing's syndrome, or shewed only obesity or hypertension. Such observations have led Kraus to doubt the pathogenetic significance

of pituitary basophilia altogether; he (41) regards it as a consequence rather than a cause; obesity would be the primary disturbance, and basophilia a secondary response of a compensatory nature.

Cushing (48) believes that the syndrome of pituitary basophilism "is almost certainly due to a hypersecretory influence of some kind" and he and Thompson (49) have reported experiments which they believe support this view. On the assumption that the function of the basophilic cells is to manufacture gonadotropic hormones, and on the further assumption that basophilic adenomas produce excessive amounts of these hormones, they attempted to produce the Cushing syndrome in the rat and dog by continued injuctions of large amounts of pituitary gonadotropic extracts. Some of the sequelae they observed were different from the human syndrome but excessive adiposity always developed. Earlier, some investigators found that following daily injections for several months of a crude anterior pituitary extract, rats showed marked increases in weight resulting mainly from storage of fat.

According to Cushing (48), the obesity of adiposogenital dystrophy is entirely different in origin from the obesity of basophilic adenoma, the former being a deficiency effect due to inactivation of the hypophysis by compression, destruction, or hypoplasia. There is no crucial evidence to prove this however.

Newburgh (28) has made some interesting studies in this connection. In many of the patients that he observed, it was found that, if placed on the proper diet, the patient lost weight as predicted: this indicated that the energy exchange was entirely normal and this he believes, is strong evidence that the patients had become obese because the inflow of energy had exceeded the outflow. Yet, the return to normal weight was found to alter little the appearance of the unusually prominent chest and abdomen and did not reduce their size any more than that of the extremities. Hence the disproportionate enlargement of the trunk could not have been due to obesity. Actually, the decalcification of the skeleton, a common finding in Cushing's syndrome, had so thinned the vertebrae that the spine had collapsed (in one case), with resulting kyphosis and shortening to such an extent that the ribs had been elevated anteriorly until they were horizontal. This had swung the manubrium forward and upward. The anterior abdominal wall necessarily also moved forward. Likewise, other patients were disfigured by protruding abdomens, barrel chests, short necks, kyphosis, and wasted musculature.

Albright, Parson, and Bloomberg (50) studied some women with Cushing's syndrome and they also emphasized the apparent girdle obesity. But they discovered this "more the result of a relaxed abdominal wall and crushed vertebrae (decalcification) than of

actual fat." They pointed out that there is a striking destruction of body protein in these patients, as evidenced by continued negative nitrogen balance. Thus, there is a great wastage of musculature and the abdominal muscles are no longer able to resist the intraabdominal pressure.

It appears to me that with evidence of this sort, many cases of regional obesity are explained that formerly were explained by way of some vague endocrine disturbance. As will be shown later when this question is specifically approached, however, there does seem to be some definite relationship between glandular abnormalities and regional obesity that cannot be easily explained by Newburgh's theory of obesity alone. No doubt there is some obesity obtained in both sets of circumstances.

Smith (51) showed that in rats, removal of the hypophysis did not cause obesity but rather loss of weight, atrophy of the thyroid, adrenal cortex, and the sex organs, and cachexia. But, if and when the hypothalamus was injured by injection of chromic acid, obesity developed regularly after operation. Thus, it is the contention of many that it is no longer justifiable ever to attribute obesity to hypopituitarism until its presence has been firmly established by long study and concomitant exclusion of the presence of other lesions.

Some have attempted to associate hypopituitarism with a low basal metabolism, as we discussed earlier, and thus account for

obesity on lessened outgo, and resultant accumulation of fat. Goldzieher (37) believes there is a fat metabolism or ketogenic hormone that is considerably decreased in pituitary disease. This inadequate production of the calorigenic hormone accounts for the low basal metabolism and so there is decreased oxidation and fat accumulation, water retention due to a disturbed salt, water metabolism, and hypoglycemia with an abnormal appetite and craving for carbohydrates and a commensurately increased caloric intake.

Thus, it seems to be within the realm of possibility that the master gland, so-called, may have some close relationship to the etiology in its own right. However, before we attempt to draw conclusions relative to the position of the pituitary, we should discuss the relationship of other endocrine glands to obesity.

As Barr (2) has pointed out, along with the changes in the pituitary with basophilic tumors, there have been concomitant changes in the adrenal cortex, so that perhaps some responsibility for "the cause" can be placed here.

THE ADRENAL CORTEX

As many have observed, the adrenal cortex is no doubt an unusual offender in the matter of producing obesity. However, if at all, as Reny (17) has pointed out, in an adrenocortical syndrome, one has obesity usually of the upper body type. The

mechanism whereby obesity is produced is not known and it has been impossible to reproduce the syndrome by the administration of adrenal cortex extract in animals. However, it has been observed that surgical removal of the affected adrenal has been followed by a rapid loss of the excess weight.

It is quite possible that obesity in some of the fruste forms of Cushing's syndrome is of adrenocortical origin, but this has not been proven. Cortical adenoma or hyperplasia is, however, among the frequent postmortem findings in unselected cases of obesity.

Thus, it appears that the adrenals have little if anything to do with obesity, mainly because evidence pointing otherwise is so lacking.

THE GONADS

Primary hypogonadism.

The experience that castration may be followed by increased fat deposition has been utilized for many years by breeders who castrated domestic animals for fattening. The fattening effect is said to be similar in both sexes and mosy pronounced when the operation is performed before sexual maturity. Tandler (52) observed a number of adult Skoptzi that were castrated in childhood (Russian religious sect) and states that they fall into two types --the fat and the tall type. The fat castrate shows general-

ized obesity with predominant fat deposits in the lower abdominal region, mons pubis, hips, thighs, and breasts; the tall castrate may be underweight but shows noticeable fat deposits in the same regions.

A report of observations on five hundred actinocastrate women showed that within one year, two hundred gained more than five kilograms and one hundred and fifty showed no change in weight.

The effects of castration on regional fat distribution are probably due to a lack of sex hormones. On the other hand, the fact that in early hypogonadism, generalized obesity is of late appearance suggests that the generalized obesity may depend on some additional factor. It may be due to a secondary change in another endocrine gland, as in thyroid deficiency, adrenal cortex hyperplasia, or pituitary basophilia.

Secondary hypogonadism.

Hypoplasia of sex glands consequent upon disease elsewhere is the meaning of secondary hypogonadism. In that due to adiposogenital dystrophy and Cushing's syndrome, obesity is a regular feature. In that due to myxedema, acromegaly or chromophobe tumors of the hypophysis, there may or may not be obesity. That hypogonadism is not the cause of the obesity associated with secondary hypogonadism, is demonstrated by cases of adiposogenital dystrophy which in response to gonadotropic treatment, develop

sexually rapidly, but remain obese.

Puberty.

There is evidence of some regional fat distritution, expecially in the female, upon entering puberty. But changes in the body weight during this time follow no definite rule: puberty may be accompanied by a gain in weight in underweight children and a loss in weight in overweight children, while in others of normal or abnormal weights, no change occurs. Variations in other glands may be responsible however, so that probably there is only an indirect relationship between sexual maturity and fat deposition.

Pregnancy.

Apparently, the increase in fat deposition during and after pregnancy is due mainly to some endogenous factor that produces an increased appetite without a corresponding increase in caloric output. What this endogenous factor is remains obscure. It may be connected with changes in the ovaries (persistant corpus luteum, cessation of follicle maturation) or with some activity of the placenta or fetus. Or it may depend upon changes in other endocrine glands.

Climacterium.

The following drawn up by a medico-actuarial modality investigation shows the average body weights of adult men and women in four height groups at twenty-five to fifty-five years of age.

In Table III is shown that obese patients who will follow a low caloric diet for an adequate time will lose weight regardless of coexisting disease or circumstances associated with the onset of obesity.

Table III

Obesity began in association with--	No. who lost wt. on low cal. diet
Pregnancies	22
Illness	23
Impaired locomotion	15
Operations	10
Increased food intake	2
Chronic encephalitis	3
Myxedema	1
Hypophyseal tumor	1
Insufficient data or negative history	69

A very high percentage of patients gave a history of diminished activity while they were gaining weight and this would indicate that many cases of "endogenous" obesity are not so, according to Greene (40). Again, the development of obesity with pregnancy in twenty percent of cases demonstrates the value of the practice of prevention of excess gain. Adequate nutrition during a long illness or convalescence does not signify that a patient must become obese. The findings furthermore indicate that diminished metabolism is of little consequence in the etiology of obesity. The patients with myxedema may gain or lose weight.

A history of diminished activity with good appetite obtained from all patients who become obese after the development of a hypophyseal tumor. A history of diminished activity with good

appetite obtained from three of the patients who became obese after the encephalitis developed and two cases in which the encephalitis antedated the obesity were known to have followed low caloric diets and lost weight satisfactorily. Such indicates that encephalitic lesions of the hypothalamus played a minor role, if any, in the production of obesity in these cases. Lesions here were not important factors in the production of adiposity in our cases of coexisting obesity and diabetes insipidus or suprasellar tumor. It is difficult to detect any difference between 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, chronic encephalitis, myxedema, etc.

Ovarian dysfunction as an etiologic factor is doubtful in view of the fact that patients with the different menstrual disorders lost body weight when low caloric diets were followed.

In summary, it is evident, according to the figures, that inactivity occurred simultaneously with gain in weight in 67.5% of cases. A history of an increase in food intake, on the other hand, was obtained in only 3.2%. A long illness or convalescence produced the inactivity in 64.3%. Ovarian dysfunction as evidenced by abnormal menses or menopause was present in 50.6%.

The incidence of obesity in myxedema, pituitary tumor, and chronic encephalitis was high, but adiposity antedated the other malady in most instances. The number of patients who lost weight

equaled approximately those who gained weight after the onset of myxedema and pituitary tumor. After chronic encephalitis developed, loss of weight occurred approximately five times as frequently as did gain in weight.

Thus, we can conclude that endocrinopathies of various kinds, play only a "helping" rold in manifest obesity. Either the association is purely an indirect one throughout, or else, if there is a direct relationship, it is so "mid-center" in the mysteries that still enshroud the endocrine system as a whole that we are unable to accurately and finally put our finger on the details of the pathology so as to come up with the fundamental etiologic agent for obesity. Certainly, the evidence seems to point to the fact that endocrine disorders are quite closely tied in to our caloric equilibrium but just how remains unanswered in many respects.

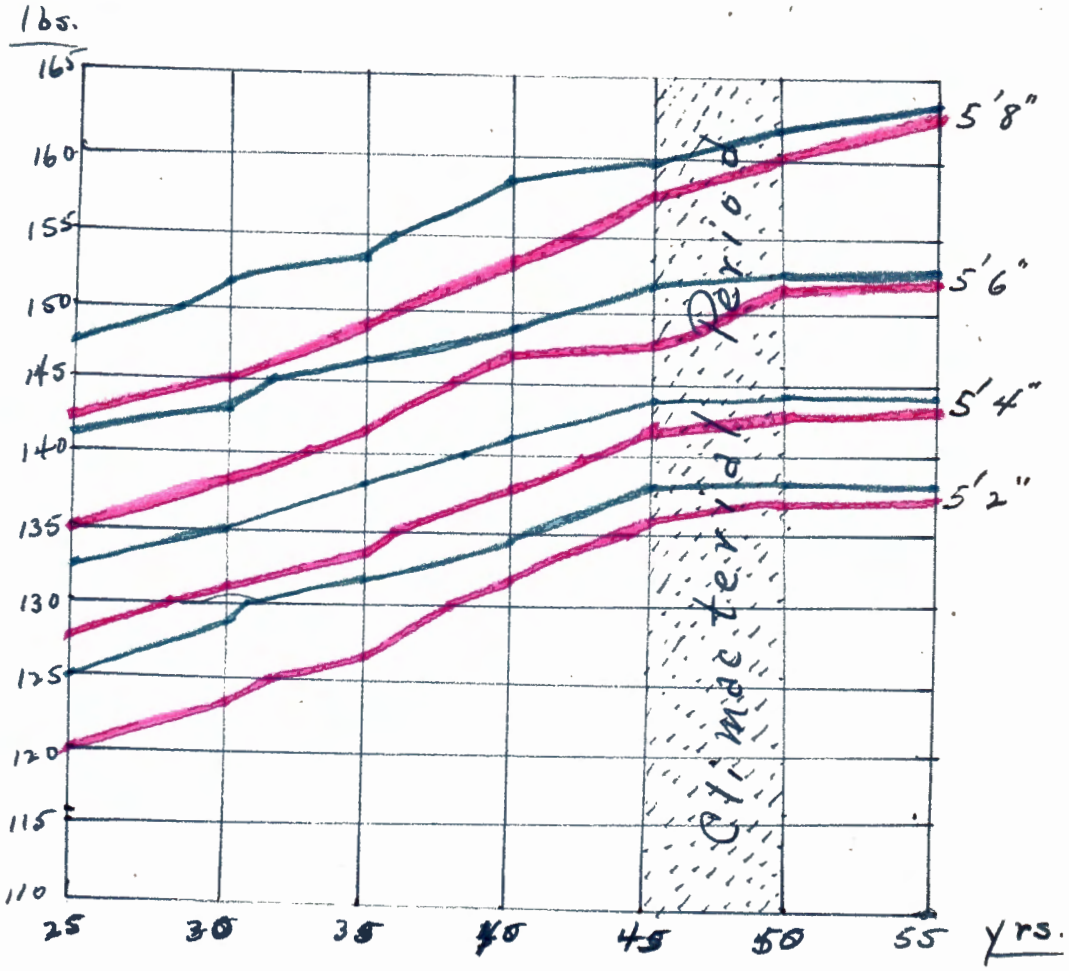
THE NERVOUS SYSTEM

That the nervous system is an integral part of our frame no one can deny. And that this system plays a very important role in the matter of our body weight can scarcely be refuted when the facts are reviewed. Certainly it has long been known that the "psyche" of our beings bears heavily on our health in its every aspect. It is known that there is some parallelism between fluctuations of our mental state and fluctuations in our body weight. This is true in the case of arteriosclerosis, senile psychoses, and general paresis as well as in other conditions. (Organic cerebral disease is usually associated with emaciation.)

AUTONOMIC SYSTEM

This part of the nervous system is the part most intimately associated with body weight. In this connection, Raab (11) has made considerable of the transport of fat, asserting that the transport from the blood to the liver normally is controlled by hypothalamic centers. He believes that: (a) a substance "lipoitrin" can be extracted from the hypophysis and that it causes a marked decrease of the neutral fat content of the blood when injected into experimental animals; (b) small amounts of this suffice to produce the effect when an injection is made into a

(Each curve is the average weights of about eight thousand women and thirteen thousand men respectively.)



It is seen that at twenty-five, the average body weight of men is consistently greater than that of women of the same height; the difference remains practically the same at thirty; it becomes slightly less at thirty-five; from forty on, the difference dwindles more rapidly, and at fifty the average weight of men

and women having the same height becomes nearly identical. Little or no change in weight occurs between fifty and fifty-five in either sex. Furthermore, it is seen that women maintain an almost even rate of gaining --0.6to 0.7 pounds per year -- between forty-five and fifty. So, women gain more weight during the climacterium than men of the same age but the diff erence is due to a decreased rate of gaining in men rather than to an increased rate in women.

Thus, the assumption seems reasonable that in both sexes, after the age of fifty, the natural tendency connected with ageing is to decrease the rate of gaining, and that this decrease, which in men begins already at forty, is postponed in women until after fifty, because of the appearance of some factor that acts against the effect of ageing on fat deposition. It may be due to a cessation of ovarian activity or to alterations in the anterior pituitary as we have already considered.

As Newburgh (28) states, the matronly figure, coming on after the menopause, is not due to "decreased sex gland, so that the secretion won't restrain the growth of adipose tissue," but is due to the less striving, more leisure time, and the feeling that now one should indulge oneself. At first, one still recognizes the signals that notify her that she has had enough, but she deliberately ignores them because she has had to "toe the mark" for so long, and from now on she is going to "humor herself."

Gradually, the warnings become so blunted that she continues to enjoy gustatory pleasures until they are finally displaced by the discomforts attendant on the ingestion of great excesses of food. This is the psychogenic aspect of obesity, and certainly deserves of our attention. A later discussion concerning this factor, as expressed above, will be attempted below.

THE PANCREATIC ISLETS

Much has been said about the pancreas and its insulin-secreting glands in connection with obesity. It is true that patients with hyperinsulinism are frequently obese. In such cases, the onset of symptoms of hyperinsulinism may coincide with the onset of symptoms of hyperinsulinism may coincide with the onset of obesity. The patients learn to relieve attacks (hypoglycemic) by taking carbohydrate; this in turn, is likely to produce a new attack causing the victim to take more carbohydrate food, and a vicious cycle keeps up until the subject becomes obese. However, in reading many case histories, it is discovered that patients have gained weight years before the onset of hyperinsulinism. Also, some with this, especially those originally lean, did not gain weight during the disease. So, it seems evident that hyperinsulinism causes obesity only in the presence of some predisposing factor. Actually, however, the incidence of hyperinsulinism in unselected cases of obesity is very low.

Clinical observations indicate that diabetes is more fre-

quent in the obese than in the non-obese individuals, and that diabetes is more frequent inthe family of obese subjects than in the family of non-obese subjectw. It is well established that obesity often precedes diabetes. Among 3094 patients of Joslin (54) 12.7% of the males and 67.4% of the females were five percent or more overweight at the onset of the diabetes; 78.5% of the males and 83.3% of the females were overweight before the onset. About fifty percent of the men and sixty percent of the women were at least twenty percent overweight at their maximum weight. Only 7.9% of the men and 6.3% of the women were five percent or more underweight.

No uniformity of opinion exists as to the basis or mechanism of the relationship existing here. The concepts that have been advanced are the following:

(a) Early, it was suggested that the primary disturbance may be a deficiency of the internal secretory activity of the pancreas; this would lead to an overproduction of sugar; the excess sugar would be promptly transformed into fat and deposited in the fat tissues, leading to obesity; later on, in some cases, the ability of the organism to transform glucose into fat would break down while overproduction of glucose would continue; this would result in an accumulation of glucose in the blood and diabetes. It appears now that this concept is of historical inter-

est only.

(b) Falta (43) believed that in obesity, the insular apparatus was hyperactive; diabetes would develop when the insular apparatus, after years of overstrained activity, finally became deficient. This is analogous to the change from hyperpituitarism to hypopituitarism thought to occur in the course of acromegaly.

That the insular apparatus is overactive in obesity is not supported by conclusive evidence, however. Then too, regarding the matter of insulin production tending to decline in the course of obesity, it can be said that the amount of available insulin is only one of several factors that determine glucose tolerance and it is possible that one of these factors is responsible for the decreasing glucose tolerance of ageing obese subjects. There is no direct evidence that obese subjects produce lessinsulin as their glucose tolerance declines. Futhermore, glucose tolerance has a tendency to decline with advancing age in non-obese subjects as well. (Rony - 17). So, Falta's contention regarding the connection of obesity and diabetes remains entirely hypothetical.

(c) The connecting link between obesity and diabetes may be the pituitary gland. It is asserted that a specific form of pituitary gland disturbance may cause diabetes and another specific form may cause obesity; simultaneous occurrence of the two changes in the gland would then produce both conditions in the

same person. The diabetes of pancreatectomized animals is partially or completely overcome by removal of the hypophysis; the anterior lobe contains a substance --diabetogenic hormone-- which is capable of producing hyperglycemia and glycosuria in animals; diabetes frequently develops in the course of acromegaly; the incidence of diabetes in children is the highest just before puberty in the overgrown child, and the incidence of diabetes in women increases at the menopause, that is, at a time when changes in the anterior lobe are known to occur and the pituitary gonadotropic hormone content inthe blood is high. So there are two types of diabetes, that of pancreatic origin and that of pituitary origin (acromegaly and Cushing's syndrome.) The majority of obese subjects who are diabetics show no signs of pituitary basophilia however, (or other pituitary disturbance), and there is no tangible evidence that both diabetes and obesity, or for that matter, either one is of pituitary origin.

(d) Another theory is that obese subjects develop diabetes as a result of overeating. According to Joslin (54), "...whenever and wherever conditions of life are easy, food abundant and relatively cheap over long periods and when large numbers of individuals become accustomed to partake of food in excess of their requirement for the expenditure of energy, the frequent development of overweight and diabetes is favored." But, in

view of the fact that only about five percent of all obese individuals become diabetics and that no one has succeeded experimentally in producing diabetes by overfeeding alone, Joslin (54) concluded that overeating results in diabetes only in the presence of a predisposition to the disease (usually inherited). But despite the same incidence of inherited diabetic susceptibility in non-obese and obese individuals, the latter would develop manifest diabetes more frequently because of the unfavorable effect of "overeating" on diabetic susceptibility.

It could be concluded that the proportionate composition of the diet, especially its carbohydrate-fat ratio, rather than the total quantity of caloric value, is of importance in that a low proportion of carbohydrate plus a high proportion of fat in the diet is conducive to diabetes in the majority of those individuals who have a predisposition to the disease. But, as we can readily see, the diet that the average obese subject commonly eats is rather high in carbohydrates, in the amount as well as in the proportion. Therefore, if Hinsworth's finding is valid for the obese subject with diabetic predisposition, the customary "overeating" of the obese would not be conducive to the development of manifest diabetes.

Rony (17) states that a low glucose tolerance may exist in obese persons for years without turning into manifest diabetes even when the caloric intake is sufficiently high to maintain

or increase the body weight. On the other hand, a reduction of weight by restricted food intake seems to have a decidedly favorable effect on "diabetic predisposition."

A low caloric, low carbohydrate diet also frequently influences favorable the manifest diabetes of obese patients, according to Rabinowich (55). He and others noticed that low carbohydrate diets usually improve the glucose tolerance in the obese diabetic while it impairs the glucose tolerance of the underweight diabetic; and Newburgh (56) pointed out that diabetes in the obese can often be cured simply by dietary reduction of weight.

So, it appears that in obese subjects diabetic predisposition is improved by low caloric, low carbohydrate diets, and aggravated by a high caloric, high carbohydrate diet. In this way, "overeating"of the obese may be a connecting link between diabetic predisposition and diabetes, that is, the reason that obese individuals with inherited diabetic predisposition develop manifest diabetes.

Our present knowledge concerning the relatinnship of obesity to hyperinsulinism and diabetes does not support the theory that an abnormal internal secretory activity of the pancreas is commonly a factor in the general pathogenesis of obesity however. Probably in certain rare cases of obesity, --those preceded by manifest hyperinsulinism-- the pancreatic islets play a major

causative role in the excess fat deposition. It is possible that mild or latent hyperactivity of the islets is instrumental in some other cases of obesity, but this has as yet not been demonstrated conclusively.

Opposing certain of the above ideas is Freyberg (57) who found that the whole effect, fundamentally, of hypoglycemia was obtained through suggestion since injections of a solution of sodium chloride increased the appetite as successfully as did insulin. Also he found that insulin had no effect on the appetite unless patients were informed that the medicine was given to help them eat more. If the common types of obesity are ever associated with hypoglycemia, the lowering of the blood sugar must be trivial, since it does not cause the classic symptoms of hypoglycemia and there is no evidence that the lesser grades of low blood sugar increase the appetite. No one has demonstrated low blood sugar in patients whose main complaint was obesity, according to Newburgh (28).

THE PINEAL GLAND

Little has been demonstrated about this gland that would incriminate it in the long list of etiologic agents for obesity. The pineal syndrome, according to Rony (17), (macrogenitosomia precox) is due to certain tumors of the gland, and commonly includes obesity. However, it is believed that this is due to the accompanying changes in the hypothalamus, the latter being discussed below.

THE THYMUS

Bernhardt (35) has included a thymic origin in his list of possibilities, and defines obesity on this basis to be associated with a low blood pressure, vagotonia, and a positive thymus shadow. However, no experimental work has been done in this regard to bring the thymus relevantly into this discussion.

In reviewing the relationship of endocrine disease to the development of obesity, we might call attention to Greene's (40) study of 350 cases of obesity, 100 cases of chronic encephalitis present for one year); 24 cases of myxedema; 22 cases of pituitary tumor; 5 cases of suprasellar tumor; 7 cases of diabetes insipidus, (these latter diseases being present for four months or longer.)

The incidence of types of menstrual disorders, and the relation of the onset of obesity to menopause and puberty are shown in Table I. The number of these patients with various menstrual disorders who lost body weight when low caloric diets were followed is also shown.

Table I

Menstrual history and relation of menopause and puberty to onset of obesity.	Number	Number of pts. losing wt. on low cal. diets
1. Normal	126	60
2. Irregular	34	20
a. Nearing menopause	4	2
3. Dysmenorrhea	7	2
4. Menorrhagia	7	4
5. Scanty menstruations	5	4
6. Amenorrhea	13	6
7. Menopause	74	10
a. Obesity began after	15	6
b. " " before	50	3
1' Menses were normal	48	3
2' " " abnormal	2	-
c. Artificial because of fibroids	4	1
8. Puberty		
a. Obesity began before	22	16
1' Menses normal	17	12
2' Menses abnormal	5	4
b. Obesity began with	1	1
1' Menses irregular	1	1

In Table II, the nutritional state of patients at the time of examination, the relation of the obesity, and the changes of body weight to the onset of the other maladies are shown.

Table II

Nutritional status	Myxedema	Pit. tumor	Chr. Encephalitis	Supra-sellar tumor	Diabetes Insipidus
Obese	6	7	16	1	1
Thin	1	4	19	2	1
Normal	11	7	52	2	5
Relation of obesity to onset					
Antedated	4	5	16	1	1
Postdated	3	3	5	0	0
Disappeared with	1	1	5	0	0
Changes in Wt. after onset					
Gained	6	5	6	1	0
Lost	5	7	33	2	1
No change	8	6	16	2	6

cerebral ventricle as compared with the amounts required when an injection is made subcutaneously or intravenously; (c) a substance with the same physical and physiological properties can be extracted from the tuber cinereum and the wall of the third ventricle; (d) the effect of the substance on blood fat is abolished after mechanical destruction of the tuber or transection of the cervical cord or transection of the splanchnics; and (e) administration of ergotamine which paralyzes sympathetic nerve endings, or of antipyrin and phenacetin which supposedly paralyzes the hypothalamic heat regulatory center, abolishes the effect of lipoitrin. On the strength of these findings, Raab (11) concluded that the hypophysis produces a specific substance which is carried through the stalk to the cerebrospinal fluid of the third ventricle, is absorbed into the wall of the ventricle, stimulates nervous centers in the tuber whence impulses pass by was of descending bundles, spinal cord, and abdominal sympathetic fibers to the liver, causing the liver to absorb neutral fat from the blood; the fat thus accumulated in the liver becomes available for intrahepatic oxidation, chiefly for the purpose of heat regulation; the hypothalamic center of fat transport is also the center of heat regulation; if the center is destroyed or does not receive the amounts of lipoitrin necessary for its normal stimulation, blood fat will not be removed by nor oxidized in the liver but

accumulates in the fat depots and obesity results. These conclusions need more confirmation but the hypothesis seems quite good.

HYPOTHALAMIC OBESITY

Erdheim, in 1909, was the first to describe "hypothalamic obesity." He reported cases of adipose-genital dystrophy in which the autopsy revealed extrasellar tumors involving the floor of the third ventricle leaving the hypophysis intact apparently. Similar cases are reported by many other authors. Obesity with or without genital dystrophy has been observed following meningitis serosa, syphilis of the meninges, hydrocephalus internus, cerebral palsy due to porencephalon involving the infundibulum, and vascular lues with softening and cavitation in the corpus striatum. In all these cases the hypophysis was stated to have been intact.

More than fifty cases of epidemic encephalitis followed by the development of obesity have been reported in the literature; over ten percent of eighty-nine cases of epidemic encephalitis observed by Grossman (58) gained weight varying from fifteen to ninety-five pounds following the disease.

It has been pointed out that epidemic encephalitis usually affects the deep subcortical ganglia but leaves the hypophysis intact. Cushing (59) found that patients with cranio-pharyn-

giomas, which may well enough have damaged the tuberal centers, show more marked obesity than patients with strictly intrasellar lesions that have not extruded themselves through the sellar diaphragm.

Obesity has been produced in experimental animals by injuring hypothalamic centers without damaging demonstrably the hypophysis, although the number of unimpeachable instances is very limited. Camus and Roussy (60) observed obesity following hypothalamic injury in the dog. Bailey and Bremer (61) reported similar experiments and results. In the rat, Smith obtained much adiposity (62) and moderate genital dystrophy by hypothalmic puncture. Others have demonstrated in dogs that hypothalamic lesions as well as removal of the posterior pituitary are conducive to obesity.

The possibility of a hypophyseal origin cannot be excluded unless it is proved that all parts of the gland remained intact. Unfortunately, in most cases of "hypothalamic obesity," histological study of the hypophysis was omitted. In the few cases where the gland was reported "macro- and microscopically intact," no information is available in regard to the tuberal portion, and it is not impossible that this part of the hypophysis which is intimately connected with the basal surface of the hypothalamus, was damaged. Also, obesity was not observed in any of three

hundred cats in which, by was of the Clark-Hersley stereotaxic instrument, unilateral or bilateral lesions in various parts of the hypothalamus were inflicted; and of nearly fifty monkeys similarly treated, only one developed marked obesity.

Cushing (59) frequently observed that hydrocephalus with walls of the third ventricle "thinned out like paper," or large tumors filling out the third ventricle and distorting its walls as to leave "no recognizable trace" of them, were not accompanied by obesity. Recently, Ritter (63) made microscopic studies of the hypothalamus in different types of obesity, including "constitutional obesity" and Cushing's syndrome; no morphologic changes were found in the hypothalamus at all.

Thus, in review, it appears that isolated injury to the hypothalamus may be the cause of obesity in some cases. Some believe that the hypothalamus and the hypophysis are a functional unit in which the regulatory action of the hypothalamic nuclei is determined by some hormone of the hypophysis. So, there may be pathological processes in any of the three essential parts of the unit: (a) in the hormone-producing elements of the hypophysis; (b) in the connection between the hypophysis and the hypothalamus carried by the stalk; and (c) in the nuclei of the tuber, inasmuch as they may disrupt the regulatory function and lead to excessive fat

deposition or excessive fat loss as advocated by Zondek (42), Cushing (59), and Raab (11).

It is further assumed that hypothalamic centers act upon fat tissues mainly in an indirect way, that is, by influencing through descending autonomic nerve fibers the hunger apparatus, endocrine glands, and the liver; these organs in turn would influence the deposition of fat tissue.

Again, animal experiments on rats seem to have demonstrated that lesions of the brain in the hypothalamic area are regularly followed by the development of obesity. Of more importance, however, is the failure to produce obesity in the other mammalian species in which the hypothalamus was injured. The negative results obtained by some investigators on a large number of monkeys casts a good deal of doubt on the proposition that hypothalamic lesions in human beings are the actual cause of the obesity that is sometimes seen in patients afflicted with disease of that portion of the brain.

And so, it may be that, with better methods for study of the hypothalamus per se, (as much as possible anyway), this structure will come into a more prominent place as the more fundamental of causes for human obesity.

THE PSYCHOGENIC FACTOR

Much has been said about how one's mental attitude alone

can be the predominant factor in the intake of too much food. Some would put all of the blame here; others would divide the blame between this and endogenous factors; still others would discount entirely this factor in favor of the endogenous causes, many of which we have considered above. It is true that if their "God is their belly," and everything the obese or potentially obese person does relates itself in a subordinate way to the intake of calories, then the exogenous etiology is the most fundamental one for our consideration.

Bruch states (64) about juvenile obesity that "the course of growth and development of obese children cannot be brought into agreement with the well defined picture of hypothyroidism or hypopituitarism. It is not reasonable to explain accelerated development as resulting from a hypofunction of glands, the growth-promoting qualities of which are firmly established." And as Newburgh (28) believes, in many of these children with so-called endocrine disorders, there is much exaggerated anxiety on the part of parents and the medical situation is misinterpreted, so that the result is the children are deprived of most of their normal outlets. They become self-centered and consider themselves deserving objects of pity and special consideration. Thus, the satisfactions derived from eating are about the only pleasures still permitted the children. No wonder they make the most of them and become obese.

If the onset is before an illness, one usually gets a history of "heart disease" with the mother limiting the child's activity altogether. Although the activity is increased later, the child still guards against strain and too much exercise. Not realizing that the need for food is greatly reduced, the mother believes that recovery will be enhanced by full feeding and spares no effort to tempt the child to eat. The young patient, suffering from self pity and egoism, accepts the food, even though he has no inherent desire for it. As time passes, conditioned reflexes become firmly developed and the feeling of satiety does not occur until the child has overeaten in the physiologic sense.

Again, Johnston and Newburgh (21) believe that the "laying on of fat is the outcome of a perverted habit. Through long training, one comes to acquire stimuli of greater intensity before he feels satisfied; or else he deliberately disregards the warning to cease eating in order to continue a little longer the pleasure that comes with eating. Some have succeeded in dulling the acuity of the sensations involved and in others, it is a combination of weak will and a pleasure seeking outlook on life."

So, these men and others like them, would discuss the fundamental causes of obesity by calling attention to the fact that the inflow of energy exceeds the outflow and that this disproportion is brought about by an abnormality of the appetite and little or nothing else. They believe, furthermore, that excessive

eating is an expression of a mood, a behavioristic response to a person's environment. They give proximate causes to which some persons respond (in part) by overeating as being: (a) overemphasis by a parent of the importance of food in a child's upbringing; (b) gratification obtained from the flavors of foods; (c) the feeling of repose and comfort produced by a full stomach; (d) the temporary respite from anguish caused by intellectual, social, or sexual failure; (e) the food habits of youth which are carried over into middle age, even though the need for food is diminished, and (6) disabling disease with its lessened energy requirement which is compensated for by indulgence in food.

However, there are many things that point away from these as being the fundamental factors in the etiology of obesity and rather point to endogenous factors. As stated previously, Reny (17) points out that it is difficult to improve by training the appetite of one who has no appetite or the child who won't eat what is placed before him. Also, it is noticed that a sudden increase of appetite and weight in adults is often accompanied by objective findings. Again, Goldzieher states that (37) although the textbook classification distinguishes between the exogenous and endogenous types of obesity, it does so without giving much consideration to the causes of excessive or imbalanced food intake. Yet, he continues, experience with diabetic or hyperthyroid patients is sufficiently convincing to show that an abnormal appetite may be but an imper-

tant symptom of an underlying disease and not just a bad habit. Overeating, especially of carbohydrates, is frequently a manifestation of hypoglycemia with an increase in weight as the inevitable outcome.

Disregarding the cases in which inordinate food consumption is a bad habit, a sign of emothical imbalance, or conditioned by occupational circumstances, excess weight expresses the inability of the body to burn up the ingested food. In this sense, it might seem that the problem of obesity narrows down to one of calories: thus, food intake exceeding the daily oxygen consumption with, let us assume, nine hundred calories would result in an accumulation of one hundred grams of fat per day. But such a purely energetic viewpoint of nutrition is not in accord with the facts, as we have attempted to make plain above.

So, although without doubt this etiology of our problem is appropriate in some selected cases, certainly it does not explain the mill run of cases. Mental make-up and imitation or training therefore are not ordinarily factors of prime importance in appetite and satiety levels in obesity. It follows that anomalies of the caloric intake in obesity must be inherent in unconditioned factors of the appetite mechanism.

LIPOPHILIA

It has been suggested that obesity is caused by a hereditary constitutional trait of the adipose cells that enables them to accumulate excessive amounts of fat. This idea has been mulled over for a long time, some observers having at least a little faith in its veracity but most declaring it to be in no way an explanation for the obesity of their patients.

We know that distribution of subcutaneous fat is rather uniform in infancy and early childhood, regional differences and variations developing later, partly in connection with sexual maturity; after middle age, a relative predominance of abdominal fat depots is almost the rule. The rather well known effect of sex on the subcutaneous fat distribution consists in a relative increase of fat deposits in the lower abdominal wall, mons veneris, thigh, and mammary region in the female; no significant changes occur in the male. Variations have been attributed to variations in the affinity to fat of the region concerned. Strandberg (65) observed the back of the hand of a girl which had been covered with skin from the abdomen. At the age of thirty years, the skin here was as thick as was that of the abdominal wall while the remainder of the skin of the hand was thin. This phenomenon seems independent from local circulatory and nervous influences as well as from humoral factors but is inherent in the portion of the fat

tissue itself. This inherent lipophilia of a subcutaneous region and its variations in different individuals may be genetically determined as we shall consider below.

It has been suggested by a number of observers that most types of segmental and regional lipophilia are due to specific glandular disturbances, although there has been no agreement as to what type is due to what disturbance. Thus lower body obesity was claimed to be due to thyroid deficiency; the girdle type of obesity to pituitary deficiency, trochanteric fat deposits to hypogonadism, and supraclavicular fat pads to thyroid deficiency; symmetrically and segmentally distributed fat deposits to pituitary or cerebral disturbance; fat deposits in the mammae, mons veneris and thighs to thyroid deficiency; and "hypertrophic obesity" (proportional deposition of fat into the parts which normally contain the most fat) to hyperpituitarism or cerebral disturbance. Such statements are entirely speculative however.

On the other hand, it is well known that the relative lipophilia of certain regions normally depends on the function of the sex glands. As a result of this relationship, sex gland influences may be instrumental in the following anomalies of fat distribution in obesity: (a) in the pelvic-mammary fat deposits (female type of fat distribution) in male hypogonads. Such deposits are known to occur in non-obese male castrates and eunuchoids, and may be very pronounced in obese hypogonads. (b) in

men usually depositing more fat in the upper than lower segment of the body when gaining weight whereas in women, having a tendency to deposit more fat in the middle or lower segment when gaining weight. Even extreme degrees of upper body obesity in men and lower body obesity in women may occur without demonstrable disturbance of the sex glands or other glands. These facts and the frequent observation of these types as family characteristics, suggest that they are genetically determined , sex-linked characters not necessarily dependent on gonadal disturbance. Progressive lipodystrophy, characterized by an utter lack of affinity to fat in the upper body segment in women, is probably but an extreme case of the lipophilia type in question; it is known to be definitely sex-linked without being related to sex gland disturbances. Other genetically determined, sex-linked lipophilia types are the trochanteric fat deposits and steatopygea in women, the latter being a racial trait in some African Negro tribes. (c) in upper body obesity in women suggestive of a masculinizing influence. This is usually accompanied by hypertrichosis and hypomenorrhea; as part of Cushing's syndrome, it may be associated with other manifestations of virilism. Upper body obesity may be very marked also in men with Cushing's syndrome; apparently, the natural male tendency to fat deposition in the upper body is enhanced by the

underlying glandular disturbance. There can be little doubt that some change in the production of sex hormones is responsible for the increased lipophilia of the upper segment in these cases. (d) in predominance of fat deposition in the lower segment in men known to occur in certain forms of adipose-genital dystrophy. Again, it is safe to assume that some hormonal change connected with the hypogonodism acts on the fat tissues in this manner, but what hormone or combination of hormones is involved is not known.

Since the sex glands are known to have definite relations to the lipophilia of these regions, it seems reasonable that glands capable of influencing sex gland function --such as the hypophysis, adrenals, and thyroid-- may indirectly affect, through the intermediary of the gonads, the lipophilia of the same regions. There is no evidence that the hypophysis, adrenals, thyroid, or other glands can control fat distribution in a direct way.

Other regional lipophilia types (double chin, fat neck, fat ankles, etc.) have undoubtedly nothing to do with the glandular system, but simply represent exaggerated forms of the regional differences in fat distribution commonly observed in normal subjects of average weight; they are more conspicuous in the obese because lipophilic regions "attract" disproportional amounts of fat when much fat is available for deposition. They are probably genetically determined and inherent in the anlage of the af-

fected regional fat tissue.

A known non-hormonal factor that may produce a specific type of regional fat deposition is chronic alcoholism. It is known that heavy drinkers, especially middle aged men, frequently develop tremendous fat deposits in the abdominal wall and cavity with relatively little adiposity of the rest of the body. The mechanism of this effect is unknown.

Goldzieher (37) has pointed out that depot fat in various parts of the body are not all equally accessible to physiologic demands and while it may be burnt up very rapidly in some parts, it may remain inaccessible to oxidation and progressively increase in other parts. (Many maintain that this conclusion is an untenable one, as we have indicated above.) So local factors are of considerable significance in the mechanism of fat deposit in and mobilization from the tissues. It may be that overcrowded fat tissue of experimental animals, within two hours after the intake of carbohydrate, an accumulation of up to six percent of glycogen which disappears but gradually either by transformation into fat or by release into the circulation as glucose, is noted.

Again, since obese persons have more fat in the blood when food is unrestricted, they must either by storing less or mobilizing more of it than do normal persons. The lowering of the blood fat level in obese persons by underfeeding is accepted by Hetenyi

(66) as evidence that they have difficulty in releasing fat from the depots in response to the increased call for energy, but it might just as well mean that fat which is being mobilized at a normal rate, according to Newburgh (28), is being oxidized more rapidly.

If it were true that the adipose tissue cells of obese persons resist mobilization of fat in undernutrition, then such persons would not lose weight, or if they did, the loss would represent the destruction of body protein. But studies made by Block (67) and others show that obese persons are less likely to go into negative nitrogen balance when underfed than are normal subjects.

Three obese females and three normal females were given constant daily diets of known nitrogen content. In each instance, with one exception, a positive nitrogen balance was maintained throughout the entire period. Blood lipids varied considerably with some tendency to rise but to fall later to nearly their initial values. In control subjects there was some tendency for a negative nitrogen balance to occur, but the blood lipids varied essentially in the same direction as for the obese subjects. Thus, from this data there is no evidence to indicate that obese subjects were oxidizing their body protein and so we're forced to the conclusion that they were utilizing their own body fat. Thus Block (67) was unable to confirm Hetenyi's (66) contention that

there is a difference in the response of the total serum lipids in obese and normal subjects to underfeeding.

So, obese persons apparently release fat from the stores as a source of energy as readily as normal persons do. Also, the respiratory quotient obtained during fasting and those obtained after the ingestion of food are lower in obese subjects; so, we have classic evidence that such persons are metabolizing more fat than the normal controls. They cannot at the same time be storing more fat or withholding more of it in the depots.

Finally, the lipophilic theory of obesity is based upon the fact that the affinity to fat can be different in different regions of the body,and subject to increase or decrease within a region, and the therefore reasonable assumption that the lipophilia of the whole organism might vary in different persons, and might be subject to change in the same individual. It is a primarily increased affinity of all fat tissues to fat. It is thought to be due to some anomaly of the intermediary metabolic processes in the fat tissues of the obese. These tissues would remove glucose and fat from the blood faster and at lower threshold levels than normally, and, when calories are needed for energy consumption, would resist mobilization of fat to a greater extent than normally. In this way, increased hunger and increased caloric intake would be created, much of the consumed food being again removed by the avid fat tissues, and this process

would be repeated until generalized obesity results. Accordingly, changes in the caloric balance and intermediary metabolism which accompany obesity would be secondary. The anomaly of the fat tissue would be of genetic origin in most cases, either as an abnormal anlage of the fat tissue itself or as an abnormal anlage of these elements of the glandular or nervous system which exert a regulatory influence on the lipophilia of the fat tissues. Acquired glandular and nervous system disturbances would cause obesity mainly through the intermediary of the fat tissues increasing their lipophilia with consecutive changes in the caloric and intermediary metabolism.

The discovery that normal fat tissue is the site of considerable metabolic activity, especially glycogen transformation, was looked upon by many as strongly supporting the theory which is now more or less fully accepted, chiefly in Germany, by a number of leading investigators of metabolic diseases (Zondek,42; Falta, 43; and Bauer, 68).

Nevertheless, the main elements of this theory remain as hypothetical as they were thirty years ago. Thus, there is as yet no direct evidence that the fat tissues of obese subjects have an increased affinity to the glucose (and fat) of the blood. It should be possible to prove this by determining the glycogen content in portions of fat tissue excised from obese and non-obese subjects following meals; but such data are not available. The results of glucose and fat tolerance tests made on obese and

non-obese persons do not support the assumption that ingested glucose and fat disappear from the blood of non-obese subjects. Neither is there any material evidence to show that the fat depots of obese persons resist fat mobilization at times of caloric need for energy consumption more than the fat tissues of non-obese subjects do. On the contrary, it appears from data concerning the basal metabolism and nitrogen output in undernutrition, as stated above, that the fat of the fat depots of most obese subjects is more readily available for energy consumption than that of non-obese subjects. Furthermore, we have no valid proof that glandular or nervous system disturbances, in producing generalized obesity, appear to affect primarily the caloric balance rather than the fat tissues. In what way obesity is initiated by pituitary, adrenal cortex, gonad or hypothalamus disturbances --by way of primary action on the fat tissues or on the hunger mechanism or some other mechanism-- is unknown. There is some evidence, as given above, suggesting that in obesity resulting from hyperinsulinism the fat tissues might be primarily affected, hypoglycemia and increased hunger being secondary, but this evidence cannot be accepted without further confirmation.

LIPOMATOSIS

This condition closely parallels conditions of the preceding

discussion, for in lipomas, one must assume a local condition which either facilitates the deposit of fat or prevents or hinders its breakdown. If this is so explained, it is not difficult to imagine that the conditions inherited or acquired in these individuals do not favor the general deposit of fat, while in obese subjects, whether as the result of heritage, cerebral lesions or endocrine factors, mesenchymal tissues are capable of storing and up to a certain point of retaining large amounts of fat. This theory was supported first by Von Bergmann and now by Bauer (69).

Hetenyi (66), referred to above, fed ten normal and eight obese people on an insufficient diet. In the normal, the lipid level was unchanged; inethe obese it fell from eighteen to forty-three percent by the end of the period. It was believed that in normal individuals tissues gave up fat as rapidly as it was needed and thereby maintained normal lipid levels in the blood stream. In the obese patients, there was supposedly a delay or hindrance in the release of fat.

When olive oil was fed, Hetenyi (66) found in the normal individual that the fat level rose abruptly, while in the obese subjects, the rise was slight, indicating, Hetenyi thought, as stated above, a more rapid deposit of fat in the tissues. Fifty cubic centimeters of olive oil were injected subcutaneously, and the blood-lipid level of normals increased from ten to forty-eight

percent while in corpulent subjects the rise was only from one to eight percent. This seems to indicate that in the obese storage is more prompt and that fat once stored is released less readily.

He concluded that the distribution of fat deposits as well as the localization of lipodystrophy present many phenomena which are explicable only on the basis of local changes in the capacity of tissues to act as depots. To solve the mystery, it would seem necessary to study local conditions and perhaps particularly factors which might influence the action of enzymes and their equilibria with fats, phospholipids, and fatty acids in the tissues.

Also, the actual weight loss of obese subjects compared closely to their predicted loss as discovered by Block in the study given above (67). The predicted values were based on the loss of body fat. Were it assumed that body fat can not be mobilized and oxidized, the predicted values for weight loss would have, of necessity, to be calculated on the basis of loss of body protein. In such a case, predicted values would be over twice the actual values. So, an agreement in values is supposedly strong evidence in favor of the view that body fat is actually utilized and adds further evidence against the existence of either lipophilia or lipomatosis.

Thus, we have little reason to put any faith into the idea of "tissue-love" for fat. What appears to be regional obesity is

in reality only a secondary manifestation of a more basic, inherent characteristic of the human being's physioanatomy.

HEREDITY

As is the case in almost any ailment with which our frail bodies are beset, obesity has been explained on the basis of heredity. It is a matter of common observation that obesity is more frequent in some families than in others. According to earlier statistics, fifty to sixty percent of the patients with "constitutional" obesity have obese parents. In Rony's (17) series of two hundred and fifty unselected cases of obesity, sixty-nine percent had at le ast one obese parent, while in twenty-four percent both parents were obese. Such a high incidence of a characteristic in parents and offspring is in itself suggestive of hereditary origin of the character, provided that joint exposure to environmental influence capable of producing the characteristic can be excluded. This is difficult to do, for often, habits of living enter in as much as do habits of eating.

Also, difficulty is encountered with in considering obesity as a racial trait. Anthropologists generally agree that obesity is more prevalent in certain races than in others. Thus, obesity is said to be common among Turkish, Chinese, Magyar, Dutch, Southern Italian, Jewish, and the Eskimo people in contrast with

Scotchmen, Prussians, Norwegians, Zulus, and Nilotic negroes, who are predominantly lean.

In two instances -- the adiposity of the yellow mouse and of human twins-- conditions prevail that allow for a clearer evaluation of hereditary and environmental influence.

After others have noticed that yellow mice are usually obese, Danforth (70) made an extensive study of this phenomenon. He mated yellow males to females of various colors; some of the descendents in the following generations were yellow, others were not. Yellow offspring and littermates of other colors were kept in the same cage and were supplied with the same food in abundance. There was no consistent difference in weight at birth, and weight curves of all offspring were practically identical until sexual maturity set in. From that time on the yellow siblings began to gain weight more rapidly than did their littermates of other colors, and were soon characterized by a marked degree of adiposity which differentiated them clearly from other mice, whether related or not. Adiposity developed in both sexes, but was more marked in females, which frequently attained a weight twice as great, even three times as great, as normal non-yellow adults. The difference in weight was due mainly to the difference in fat content; subcutaneous fat as well as intra-abdominal and other visceral fat was excessive. In view of the fact that all littermates

were raised in the same environment, there can be no doubt that adiposity of the yellow siblings is a true hereditary characteristic.

In man, identical twins offer advantageous material for it is generally assumed that identical twins are genetically identical throughout and that differences in a pair of twins (identical) are due to environmental influences. Accordingly, all inherited elements of the mechanism that regulates body weight are identical in identical twins, and differences in body weight will indicate effects of environmental influence.

It has been found, as Reny (17) states, that the body weights of identical twin siblings are rarely identical although usually they are very close. A comparison of the average variability of body weight with that of other anthropological measurements was made, among others, by V. Verschuer (71). He studied fifty-seven pairs of identical twins; their age varied from three to fifty-one years. The "average percentual variation" of twenty-seven different measurements was calculated. It was seen that body weight was more variable in identical twins than was any other anthropological measurement. Similar results were obtained by Newman (72), Freeman, and Holzinger, this indicating that weight is more susceptible to environmental influences than are other measurements. Also, it showed that the variability of body weight in identical twins is much more limited than it is in

fraternal and non-sibling twins. This seems to point to the dependence of body weight on genetic factors. Also, Newman observed nineteen pairs of identical twins who had been separated from each other since early childhood (72). There was considerable difference in weight found only in five pairs and their histories revealed extreme environmental differences, Ten pair showed a difference in weight of less than five pounds, demonstrating the preponderance of genetic determination of body weight over the average environmental influence.

Again, Fellows (73) conducted examinations for the Metropolitan Life Insurance Company and found an incidence of familial obesity ten times greater among those who were normal or lean. Also, Gurney (74) found an incidence of obesity in seventy-three percent of the offspring of two stout individuals, forty percent in the children of one stout and one normal parent, and only nine percent in the children both of whose parents were lean.

As to the genetic pattern of the inheritance of obesity, much has been speculated about but very little proven. Family trees of twenty-five obese subjects (diagnosed "endogeneous obesity") have been investigated, and (a) in almost all cases, at least one of the parents was obese, and (b) when one of the parents was obese, about one half of the offspring were obese. So it can be concluded that obesity was probably inherited by Mendelian trans-

mission of dominant multiple factors. These views are held by Bauer, Fischer, and Lenz (68) as well as other investigaters.

Davenport (75) has brought some conclusive evidence forward, pointing toward the idea that inheritance of obesity follows Mendelian patterns. His conclusions were: (a) the results of the study indicate segregation, that is, the dissociation of two unit characters from each other in the course of the formation of the germ cells. This is important in view of the fact that segregation is recognized as the strongest single proof of Mendelian inheritance. (b) The factors that make for a stout build dominate to a greater or lesser degree over the factors that make for a lean build. This means that a stout build results from the action of positive (dominant) factors, whereas leanness results from the absence of such factors or is due to recessive factors. (c) It is not likely that body build is the result of "blended inheritance, although it is true that genetical phenomena which are explained by the assumption of multiple factors can, as a rule, be equally well explained on the theory of blended inheritance."

Thus, the ultimate problem is which organ or tissue carries the genetic factors that make for the fat content of the body. This problem is quite lacking its solution.

It is true that many authors have little sympathy for the doctrine of "inherited obesity," many feeling like Newburgh (28) that "no internal secretion is capable of so changing the meta-

bolism that the total amount of fat in the body will increase unless the inflow of calories is greater than the outflow." He believes that while shape is inherited, obesity is definitely an acquired characteristic. He admits that women normally possess more fat than men, at least in certain regions as stated above, and that while it is true that deposition of excessive fat in the central regions of some women is an inherited characteristic, it is also true that there would have been no extra fat to deposit in those regions had the intake of food not been overabundant. Thus, we can see that some who are opposed to the fundamental idea of this theory eat the same time admit that perhaps there is some basis for the hypothesis, but that, be that as it may, still obesity can develop only in those individuals who, for some reason, known or unknown, take in more calories than they put out. The latter author believes that environment far outweighs heredity in its causative value for obesity. A person's desire for food is greatly affected by the character of his world, so that one of the reactions of the human being, so responsive to the flood of stimuli impinging on him, takes place in the sphere of appetite and obesity is a product of one's environment rather than of one's inheritance.

In conclusion, it might be well for us to attempt a classification of the primary causes of obesity. It is important that, whatever the underlying causes may be, we should recognize the fact that obesity, in the vast majority if not all of the cases, is immediately due to a disproportion between caloric intake and output in which intake exceeds output. Few authorities disagree on this point. The differences of opinion arise when we attempt to decide upon the nature of the underlying pathology that results in deposition of adipose tissue over and above the so-called normal.

Thus:

A. Acquired "specific" disturbances of the body weight regulatory apparatus.

1. Cortico-cerebral (psychogenic disturbances of the appetite mechanism in cases of psychoneurosis and psychosis; overeating as a result of "perverted eating habits.")
2. Hypothalamic-pituitary deficiency (destructive processes in that region such as postencephalitis, tumors, internal hydrocephalus, syphilis, and xanthomatosis.)
3. Basophilic hyperplasia or tumor of the pituitary.

4. Hyperplasia or tumor of the adrenal cortex.

(This constitutes etiology in a rather small percentage of patients perhaps, but at least, they are rather "specific" in nature. Usually, these patients become obese more or less suddenly in connection with the simultaneous development of some manifest cerebral or glandular disturbance.)

B. Essential idiopathic obesity

(No doubt this is the unexplaining explanation for a good majority of cases. The etiology is unknown! Apparently, there is present a constitutional anomaly of the homeostatic body weight regulatory mechanism manifested by a tendency to upward adjustment, but whether the anomaly is located in

1. Nervous regulatory centers,
2. Endocrine system,
3. Organs controlling intermediary, metabolic processes, or
4. Fat tissues themselves

is not known.)

C. Mixed forms in which essential obesity is associated with acquired or constitutional disturbances in the sphere of the body weight regulatory apparatus.

1. Associated disturbance is of a "specific" nature, (as in A), or is of potential specificity:

a. Thyroid deficiency

b. Hypogonadism

c. Hyperinsulinism

2. Obesity and associated disturbances are linked elements in a heredodegenerative constitution.

(Here, "essential" as well as specific elements are present. There is a history of obesity in the family; the subject has often been obese since childhood; there may be signs of cerebral or glandular disturbances. In others, the additional element appears to be a constitutional anomaly, it having been present since early life, and there being evidence of a hereditary origin. Mental deficiency, anomalies of growth, genital dystrophy, anomalies of puberty, hirsutes, glycogen storage disease or other cerebral, glandular, or metabolic anomalies may be found, in single form or in any combination. Such anomalies may be "specific" elements of the "essential" disturbance of the homeostatic mechanism or else represent manifestations of an abnormal constitution linked with, but otherwise independent from the "essential" anomaly of the mechanism. The first alternative may be accepted for certain cases of adiposegenital dystrophy. It is reasonable to assume that obesity as well as genital dystrophy and other signs of the syndrome are of pituitary-midbrain origin. Constitutional adiposegenital dystrophy may thus be regarded as an es sential obesity with known localization of

the essential disturbance of the homeostatic mechanism and the additional anomaly remains a matter of opinion.

In others, constitutional anomalies which have no conceivable causative connection with obesity are independent manifestations of a multiple heredodegenerative constitution.)

And so, it is evident to the reader that there remains to be more clearly elucidated many of the factors discussed above, before we have an individually accurate etiology of obesity. There is little doubt in my mind but what various and sometimes independent factors are at play in the multitude of patients harrassed by this malady. Certainly, the same set of circumstances do not obtain in each case, but one mustwork out the problem with the patient as he presents himself, for he is a "law unto himself." The answer, however, is probably as simple in some cases as it is complicated in others.

Thus, we have attempted to discuss the factors regulating the body fat content and to note the most important factors contributing to a derangement of the mechanism involved in this regulation.

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