1934

Etiology of obesity

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THE ETIOLOGY OF OBESITY

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A Thesis

Submitted to the Faculty of the University of Nebraska College of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

1934

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I Introduction

Overnutrition is prevalent in our country, and obesity is one of the most common diseases. Perhaps it is more discussed by the laity than any other disorder. Daily, the attention of millions of Americans is attracted to excessive weight through their newspapers, magazines and radios. Preventatives and cures of every description are offered for sale--salts, pills and tablets to be taken internally; creams, lotions and girdles to be applied externally. Dietary fads sweep the country, often leaving their devotees with seriously damaged health. Every morning, after the children have been hurried off to school, thousands of housewives from Maine to California are synchronously "doing their exercises" while the man on the radio counts "one, two, three, four!". Millions of dollars are spent in an advertising campaign to induce Mr. and Mrs. America to reach for a cigarette instead of a sweet. Truly, obesity is in the limelight.

It should not be thought that this propaganda is entirely harmful. Every physician knows that obesity has serious complications; every insurance man knows that the risk is greater for a man who is overweight. But while the promoter and the advertiser are enjoying the earnings of their protege, what is the medical profession doing to stop this tremendous waste of money and energy? How is it going to lessen the dimensions of

the national bulk?

For several years some of the best minds in the profession have been working on the problem of obesity. Their work is far from complete, in fact there is not unanimous agreement on the work that has been done. But great strides have been taken and important ground has been covered. It is the purpose of this paper to present the portion of that work dealing with the etiology of obesity.

Obesity may be defined, simply, as an excessive accumulation of fat in the body. This immediately calls for a definition of normal weight which is not such a simple matter. Every layman recognizes marked corpulence as obesity, but there are often outspoken differences of opinion among nonmedical observers as to what constitutes optimal weight, that is to say, the point where overnutrition (obesity) and undernutrition (emaciation) respectively begin. Nor is the layman alone in doubt; physicians with their scientific training have had difficulty in laying down any general rule that will sharply separate overnutrition from normal nutrition and from undernutrition in all persons. There are so many individual differences in body-build and in constitutional make-up that a rule admittedly applicable to one type would be found to be inapplicable to a second contrasting type. Obviously, then, in formulating a medical definition of optimal weight, allowance must be made for these different types; any conception formed of what constitutes ideal weight must be regarded as abstract,

and a fairly broad zone must be left on each side of it before a weight should be regarded as either too high or too low. Barker[2] states that this zone should be ten per cent., Tileston[75] would place it at 15 per cent.

Body weight is definitely related to age, to stature and in less degree to sex. From medical-actuarial tables and from long empirical observation, the average weight of healthy adults of different heights have been recorded, and rough-and-ready methods of determining quickly the ideal weight of adults from their height have been devised.

The formula devised by the late Dr. Clyde G. Guthrie[31] is used at the Johns Hopkins Hospital. It is simple and accurate. According to this formula, Ideal Weight in Pounds = 110 plus (5.5 X number of inches taller than five feet). Weights ten per cent. above or below the abstract ideal weight thus indicated are considered to be still within normal limits.

II Normal Fat Metabolism

To understand why one person is of normal weight, another fat, and a third lean, we must be familiar with some of the more important chemical studies bearing upon the metabolism of the body. Let us consider first, then, the fat metabolism of normal persons.

In the healthy human being of normal weight, approximately one-sixth of that weight is fat stored as reserve material for supply of energy to be called upon in case of need.[2] Thus, a normal man weighing 70 kilograms will contain, say, 12 kilograms of fat, of which 9 kilograms will be stored in

certain reserve depots of fat, thus preserving a potential combustion value of eighty thousand calories or enough to cover the total energy requirements of his body for about a month. The normal depots of fat storage lie in the connective tissues of the trunk and the extremities, especially in the subcutaneous tissues. The distribution of the stored fat varies somewhat with sex and, as we all know, in different persons of the same sex. In men, fat tends to be deposited in the subcutaneous tissue of the neck and of the abdominal wall, whereas in women the breasts, the abdomen, the buttocks and the thighs are sites of predilection for fat storage.

Human and animal fats consist of triglycerids of oleic, palmitic and stearic acid. They are derived from the foods ingested, not only from the fats eaten, but also from the carbohydrates and from the amino-acids of the proteins through chemical transformations within the body. In fat metabolism, a most important role is played by the ferment lipase which, besides having the power to split fats into their component fatty acids and glycerin, can also, in certain circumstances, act in the reverse direction and synthesize these components to neutral fats. It now seems probable that the fats of the foods, on absorption by intestinal epithelium, are split by lipase and are again resynthesized before passing into the chyle to go over into the blood. Just where the carbohydrates and the amino-acids are transformed into fats has been much discussed; however, that both the liver cells and the fat cells

of the connective tissues are sites of such transformation seems certain, since both lipase and glycogen are demonstrable within them.

The available calories of the food ingested represent the potential energy added on eating; for 1 gram protein, 4.1 calories; for 1 gram carbohydrate, 4.1 calories; and for 1 gram fat, 9.3 calories. From the foodstuffs taken in and assimilated, the structure of the body is maintained and the energy involved in muscular work and in the production of heat is supplied. A certain minimum of protein is necessary for growth, regeneration, and adaptation of the bodily tissues, for the production of external and internal secretions and for the maintenance of the blood. The energy for work and heat production is derived from oxidations within the body of the carbon and hydrogen of fats, carbohydrates and amino-acids. If more energy is used than the food supplies, the stores of the body are called upon and the body loses weight; if less is used than the food supplies, the surplus is stored as fat and the body gains weight. Changes in the water and salt content of the body can be responsible temporarily, it is true, for decrease or increase in body weight, a fact that may for the moment be disregarded since ultimately body weight is determined, according to the law of conservation of energy, by the balance between caloric intake and the caloric expend-iture.

This balance is a remarkable thing. There is no stranger

phenomenon than the maintenance of a constant body weight under marked variation in bodily activity and food consumption. We may gain a pound or two today and lose as much tomorrow, due in the main to water exchanges, but our depot fat remains about the same from year to year, despite the fact that the intake of food fluctuates and activity varies from one day to another. To take a specific instance,[22] a man, aged forty years, now weighing 165 pounds weighed the same amount (75 kilograms) twenty years ago. If during that period he has consumed an average of 2500 calories a day, the total for the 20 years would amount to 18,250,000 calories. The amount of extra fat stored in or lost from the body could hardly be more than 1 kilogram or 9300 calories. This means that the total intake of food must have been adapted to the total expenditure with an error of only 0.05 of one per cent. This is an extraordinary exactness which is equalled by few mechanical devices and almost no other biological processes.

Still more remarkable is the fact that when we lose weight, as a result of illness or of simple starvation, we come back, when we eat again, to about the same level as before. Such remarkable equilibrium demands a refined mechanism of regulation, interference with which explains why some men are fat and others are lean, and why a man's weight may remain quite constant for years and then shift in the course of a few months to another level.

There is more to this equilibrium than can be explained

by the law of conservation of energy. That is, if one's energy exchange each day were 2000 calories, and one were to eat in excess of this amount as little as 90 calories of fat or carbohydrate, this would "stick to the ribs" so to speak and this amount (10 grams of fat) accumulating day after day would mean in the course of ten years not less than 36,000 grams, or eighty pounds of extra weight. The ninety calories of excess food causing this monstrous result would be contained in a small pat of butter or a single chocolate cream!

We know that such a thing does not happen, but why not? How is it that most of us escape adiposity? We do not measure and weigh our intake; if we did, we could hardly attain an accuracy which would be greater than plus or minus 100 calories for the day's allowance. Instead, we depend on our appetites which warn us to stop when we are satisfied or prompt us to eat when food is required. Moreover, we hoodwink our appetites by various tricks. The whole artistry of cookery is developed with the prime object of inducing us to eat more than we ought. Why, then, do we not all grow fat?

Of course, there are many people who maintain constant weights only by frequent use of weighing machines and careful observations of the tightness of the waist bands of skirts and trousers. We must remember, however, that obesity is rarest in those savage tribes among whom bathroom scales are unknown and skirts and trousers at a minimum.

When we discover why it is that not all of us are fat

we will have settled most of the obesity problem.

III Heredity

The evidence for an hereditary factor in obesity is impressive. Von Noorden[54] estimated that 80 per cent. of all cases of so-called exogenous obesity are familial. 70 per cent. of the cases studied by Tileston[75] gave a history of obesity in other members of the family. He doubts however if the excessive weight is inherited--more probably the inheritance is of fat-forming habits. Fat parents develop fat children because they overfeed and under-exercise them as they did themselves. Of course many families are marked by a common stamp, some being tall, some lean, some better covered, but these are normal conditions whereas corpulence is abnormal. In Christie's[18] series of 75 cases of adiposity, 28 per cent. were members of families which ran to fat and frankly blamed their pedigree. Obesity, he says, is largely an acquired disease and the knowledge of how to acquire it is propagated from parent to child.

Hereditary obesity is called a "palpable fallacy" by Newburgh[51] who thinks that persons with "familial obesity" have succeeded in dulling the acuity of their sensations of satiety by following the example of their overfed elders.

Barker[2] on the other hand states that obesity is, in many persons, due to an inherited disposition to store excess of fat, for obesity "runs in families--the fatty phenotypes being determined by their genotypic dispositions". Instead of being able, like normal persons, to trust their instincts with regard

to the intake of food and liquids and with regard to physical exercise, "these persons have faulty automatic infrapsychic regulators of their body weight and, if they are to prevent the development of obese phenotypes, they must learn how to inhibit the influences of their anomalies of constitution by consciously imposing restrictions upon themselves that are out of accord with some of their instinctive feelings and desires". This theory is also sponsored by Du Bois.[22]

The endocrine disorders which are alleged to be influential in some cases of obesity also have their roots buried deep in the family soil, according to Beck. These endocrinopathies follow somewhat the Mendelian laws. Heredity as a factor has been observed in goiter, myxedema, cretinism, diabetes, gigantism and Addison's disease. Because of the analogy between the thyroid and the pituitary, Beck believes it is reasonable to suppose that the same hereditary tendencies obtain in both glands. He has noted hypophyseal dystrophia occurring in several members of one family.

IV Race

Closely associated with the problem of heredity in obesity is that of racial adiposity. With those groups of men whose food supply is intermittent, reserves of fat are accumulated on the body during times of plenty to live upon during periods of poverty. Some tribes of North America and Central Africa swing annually from the extremes of corpulence to excessive leanness. In the Antarctic a thick layer of adipose

tissue is necessary to keep out the cold, and the Eskimo develops it.

Uncle Sam, once lean and gaunt, no longer typifies the American citizen who has assumed, as the result of prosperity, more John Bull-like proportions. The corpulent German of pre-war days had disappeared by 1918. In all of these cases, however, race does not seem to be the deciding factor in the obesity. Environment and habit are the etiological agents. Perhaps Jews are cited most frequently as the stoutest race in the world, but their food is probably the most fat-forming of any.

V Climate

Climate plays a part very similar to that played by race. It is a matter of environment. In the temperate zone summer most people lose weight; in the winter they gain it. Perhaps this is due to nature accommodating the body to external conditions, but more likely the warmth and quiet of indoor life during the winter months helps increase the weight, while the out-door exercise in the warm ones tends to the loss of it. Also, summer weather is not as likely to induce a hearty appetite as is winter weather.

VI Age

There are certain times in the life of an individual when obesity is most likely to develop. Age here is not the fundamental cause; endocrine activity, food intake in response to growth demands, variations in activity and mode of living, and

many other conditions decide whether or not one is to be obese at a certain age. However, age is used by some[24] to classify obesity, so a survey of this field is not out of place.

The infant in arms must accept the fare which is provided, although nature occasionally makes a blunder in regard to the quantity as well as the quality of the mother's milk. Frequently unduly fat babies result. It is the long-continued slight excesses which produce in time the fat child.

In bottle-fed babies an excessive allowance of starch and sugar in certain proprietary foods may result in obesity. The fat hypothyroid child must be distinguished, of course, from the dietetically fat infant.[18]

The growing child, like other young animals, is rarely fat. On the contrary leanness is typical of the intervening years from infancy to maturity. The maintenance diet of the average school-boy should exceed that of the average adult on account of the claims of growth--3500 calories a day compared with 2500.[18] Growth insists upon an abundance of exercise and the adolescent child usually gets it. Nevertheless, obesity does sometimes occur, and is most frequent around the age of puberty. Roughly, 3 per cent. of the boys become stouter at that time, and a slightly higher percentage of girls.[18] Christie states that about half of them belong to the "endogenous" group and show signs of a pituitary or thyro-pituitary defect, but the others are corpulent without obvious cause. Possibly these have stopped growing temporarily or reduced the rate, as frequently

happens. They lose their excess of fat as they grow up, without having altered their daily habits and without any treatment.[75]

There are two periods in men's lives when they tend to corpulence.[18] (1) After giving up the athletic life to enter business, perhaps to marry and start a home of their own. (2) After attaining worldly prosperity, when they begin to "ease off". These are times when activity wanes and appetites should decrease, but do not. Nature is counting calories, however, even though men may have forgotten to, and bay windows develop.

There are three occasions in particular when women become fat.[18] (1) Immediately after growth has stopped. Young women suffer from adiposity four times as often as men of the same age. Various explanations have been offered, which will be discussed later. Briefly, these theories involve the influence of the interstitial cells of the ovaries upon the pituitary and thyroid functions, after the onset of menstruation and maturity. (2) After child-bearing. Many obese females date their corpulency to motherhood. Starved of social and athletic pursuits on account of carrying and nursing the baby, young mothers are encouraged to eat to excess of specially selected, highly nutritive foods in order--so it is imagined--to maintain their strength and the better to suckle their infants. Most mothers reduce their figures later on by diet, but some do not try. Successive pregnancies add to the embonpoint. (3) At the menopause. The physiological decline of the ovaries or their surgical removal is accepted by the

vast majority of physicians as sufficient reason for obesity. Tileston, however, states that the menopause exerts little influence, the weight remaining stationary or decreasing quite as often as it increases at this epoch. Many women become less active at this time, sit around more, very often eat more, and sometimes develop capricious appetites. In consequence they suffer from an upset of the physiological equilibrium, and obesity develops. Obesity in its relation to menstruation, pregnancy, lactation and climacteric will be discussed in detail under another heading.

VII Sex

The relationship of sex to obesity was mentioned above. There is little else to be said, except for presenting an interesting hypothesis set forth by Wilder[81]. He points out that the female of other species is not, as a rule, more obese than the male, but the females of the human race are more obese, especially in the child-bearing age. Very few young men are overweight, but many young women are either fat, or struggling to avoid it. "We may be witness here to an adaptation for race survival acquired in the struggle for existence in the nebulous time of the beginnings of homo sapiens when living conditions were precarious, and the young required the continued presence of the mother. It may be presumed that the pithecanthropic male took the responsibilities of fatherhood relatively lightly, foraged mainly for himself and found his food with reasonable regularity. The female, on the other hand, was confined by her

offspring to her cave or its immediate environs and must have had to endure long periods of fasting. The ability to store food as body fat was for her a singular asset, the utility of which many of her present day descendants are little prepared to appreciate."

VIII Occupation

The civilized life today is very unnatural. The whole method of earning one's living has changed in recent years. This is an age of intensive industry, but it is mechanized. The fireman of the modern ship feeds his furnace by turning on the tap of an oil spray, whereas his predecessor had to feed his boilers by shoveling in the coal. Labor in many factories is merely the controlling of an automatic instrument. Lifts exist in hotels, offices and houses to save muscular exertion. Brains have replaced brawn, but intellectual activity does not burn calories. Thus, occupation must be granted a large say in the production of corpulence.[18, 51, 2]

Attention is often called to brewers, inn-keepers, bakers and butchers as examples of people who become fat because of great caloric intake. However, in Bauer's series of more than 400 cases he could not establish any relationship between obesity and those occupations that are reputed to allow opportunities for overfeeding.

Silver[64] also doubts that occupation plays a part. If it did, all sedentary workers would be fat and all laborers thin. However, the clerk who is "nothing but skin and bones" is too

well known to make it necessary to insist upon the lack of correlation between occupation and obesity.

Although it is not proven that obesity results from occupation, it is known that sometimes "occupation" results from obesity. For instance, the chances of marriage for the Tunisian girl are few, unless she be fat. Hindu money-lenders fatten on purpose because corpulent exteriors advertise their richness and their ability to lend.

IX Endogenous and Exogenous Theories

Ever since von Noorden[54] introduced the classification of exogenous and endogenous obesity this has been the battle-ground for many of the most heated arguments over the etiology of obesity.

Exogenous obesity results simply from an excess of intake of food over the output of energy in an otherwise healthy individual. There is a positive energy balance because the patient eats more than he uses. Henry VIII may be cited as an example of this type.

Endogenous obesity assumes an alteration of the function of one or more of the endocrine glands, which appears to be the cause, either directly or indirectly, of the obesity. In most instances the basal metabolism has been found normal; in a few it has been found definitely decreased.[75] Joe, the fat boy in "Pickwick Papers" is illustrative of this type.

The arguments given in support of the theories regarding the endogenous and exogenous derivation of obesity will be

considered in detail when we come to the discussion of the metabolism in obesity. At this time, however, some of the main points will be covered so that later we may refer to this classification with full understanding of its meaning.

From what has been said, it will be seen that if the potential energy of the food eaten and assimilated exceed the energy expended in resting metabolism, in muscular work, and in the production of heat, that is to say, if the total caloric intake exceed the total caloric output, a positive balance will result and weight will be increased owing to storage of fat. In the last analysis this is true of every form of obesity; accordingly, one may say that each person who is obese has eaten more than was required to meet the expenditures of energy that he has made. Newburgh and Johnston[52] stop at this point. That statement unqualified might, however, be very misleading, for it might spread the view that obesities are due always to gluttony or to laziness! Though gluttony-obesity is well known and laziness-obesity also, both being referred to as "exogenous" obesity, we must not forget that there may be for their origin certain "endogenous" components also that account for excessive or perverted appetite, or for other disturbances of function that lead to failure of the mechanism that normally maintains unconsciously the energy equilibrium of the body.[2]

Newburgh calls endogenous obesity a "misconception". Through a series of painstaking experiments[52] he has shown that

in obese patients the energy expenditure is less than the caloric intake and that the patients are on a positive energy balance. He has also shown definitely that if the energy intake be reduced below the output these patients lose weight. However, Silver and Bauer[64] criticize his conclusions because he has not explained why it is that these obese patients consume more food than they need to maintain normal weight or why their energy expenditure on a given caloric intake is less than that of normal people.

They insist that the endogenous nature of ordinary obesity does not deny the principles of the conservation of energy, and that it accepts as obvious the fact that obesity is due to an intake of food that exceeds the energy output. However, it goes further and attempts to explain the mechanism of this disturbance. Gigon[27] also denies the existence of simple exogenous obesity. Du Bois[22] attacks the word exogenous on the grounds that greediness and laziness certainly rest within the body.

Wilder[81] states that the terms exogenous and endogenous carry little significance. Big appetites and lack of exercise play an important part in both of these types, and what makes for gain in weight in the endogenous case may be equally involved in the over-weight from gluttony. "The term constitutional should be applied, in my judgment, to all cases of obesity which are not strictly secondary to acquired lesions of the brain and thyroid gland", he states.

Lauter[40] and Bernhardt[11] are two more authorities who hold

opposing ideas regarding the etiology of obesity. The former attributes obesity chiefly to exogenous factors; the latter considers obesity chiefly endogenous in origin.

That obesity is basically endogenous is believed by Rony,[60] who develops his theory in an interesting manner. Although obesity, generally, is due to some disturbed mechanism in the body, nevertheless outside causes (exogenous) exert a strong influence. The situation in this respect seems to be similar to that in diabetes. The underlying disturbance of the carbohydrate metabolism in diabetes is unquestionably endogenous but we know that the degree of the disturbance depends to some extent on certain exogenous factors, such as food intake. Thus it has been observed that the sugar tolerance of diabetics may be considerably improved after a continued regime of dietary restriction and again aggravated after continued over-indulgence in carbohydrates. It is generally assumed that over-indulgence in carbohydrates constitutes undue strain on the already deficient insulin production causing additional exhaustion of the islets. This additional exhaustion can be relieved by continued low carbohydrate diet. Such observations demonstrate how an exogenous factor may actually influence an underlying endogenous disturbance.

Similar phenomena can be observed in obesity, when attempts are made to reduce the weight. Some obese persons after living on moderately low caloric diets for a prolonged time with considerable loss of weight can remain around this so

attained lower level indefinitely without effort. As Rony puts it, "either a new lower level of the fat regulating mechanism was established, or this lower level may correspond to the basic level of the fat regulating mechanism of such a patient whose basic level has been previously aggravated by overindulgence, and then restored after prolonged 'underfeeding' to its basic level. This basic level cannot be further reduced by exogenous influence.

"We believe most cases of human obesity are basically cases of essential or endogenous obesity and that the underlying disturbance of the body fat content regulating mechanism may be modified to a certain extent by exogenous factors."

X Endocrine Obesity

The evidence for placing the blame for many cases of obesity upon the endocrine glands is tremendous. In fact, it was not until recent years that the role of these structures in causing adiposity was questioned. Today, many believe in the theory; many do not. The evidence on both sides will be presented.

1. Obesity of hypophyseal origin.--Frohlich was the first, in 1901, to call attention to the association of obesity of a peculiar form and dysgenitalism with a lesion of the pituitary. The discovery that these changes are due to diminished functioning of the gland, or hypopituitarism, was made by Cushing[21], to whose work we owe so much of our knowledge of this subject. Frohlich's syndrome, or dystrophia adiposogenitalis is defined

as a clinical syndrome having girdle-mammary-mons adiposity with genital hypoplasia or abnormal gonadal function associated with antero-pituitary deficiency.[24]

The question as to what portion of the pituitary gland is concerned in the development of obesity is still a matter of considerable doubt.[4] Experimentalists generally, however, agree that anterior lobe deficiency is the primary cause. This view is based on the fact that the syndrome with its characteristic obesity, develops after partial removal of the anterior lobe, or after removal of all of the posterior lobe and a large portion of the anterior lobe; and that, on the contrary, no symptoms develop after the complete removal of the posterior lobe. Cushing[20] and his associates attribute the cause to posterior lobe deficiency, which acts by increasing carbohydrate tolerance with resultant accumulation of fat. Both views may be in a measure correct[4] and therefore it seems best, for the present at least, to regard both lobes as factors, which is in accord with the opinion of Schmidt and May[63] who believe that the active principle of the posterior lobe is derived from the Tethelin produced by the anterior lobe.

Regarding the pathology present in the gland, many types have been observed. For our first description of an associated obesity with an hypophyseal tumor credit must be given to Mohr (1840)[49]. In a cursory review of the literature the following varieties of hypophyseal lesions have been encountered: adenoma, glioma, psammona, metastatic carcinoma, adenocarcinoma, teratoma,

sarcoma, angioma, cystoma, steatoma, chondroma, fibroma, gumma, tubercle, embolism, trauma, hydrocephalus, strumata and some unidentified.[4] An interesting example of trauma is seen in Madelung's[46] case of a girl nine years of age in which a bullet lodged in the sella turcica, producing all the symptoms of dystrophia adiposogenitalis.

Tileston points out that tumor of the interpeduncular region by pressure on the gland, or by obstructing the discharge of the secretion of the posterior lobe through the infundibular stalk, may lead to the symptom complex. Furthermore, internal hydrocephalus, if of a high grade, may by dilatation of the third ventricle lead to a similar obstruction. Hence a condition of "cerebral adiposity" has been described, due to hydrocephalus without a direct lesion of the hypophysis.

It is also a well known fact[4] that hypopituitary states frequently occur secondary to functional disorder in the pituitary itself (hyperpituitarism) or are associated with functional insufficiency of other internal secretory glands, especially the thyroid and sex glands, which may be primarily involved. Thus, in tracing the cause of hypopituitary obesity it is necessary to ascertain, if possible, whether the effects were primarily produced on the pituitary or secondarily through the medium of the other glands, i.e., thyroid, thymus, gonads, adrenals, etc. This interrelation and interaction of the glands mentioned led to the designation Insuffisance pluriglandulaire by the French authors Claude and Gougerot;[19] a clinical condition

which has now become generally recognized, and recently much elaborated by Timme[76] and others. Obesity is one of its outstanding symptoms.

2. Thyrogenic obesity.--With diminished thyroid activity obesity might well be expected since the rate of expenditure of energy is appreciably reduced in this condition. Bram[15] divides all cases of thyrogenic obesity into two divisions:

a. Physiological thyroidal obesity. This includes cases seen during puberty and adolescence, after parturition, after such infectious diseases as typhoid fever and pneumonia, and as an incident to middle age and senility.

b. Pathological thyroidal obesity. This includes the idiopathic form, cases following iodine administration, those preceding Graves' disease, and cases incidental to Frohlich's syndrome.

The obesity incident to puberty and adolescence is usually transient and associated with some thyroid swelling. As a result of functional strain upon the thyroid the organ undergoes varying degrees of hypertrophic or colloidal swelling. The basal metabolic rate is almost invariably low, from minus ten per cent. to minus thirty per cent. Also there exist in varying degree other evidences of thyroid underfunction. The increase in weight may be between ten and forty or more pounds above the conventional standard.

The thyroidal obesity observed after parturition also is due to a somewhat exhausted thyroid because of the recent strain

made upon it in taking care of the interests of both mother and unborn child.[15] Goitre which may have begun during pregnancy may not tend to persist. Should postpartum obesity be excessive and the basal metabolism reach minus twenty or lower, myxedematous manifestations may be observed.

Another form of thyroidal obesity, with or without thyroid enlargement, is often observed after convalescence from infectious diseases. Here, too, it is a question of relative thyroid fatigue because of demands made upon the organ by the infectious process. In the occasional instance of this sort we may observe the presence of myxedematous symptoms.

Bram cites another type of thyroidal obesity--"abdominal obesity" or the "bay window". This occurs in middle age and early senility. The cause here is somewhat different from that of the foregoing types, being thyroid atrophy rather than hypertrophy, the accompaniment of circulatory and other changes incident to added years. Advancing years are likewise responsible for sluggishness of bodily activity and occasionally the taking of more food than is required, and these factors are additional causes of weight increase. The obesity may be out of proportion to the metabolic findings. Indeed, one frequently finds in these cases that the basal metabolic rate is but little below normal, although there is an accompanying set of evidence for thyroid underfunction.

Tileston attributes the obesity following acute infectious diseases to thyroiditis, instead of to the "physiological action"

explained by Bram. Other authors state that this increase of weight is due to the prolonged convalescence with much rest and highly nutritious diet--purely "exogenous" factors.

That the gain in weight in myxedema and some other hypothyroid states is not due to fat deposition is pointed out by Grafe and Eckstein[29] and Wilder.[81] Thyroidectomized animals gain very rapidly in weight, largely owing to the retention of water, and the loss of weight following thyroid administration is largely due to loss of water from the tissues. In myxedema the increased weight is due to an albuminous fluid resembling mucin.[75] Therefore, although qualifying under the technical definition of obesity, thyrogenic adiposity usually presents no problem of abnormal fat metabolism.

While it is generally expected that hypothyroidism be associated with excessive weight, many exceptions occur. In the series of cases studied by Lawrence and Rowe[41] it was found that in only 21 per cent. overweight was a definite symptom, while 32 per cent. were definitely underweight. In the series of 88 patients presented by Warfield[79] only 21 were overweight, while 22 were underweight, and in the remainder there was no change in weight. In Bram's series of 240 cases, 19.6 per cent. were definitely overweight.

3. Pituitarothyroidism.--This is a biglandular syndrome in which the previous history and hormonic evidence indicate the superposition of a thyroidism upon a precedent pituitarism.[24] In a series of one hundred cases of hypothyroidism

studied by Beck[4], 20 per cent. showed evidence of hypophyseal fat dystrophy; whereas in a series of forty-six cases of dystrophia adiposogenitalis 27 manifested symptoms of hypothyroidism. The gonads may also be involved in this syndrome. The source of the glandular deficiency can sometimes be ascertained by means of the cosmetic effect produced through localized deposition of fat upon the configuration of the body[4]. Thus the supraclavicular folds are indicative of thyroid deficiency; pads of fat about the eye-balls, mons and mammary glands suggest gonadal deficiency, while the classical girdle obesity points to hypophyseal deficiency.

Engelbach divided this condition into adipose and non-adipose types however, so its relationship to obesity as an etiological factor is uncertain.

4. Hypogonadal obesity.--Under this term are grouped those gonadal deficiencies due to castration or primary inherent disorder of the generative organs. A distinctive adiposity occurs during the course of the gonadal inactivity in both sexes, in the majority of cases at the approximate age of thirty in the female and thirty-five in the male[24].

Tileston states, however, that the adiposity is not characteristic; it resembles that of hypopituitarism, as shown by Tandler and Grosz[73]. But the distribution of the fat is different from that of ordinary obesity, because it infiltrates the voluntary muscles.

On the other hand, it is said[81] that corpulence is not an

obligatory consequence of castration whether in the male or in the female, and there is little evidence to indicate that the secretions of the gonads play more than a minor role in the control of weight. When gain in weight follows castration, it may be explained as a rule on the basis of diminished physical activity; such depression of the basal metabolic rate as is seen after ovariectomy or castration is usually moderate in degree. Amenorrhea, so common among obese women, is a result of obesity rather than a cause of it.[2] It is almost invariably controlled by a suitable course of reduction.

5. Obesity and the pineal gland.--A high grade of obesity may be associated with tumors of the pineal gland, as shown by Marburg[47] and Leschke.[42] Such cases are characterized by precocious sexual and genital development, skeletal overgrowth and the signs of a tumor in the region of the corpora quadrigemina. Cushing points out that the adiposity might well be due to the accompanying hydrocephalus with obstruction of the pituitary discharge. Wilder[81] also doubts that it is the pineal tumor per se that causes the obesity, stating that the adiposity "is probably due to pressure on the diencephalon and injury of its metabolic centers".

6. Obesity and the adrenal gland.--A very similar clinical picture has been described in a rare type of adrenal tumor occurring in childhood, in which there are obesity, skeletal overgrowth, pilosity, premature sexual development and mental dulness. The symptoms are apparently due to overactivity of the adrenal cortex. Cecil[17] describes the obesity thus: "The

distribution of the fat is on the abdomen, chest, buttocks and hips. The face is full and unsightly, owing to deposits of fat in the cheeks, under the chin and in the neck".

7. A possible role of the pancreas in storage of fat is suggested by the frequency with which the development of diabetes is preceded by gain in weight. It has been thought that hyperactivity of the islets may anticipate the later state of their functional incapacity. This idea has been reinforced by the observation[81] that when insulin is injected into persons receiving food rich in carbohydrate, the respiratory quotient rises higher than it does without insulin, and frequently goes above unity. The use of insulin in cachexia also has been found to stimulate gain in weight. Wilder believes the matter is still problematic, and suggests that the intense hunger which is provoked when hypoglycemia is produced by injections of insulin may explain the benefits observed from such treatment.

8. At this point a curious polyglandular syndrome should be mentioned, in which enlargement of the salivary glands, and sometimes of the lacrimal glands, is a conspicuous feature. The condition thus resembles the Mikulicz syndrome, but differs from it in the involvement of the endocrine glands, and in the fact that in Hammerli's[32] case, the only one coming to autopsy, a simple hyperplasia of the salivary glands was found. In addition to the salivary glands, the thyroid was involved in most of the cases, and dysgenitalism was frequent.[24] The hypophysis was occasionally affected. Signs of status thymolymph-

aticus were frequently observed. In no less than eleven out of the twenty-six cases reported by Berthon[12], obesity was present. It is probably ascribable to disease of the thyroid.[75]

An attempt has not been made to present all the glandular syndromes in which obesity occurs. Enough has been given, however, to show why so many authors enter a strong plea for the acceptance of the endocrine theory of the etiology of obesity. The arguments of the opposition, however, seem equally strong.

When an authority such as Wilder states that "the inferences of endocrine responsibility (for obesity) are largely speculative" one must at least give the idea consideration. Nobecourt[53], speaking on the basis of a wide clinical experience in Paris, asserts that "actually, the existence of obesity of hypophyseal origin is far from being demonstrated".

Bernhardt[11] makes this statement: "Surveying the whole literature of obesity, especially since 1900, and adding to it the new investigations of my own, one must come to the conclusion that the ideas we have had until now upon the pathogenesis of obesity are not apt to explain all the different facts involved. It is impossible to consider a certain endocrine gland as the cause of obesity. Many of them may be of importance. However, never the endocrine gland alone gives the decision, for we see the same disturbances of the gland without an obesity resulting. Hypothyroidism is found very often without obesity and so are hypogenitalism and hyperpancreatism, etc."

In the same vein, Barker[2] writes that the endocrine regulation is very complex, all the hormones passing into the blood to act upon other endocrine glands and upon the fat cells, partly directly upon the latter, partly through the intermediation of the nervous system. No one gland can be blamed for the production of corpulence. The thyroid hormone has a direct effect upon the metabolism of the body at rest and the hypophyseal hormone has an influence upon the energy spent in digestion and assimilation (so-called specific dynamic action of foods). "Clues are gradually being obtained as to the nature of the influence of other hormones, but knowledge in this domain is still too meager to make discussion of it at this time profitable", he concludes.

XI Basal Metabolism

Some of the earliest investigators of the causes of obesity thought that the solution would be found in the study of the basal metabolism. "It must be", they thought, "that the metabolic rate is lowered; these people have an unusual conservation of energy, and so they get fat."

Rubner[62] in 1902 was the first to shatter their hopes. He measured the gas exchange of a fat boy and his thin brother and found, of course, that the fat boy had the lower metabolism per kilo body weight. But when reckoned according to surface area, there was no difference. He concluded that at least in cases of "exogenous" obesity, there was no depression of the basal metabolic rate. Von Noorden, seven years later,

covered the ground more thoroughly and arrived at the same conclusion.

However, it took a little more time and considerably more arguing to determine the influence of the basal metabolism in "endogenous" obesity. Those authorities defending one side pointed out that in myxedema, castration and convalescence, conditions in which there is usually a lowered basal metabolic rate, there is also obesity. The opposition countered by citing hypophyseal cachexia, Addison's disease and pluriglandular insufficiency, conditions in which there is a profound depression of the basal metabolic rate, and thinness! How could it be that the Eskimos, an obese race, had high metabolic rates[64] while the thin East Indians had rates lower than normal?[67] In other words, why is it that a depression of oxidative changes is not always accompanied by an increase of weight?

Through the years, hundreds of experiments have seemed to establish to almost everyone's satisfaction the fact that in endogenous obesity (with the exception of myxedema and cretinism) there is no lowering of the basal metabolic rate. Lauter[40] studied a large number of patients of both the endogenous and exogenous types and came to the conclusion that there was no essential difference in their metabolism. Only a few showed a basal heat production below the Harris-Benedict standards.

In the study of over a hundred cases of obesity of different types, Bernhardt[11] found that in about 66 per cent. the basal metabolic rate was within normal limits. In about 24

per cent. there was a high rate, and only in about 10 per cent. a more or less marked decrease could be noted. The same conclusions have been reached by Strouse[70], Wilder[80], Grafe[29] and others.

Du Bois[22] feels that it is possible that sleep in the obese is accompanied by an abnormal lowering of metabolism, but there is as yet no evidence one way or the other.

Grafe and Koch[30] reported some interesting observations which show that overnutrition, if excessive, may actually increase the basal rate. Their first case was an emaciated man on whom a gastro-enterostomy had been performed for pyloric stenosis. When placed on a high calory diet the gain in weight was much less than that expected. Metabolism experiments explained this deficiency. The basal rate, recalculated according to the Du Bois height-weight formula, rose from minus ten per cent. to plus 27 per cent., and the total heat production increased 80 per cent., though the weight rose only 50 per cent. Similar results were obtained in the case of an asthmatic boy of 15 years who displayed a voracious appetite. This boy showed a marked increase in the metabolic rate when placed on a diet of 100 calories per kilo, but failed to gain weight.

One of the most original pieces of work on basal metabolism in obesity has recently been done by Rony[60]. Since Strang and Evans[68] share his views, the following will be in the nature of a review of both articles.

A consideration of the definition and method of calculating the basal metabolic rate reveals that the statement that

basal metabolism is normal in obesity may be misleading unless all the factors that enter into the calculation are kept in mind. When the basal metabolic rate of obese persons is calculated, the "normal" standards for the patient's sex, age, height and weight, obtained from statistical tables, are simply those of obese individuals. The basal metabolism of an obese person is, in fact, compared with that of another obese person. A variation of plus or minus ten per cent. in basal metabolic rate in obesity only indicates that in this condition the basal metabolism of similarly built individuals varies little. And, unless one keeps in mind the fact that by definition the basal metabolic rate is an expression of the number of calories produced per square meter of skin surface, one is likely to be misled. The statement that the basal metabolic rate in obesity is normal means only that per square meter of surface the obese, the lean and the average normal weight individuals produce approximately the same number of calories. But as a matter of fact, the total basal metabolism of an obese person is generally greater than if that obese person were normal in weight. Obviously, then, the statement of the basal metabolic rate of the obese does not afford a direct comparison with corresponding individuals of normal average weight.

In order to obtain a direct comparison between the obese and the normal weight individual Rony believes that the 24-hour basal caloric production of obese subjects should be compared with that of normal average weight persons of the same age, sex

and height. When this is done, a marked difference is found, obviously. For example, an obese patient weighing 349 pounds has a total 24-hour basal metabolism of 2,264 calories with a basal metabolic rate of plus 4.5; but if this patient were of normal average weight--129 pounds--the normal total basal metabolism would be only 1,405 calories. The extra weight with increase in body surface has caused an increase in total metabolism of 859 calories, or an increase amounting to plus 61.5 per cent. It is suggested that the per cent. increase or decrease in the 24-hour basal metabolicm of an obese or lean subject over or under that which would be presumably manifested if the subject were of normal average weight be called the "basal metabolic ratio".[60]

The metabolic ratios of fifty unselected cases of obesity observed at Northwestern University were taken. A study of these figures reveals that thirty-one of fifty cases had a basal metabolic rate within plus or minus ten per cent. There were four cases between -10 and -20 per cent. and three cases below -20 per cent.; eight cases between plus 10 and plus 20 per cent., and three cases above plus 20 per cent. These findings conform with those of other observers. However, when the basal metabolic ratios are calculated by comparing values of the 24-hour basal metabolism of the patient in calories with the 24-hour basal metabolism of the normal weight person in calories, the ratio is positive in all but one; that is, the total caloric production under basal conditions is greater in all but one of the

obese patients than it is in corresponding subjects of normal average weight. It is to be noted that the metabolic ratios vary widely, however, from plus three per cent. to plus 111 per cent., the average increase for 100 pounds over-weight being plus 30 per cent. This compares well with Lauter's data obtained by a similar calculation.[40]

The metabolic ratio of five healthy under-weight or lean subjects as observed by Benedict and Joslin[7] was found to be negative in each case indicating that the 24-hour caloric production under basal conditions of underweight healthy subjects is considerably less than that of corresponding normal average weight subjects.

While the surface area law is a valuable empirical law for metabolic calculations, it cannot give us any clear information as to the origin of the higher metabolism in obesity. The basis of the relationship of surface area to basal metabolism is not yet clearly understood, and the existing statistical data do not apply to patients with "odd deposits" of fat. It has been thought that larger body surface requires higher metabolism in order to maintain the body temperature which otherwise would be lowered by the increased heat elimination through the larger body surface. It is believed by many that the basal metabolism is proportional to the surface area because of some more fundamental factor which is itself proportional to the surface area. Thus, according to Benedict and Talbot[8], the body surface has no significance in connection with heat production

except that it is normally proportional with the active mass of protoplasmic tissues, and this active mass determines the fundamental metabolism.

Regarding the question of why obese persons have a relatively higher metabolism, the following considerations are suggested. Some part of the excess basal metabolism of the obese may be accounted for as the metabolism in the excess fat tissues; but this part can account for but a fraction of the basal metabolic ratio. It was stated above that 100 pounds over-weight is usually associated with basal metabolism ratios around plus 30 per cent. If all of this excess were due to metabolic activity in the excess fat tissue, this fat tissue would be from one-third to one-half as active metabolically as the rest of the body. This is hardly conceivable. Undoubtedly some tissues developed along with the excess fat of the obese, such as additional interstitial tissue, vessels, skin and subcutis may be metabolically quite active and even the mass of fat cells proper may have, at least at times, some metabolic activity, but it is probably safe to say that the larger part of the observed excess basal metabolism cannot have its origin in the excess tissues.

If we consider an obese person as composed of excess fat tissue and basic tissues, we must conclude from the above that the larger portion of the excess metabolism originates from the basic tissues as an actual increase in their normal metabolic activity. All or only some parts of the basic tissue mass may

may be involved. Thus the work of the heart is evidently increased in the obese, even at complete rest. And the respiratory movements of the heavier chest require additional energy production in the respiratory muscles; furthermore, obese persons are frequently dyspneic, which necessitates increased work of the respiratory muscles, even at complete rest. This extra activity of the heart and the respiratory muscles can easily account for from five to ten per cent. in the basal metabolic ratio of the obese.

Another factor which may contribute more or less to the positive basal metabolic ratio of the obese, representing an increased metabolism in all basic tissues, is the effect of the so-called "luxus consumption". This will be discussed below, but suffice it to say that this theory accounts, probably, for as much as 20 per cent. in the value of the basal metabolic ratio of certain obese persons.

In other cases the high metabolic ratio may be due to increased metabolism in all of the protoplasmic structures because of over-activity of the thyroid gland. Obesity and hyperthyroidism are by no means incompatible, as has been frequently reported. A case will be cited at the conclusion of this paper.

Summarizing the theories of Rony, Strang and Evans, the basal metabolism of obese persons when compared with the basal metabolism of average weight persons is usually high. This, they believe, is partly due (1) to the metabolism of the excess

fat tissue and additional interstitial structures, (2) partly to an increase in the work of the heart and respiratory muscles, (3) partly--in some cases--to luxus consumption on account of previous over-feeding, or (4) in other cases, to a latent hyperthyroidism. In order to obtain a true comparison of the basal metabolism of the basic tissues in obese and normal weight persons, the first three factors would have to be eliminated--a task which cannot be performed with satisfactory accuracy. Until that can be done, we can say nothing of the basal metabolism as an etiological factor in obesity. This concludes the argument of Rony, Strang and Evans.

XII Muscle Activity

Unquestionably, any normal person will deposit fat if his muscular activity is decreased without the food intake being decreased. Therefore, the question of whether or not the caloric production derived from muscular work is diminished in obesity must be considered.

Lauter[40] emphasizes that the biggest factor in obesity is muscular activity with all its internal components. The question is not "does the fat man eat much or little" but "does he eat too much in relationship to his activity".

Physical work is known to increase the basal caloric production in every normal person during the time of actual work and also for some time (15-30 minutes) after the work was done. This increase during and after physical work may be called the "specific dynamic effect of muscular activity"[60]. It might be

possible that this effect is diminished in obesity. Obese persons, then, would be able to perform the same amount of physical work with the expenditure of fewer calories than normal persons.

But this does not seem to be true. Lauter[40], Strouse[72], Bernhardt[11] and others have found that obese people show, as a rule, the same increase of metabolic rate during muscular work as normal people. In fact, when forced to heavy work they show a higher increase and mostly a longer lasting increase than normal people. Wilder[91], Strang and Evans[69], and Rony[60] have also found that there is no evidence of energy economy here.

Why, then, do not obese patients work themselves thin when performing their daily tasks? Here is a possible answer: because of an habitual inactivity, obese persons might generally perform less physical work in their everyday life than do normal persons, thereby saving a certain amount of calories in their 24 hour total caloric output.

By its nature, this question does not lend itself to experimental investigation, and therefore, in trying to answer it we will have to be satisfied with estimations based on everyday observations. The fact that an obese person has to move a greater weight with every step he makes indicates that, other things being equal, the obese would perform more physical work in his everyday life than his normal partner. On the other hand, it cannot be doubted that many obese persons more than compensate for this excess of work by what they save through their lack of

impulse to muscular activity. Frequently, of course, the "laziness" of the obese is chiefly secondary, being simply due to the effect that overweight would have on the activity of any normal individual. In other cases, however, the laziness is evidently primary, a genuine characteristic. Lauter connects this with the "endogenous" theory, stating that "the patient with endogenous obesity lacks not the possibility but rather the impulse to movement. The impulse to move, the activity and effectiveness are bound up closely with the endocrine system."[40]

But it should be kept in mind that not all obese persons are physically inactive. Quite a few of them show remarkable muscular activity although greatly handicapped by their excessive weight, shortness of breath, profuse perspiration, etc. It is well known that some of the wrestling champions who certainly have plenty of exercise possess not only powerful muscles but excessive fat deposits as well. It is a fact that many normal individuals who have been accustomed to strenuous physical work gain weight later when they settle down to a more quiet life. But even complete lack of physical exercise does not always result in obesity. Some children, for instance, forced to inactivity by infantile paralysis or by organic heart disease will become obese, others will not. There is a class of constitutionally thin persons, the asthenic type, who are characteristically inactive with lack of impulse, and fatigability. Among normal weight persons we find some physically extremely

active as well as some extremely inactive types. Evidently there is no parallelism between body-weight and amount of muscle activity as far as different persons are concerned, although there is a parallelism, to a certain extent, between these two features, in the same individual.[60]

Accordingly there is no evidence that the caloric production derived from muscle activity would be generally reduced in obesity; thus, inactivity or muscular exertion alone do not determine obesity.[60, 40, 22, 64, 91, 68]

XIII Appetite, Food Intake and Energy Output

It is a well known fact that appetite is closely associated with muscular activity, so at this point it would be well to consider the relationship of these combined factors to obesity, from an etiological aspect.

The common idea that in obesity there is an increased consumption of food, and in leanness a diminished consumption of food comes up for questioning first. It is true that a large number of lean persons have poor appetites, eat little and prefer foods low in carbohydrate and fat content; but another class of lean persons is conspicuous for its excellent appetite; others again do not differ in their eating habits from the majority of normal weight persons. Similarly, many obese persons are characterized by increased appetite and food intake, whereas a number of them apparently have no abnormal eating habits, and some of them eat surprisingly little.

Regardless of the absolute amount of food intake and mus-

cular exercise it might be possible that the difference between these two factors is a constant characteristic in obesity. We should expect then to find always a relative excess of food intake over muscular activity in obesity.[60]

Common observations, however, show clearly that the expected discrepancy between food intake and exercise is not necessarily present in obesity.[60] Obese "big eaters" are frequently quite active, while a number of obese persons of the inactive, lazy type, justly claim moderate eating habits.

It may be objected at this point that a slight difference in the balance between intake and output might not be detected on simple observation, and that such a slight discrepancy may yet be present in all cases, resulting in time in considerable gain or loss of weight. For example, a person who takes three pats (one ounce) of butter, or its equivalent, extra per day above his needs may gain a pound in weight in two weeks or twenty-five pounds in one year.[2] Nor can one easily take enough exercise to burn up an extra intake of fat; as an illustration, Benedict[5] has pointed out that the working off of one pat of butter (one-third ounce) or its equivalent, requires an amount of muscular activity equal to that involved in climbing to the top of the Washington monument!

What, then, is the mechanism that allows patients to remain for a long period of time in a positive energy balance? Why do they persistently exceed their caloric necessity? Silver and Bauer[64] and many other authors believe that to answer these

questions we must center our attention upon perversions of the normal relationship between appetite and energy expenditure. When the regulation is perfect the individual is in equilibrium and there can be no question of obesity. It is only when the mechanism fails and the appetite exceeds the energy requirements that obesity appears.

To result in obesity this regulatory mechanism may be affected at two points. Either the appetite may increase or the energy expenditure may decrease, without the proper regulation of the opposing function.[64]

The following explanation of this is given by Du Bois:[22] "In the normal man, we may assume that the adjustment of expenditure and intake is made in the following manner: His food for a given day is determined by his appetite which corresponds roughly to the demands made by the muscular activity of the previous 24 hours. Some of the food is deposited in the depleted store-houses of the body. Some of it which is not so deposited produces a rise in metabolism on account of its specific dynamic action. This, on the average, only amounts to six per cent. of the caloric value of the food, but after a heavy meal, especially one containing protein, it may rise to 30 or 40 per cent. In this manner, some of the excess food is burned and wasted just as a surtax diminishes a large income. There may still be an excess of intake over expenditures. This is usually stored as body fat and we must remember that it only requires three ounces (100 grams) of fat to contain an

excess of 900 calories. When well nourished, the individual tends to become more energetic and it is quite possible that he will soon burn up his fat by extra work or exercise which would not have been undertaken had it not been for the overfeeding. Even if the store of a few ounces of fat remains for a few days or a few weeks it may be called upon at a time when there is a temporary depression of the appetite below the point where it balances the requirement.

"Let us suppose that at another time this same individual eats less than enough on a given day to cover that day's need. The food, after it has been digested, is transported to the depleted tissues with little or no specific dynamic action and is thus utilized more economically. The deficit in calories is made up by drawing upon the body protein, glycogen and fat. Should this deficit continue for many days there would be a gradual lowering of the basal metabolism and a tendency toward restriction of activities due to a lack of energy and initiative. There would also be in a normal man an increased appetite which would repair all previous losses as soon as sufficient food became available. Incidentally, we may ask ourselves why a given individual 5 feet 10 inches tall with a normal weight of 165 pounds shows an increased appetite if his weight drops to 160 pounds, whereas there are thousands of his contemporaries of equal height who habitually carry a weight of 160 pounds without any increased appetite."

This question cannot be answered without an understanding

of exactly what appetite is. This is not the place to discuss the complete physiology of appetite, but enough will be given to clarify its relation to obesity.

Appetite is an urge to eat, compounded of the sensation of hunger and the feeling of repletion.[81] Either element may be abnormal. We encounter persons who experience extreme hunger, but who are quickly satisfied, and others who are never very hungry and yet slow to be satisfied. The two often go together, that is, the persistence of hunger and retardation of satiety.

Hunger may result from sensory impulses afferent from the stomach, or its stimulation may arise in other tissues, or originate from the composition of the blood. The best evidence for stimulation by the blood is the desire for food that accompanies hypoglycemia. It was thought for a time that hypoglycemia caused contractions of the stomach, but Heinz[33] shows that the hunger which follows an injection of insulin may occur in the absence of gastric contractions. Similarly, the sensation of repletion may be aroused by a variety of stimuli. It is Kestner's[37] belief that mere distension is not sufficient to give the feeling of satiety, for it is not experienced when the stomach is artificially distended. Strang and McClugage[69], in their experiments on specific dynamic action, see an indication that the rate of the change of metabolic rate which is determined by the ingestion of food is faster in thin subjects and slower in obese subjects, and conclude that satiety is affected according to this rate of change. Whatever the mechanism of stim-

ulation, it is clear that the urge to eat is a result of hunger and the desire to stop eating the result of the feeling of repletion, and that abnormalities of either of these feelings will result in gain or loss of weight.

To explain, then, why the individual five feet ten inches tall with a normal weight of 165 pounds will develop an increased appetite when his weight falls to 160 pounds, we must assume that there is a mechanism which is set to control his weight at the former level. A reduction in weight below that will cause increased appetite, an elevation in weight above that will cause decreased appetite.[22]

That is the normal regulation, but what is the cause of the abnormal regulation which makes an obese person hungry although his weight is far above the normal?

We may say that there are two causes: voluntary and involuntary.

Self-indulgence and the acquisition of perverted habits of eating are voluntary causes. There are people who think of Heaven as a place with good restaurants in it. The gourmand enjoys that sense of repletion which comes with a distended stomach. Through long training people like this have come to require stimuli of greater intensity before feeling satisfied; or else they deliberately disregard the warning in order to continue a little longer the pleasures which come with eating. Newburgh[51] states that the mental make-up of these people resembles that of the chronic alcoholic.

The following explains the involuntary causes of polyphagia in obesity: There are persons who in the past have accurately met their energy requirements by taking in just the right amount of food, but who have entered a new state in which the utilization of energy is less than formerly. The established habit of providing the body with a fixed number of calories continues even though the requirements have fallen.[51] The lessened outflow of energy has many causes. 1. The basal metabolic rate remains normal but the total calories used are lessened because of advancing years, the acquisition of worldly goods, change of occupation, etc. 2. The basal rate becomes abnormally low as a result of myxedema or other diseases of the endocrine glands.[51] In these persons there is also a diminution of general activity. However, adiposity does not always develop in this second class. It occurs, commonly, under these circumstances because the firmly established habit that for many years had supplied the ideal amount of energy does not change easily.

Silver and Bauer attempt an explanation along opposite lines. They say that the appetite is caused by the obesity, not the obesity by the appetite, and point to the experiments of Putnam, Benedict and Teel[58] for support. In their studies in the experimental production of acromegaly in dogs by the injection of hypophyseal extracts, they noted rapid growth and enormous increase in appetite. "One would scarcely say that the anterior lobe of the pituitary gland stimulates the appetite in the sense that bitters do. One would not say that

these dogs grew because they ate more. They ate more as an inescapable result of a newly instituted tendency to growth which is a specific action of the anterior pituitary lobe. The dogs did not grow because they ate more, but they ate more because they were growing. The increase in appetite is a result, not a cause."[64]

Accordingly, Silver and Bauer say that increased appetite alone does not necessarily result in obesity. In the cases of hyperinsulinemia with hypoglycemia and extreme hunger periods, obesity was not noted although the patients were fed large amounts of carbohydrate to combat the hypoglycemia. This does not lend support to the suggestion of Falta[25] that obesity has as its basis an increased appetite conditioned by hyperactivity of the insular apparatus.

Food intake occasioned by appetite and muscular exertion are very important factors in obesity, but these are not primary causes. They explain why some people get fat, but do not tell why we are not all obese, which, as has been said before, is the crux of the problem.

XIV Specific Dynamic Action of Foods

Another metabolic study which may throw some light on the question is that of the specific dynamic action of foods. This phenomenon is the stimulation of the oxidative process in the body cells caused by the amino-acids as they circulate in the blood (Du Bois). With mixed meals this stimulation of metabolism usually amounts to about ten per cent. of the basal calories for 24 hours, and has been called the cost of digestion.[81]

Jaquet and Svenson[36] seem to have been the first to observe a low specific dynamic action in obesity. Later Plaut,[56] Grafe,[28] Kestner,[37] Strouse[78] and Bernhardt[11] studied this phase of metabolism and all agreed that this lowering of the specific dynamic action is a constant finding in obesity. They hold that a saving in oxidizable body materials results which must lead in time to considerable fat deposition. They consider the low specific dynamic effect to be a primary characteristic and an important etiological factor in obesity.

On the other hand, in a large number of normal persons Benedict and Carpenter[6] found the specific dynamic action in several instances as low as three per cent. and as high as 33 per cent., and Lauter's careful tests on obese persons resulted in the finding that the specific dynamic effect of foods varies just as widely in the obese as in the normal. More recently Bernhardt, who originally favored the theory, has modified his original statements, saying that "sometimes also a normal specific dynamic action can be found (in the obese)". Wilder[91] also states that the findings are too variable to warrant any conclusions.

But assuming for the sake of argument that the specific dynamic action is uniformly low in obesity, what would be the significance of this fact?

We must remember that the specific dynamic action throughout the day only amounts to ten per cent. of the total metabolism. If this were lowered to half that amount in obesity it

it would make the metabolism only five per cent. below normal, a figure which would not explain the enormous discrepancies between the food intake and weight.[22]

Silver and Bauer point out that in those conditions in which there is an almost complete abolition of the specific dynamic action, as in Simmond's disease, cachexia rather than obesity is the rule. This, they say, is enough to warrant discarding the specific dynamic action theory of the etiology of obesity.

Then, too, if this action were uniformly lowered in obesity, it might well be the result of the obesity, instead of its cause. Many corpulent people habitually overeat and become accustomed to big meals including large amounts of protein. It is reasonable to expect that a large test meal consumed by such persons will stimulate their basal metabolism to less extent than a similar test meal ingested by normal weight persons with moderate eating habits. In these cases the low specific dynamic effect may not be a primary characteristic, but merely one of the consequences of chronic overeating.[60] Also, if there exists a tendency to deposit foodstuffs rather than to burn them, the specific dynamic action will be decreased.

To summarize, there is still a question as to whether the specific dynamic action of foods is lowered in obesity, and there is also doubt as to the significance of this lowering, if it is present.

XV Negative Phases

Interesting metabolic studies have been made by Bernhardt along still another line, by means of which he discovered the "negative phases" in the metabolism of adipose individuals.

He kept the obese for three to four weeks and longer on a diet that was in its caloric content equal to the amount of the basal metabolism of these patients. He laid stress on the fact that these people performed light muscular work, mostly by walking around for a certain time during the day. The patients who were held on that strict diet equal to their own basal metabolic rate were kept under rigorous observation. The fluid intake was restricted to 700 to 800 cc. and the amount of salt did not exceed 7 gm. daily so that there was no possibility of retention of water or salt.

Nevertheless nearly all the patients who showed "endogenous" obesity did not lose in weight during this diet. Some of them even gained weight noticeably. These experiments were repeated with the utmost accuracy and "today I can state with absolute conviction that most of the patients...if held on a diet equal to their own basal metabolic rate, even for weeks, will not lose in weight but may sometimes even gain weight during this period".

Continuing his work, Bernhardt found that during muscular work the metabolic rate increased in about the same amount in obese as in normal persons. The results of these two investigations seem to be in sharp contrast. To use Bernhardt's

own words: "After repeated attempts I succeeded in analyzing the whole problem. I could state by taking the metabolic rate of these patients with only very short intervals during the whole day that there are periods where the metabolic rate is markedly less than that taken in the morning. I call these periods of decreased metabolic rate "negative phases". They occur most noticeably in the time following light muscular work but also very often after the intake of food. These negative phases also occur during sleep."

In short, the metabolism of these obese patients would rise in a normal manner during the exercise, but would fall rapidly and reach a level lower than the original basal level for a time sufficient to compensate for the extra energy expended during the exercise. Bernhardt thinks that this is the most important factor in the genesis of obesity.

Wilder[81] repeated these experiments and found the results to be discouraging. In the first place, although he studied subjects selected for the endogenous character of their obesity, he could obtain nothing other than normal losses of weight with diets planned like those of Bernhardt. In the second place, although he studied the metabolism of these and other subjects during periods of work and recovery, he never observed any depressions of metabolic rate comparable to those described by Bernhardt. Indeed, Wilder believes that if such rigid control of the diet is maintained and observations continued for periods long enough to avoid confusion from the water retention,

overweight subjects will inevitably lose weight; also that if extreme care is exercised in the determination of actual basal metabolism before experiments are started, negative phases will be seen infrequently, if at all.

Rony[60] thinks it necessary to await the results of confirmatory experiments before correctly evaluating this peculiar behavior of the metabolism. He points out that these negative phases are found in only less than half of the obese persons examined, and seem to occur only in obese persons with unusually high basal metabolic levels.

XVI Luxus Consumption

When a man like Grafe who has contributed so much of value to the literature presents his own pet theory of the etiology of obesity, it must be considered. His is the conception of "Luxus Konsumption".[28]

According to this view, an excess in nourishment would be burned up and not stored in the body. This would explain very nicely the maintenance of a constant weight. It would furnish a plausible antithesis to the economy of metabolism which accompanies undernutrition. Although it resembles the specific dynamic action of food, it is not exactly the same because it is found fourteen hours or more after the last meal, a period when the specific dynamic action no longer exerts its effects unless the previous meal has been unusually heavy.

Grafe presents the study of three healthy men whose abnormally high metabolism he ascribes to this phenomenon. The

first was a 32 year old colleague who "astonishes his table companions with his enormous food consumption". His metabolism was 16.5 per cent above the average normal. The second was even higher, plus 39 per cent., but there were a few symptoms such as nervousness and vasomotor instability which suggested a possible thyrotoxic origin for the large appetite. The third, with metabolism 16 per cent. above the normal also showed a disproportion between weight and food consumption. Grafe believes that the thyroid plays an important if not determining role in this luxury consumption. He points out that not all men exhibit this regulatory capacity, otherwise there would be no obesity.

In a discussion of this theory, both Rony[60] and Du Bois[22] state that it is a very attractive hypothesis, although Wilder[91] does not accept it. The former applies it to his idea of the "basal metabolic ratio" discussed above, and states that luxus consumption may be responsible for as much as 20 per cent. of this ratio. Du Bois, although thinking it attractive, believes it should be more adequately demonstrated.

XVII Minor Metabolic Studies

Three more studies in the field of metabolism deserve presentation because of their possible importance in the etiology of obesity.

The first is some work done by Wang, Strouse and Saunders.[78] They prescribed a high-fat diet for twelve obese, six normal and six abnormally thin subjects, with the result that the respiratory quotient was constantly higher in the obese subjects,

which may signify one of two things: either the obese subjects are less able to oxidize fat, or they deposit it more readily. Wilder, however, says this may be explained equally well on the assumption that the better nourished subjects had relatively larger stores of glycogen and made use of them when deprived of other carbohydrates.

The second piece of research is that of Arnoldi[1] who noted that diets rich in carbohydrates cause higher respiratory quotients in obese than in normal subjects. He has taken this as evidence that the former convert carbohydrates to fat with unusual facility. Wilder emphasizes the fact, however, that the respiratory quotients in these experiments have rarely exceeded unity and unless this occurs no one can tell whether the elevation means more sugar burning, or more turning to fat. Both processes raise the respiratory quotient.

Finally, Kugelmann[39], in von Bergmann's clinic emphasized a difference between normal and obese subjects in the degree of the ketone formation that follows starvation. He found it greater in the obese subject, attributable, he suggests, to small reserves of glycogen. From this assumption the conclusion is reached that the fat person converts carbohydrate to fat more readily than he stores it as glycogen. Here, again, another explanation is equally probable[81]: unusual ease of mobilization of the fat of the obese subject or mobilization of a relatively greater amount.

Having considered the various metabolic activities that

might be of importance in the etiology of obesity, we must conclude that not in a single instance do the authorities agree.

XVIII The Theory of Lipophilia

Is there something, then, in the body cells themselves that works for the unnatural deposition of fat?

Von Bergmann, in 1909, was the first to advance this theory. He believed that the primary cause of obesity lay in the fat tissue itself, a sort of lipomatosis universalis. He also called the condition "lipophilia". The only favorable comment on this theory to be found in the literature is Grafe's, who states that it is a plausible and stimulating hypothesis, but there is no proof of its correctness.[23] On the other hand, a storm of protest broke over the theory, rumblings of which are still heard, a quarter of a century after its promulgation.

Barker believes that some part of the obesity problem lies in the fat cell itself. Whether the cell "is to synthesize glycogen to fat and hold it, or is to deliver fat to the lymph and blood after splitting by lipase, is now thought to depend upon the changes in cell organization in which there is spatial separation, or union, of substratum and ferment due to the construction, or to the breakdown, of plasmatic partitions, that is to say, to colloidal chemical reactions with formation of gels and sols". It is well known that such reactions are associated with changes in the local binding of water. It is also interesting to note that insulin increases both water and fat reception by the tissues, whereas thyroxin

simultaneously dehydrates tissues and diminishes the amount of fat stored in them. This is an important piece of evidence for the "endogenous" school of thought.

The old idea of lipophilia has recently been resurrected by Silver and Bauer[64], although it is hardly recognizable in its reincarnation. The following is their line of reasoning:

That there is an independent, local, predestined tissue disposition to obesity is proved by those cases reported where an autogenous tissue transplant from the abdominal wall to the back of the hand has been made. It is known that the back of the hand rarely becomes fat, yet in these cases a distinct, local, unilateral obesity occurred at the site of the transplant. This indicates that the transplanted abdominal wall, separated from its previous nerve and blood supply, retained its lipophilia, that is, its irresistible tendency to accumulate fat.

Their concept of obesity considers this exaggerated tendency of some tissues to store fat, and possibly water and salts, as the primary factor in the causation of the obese state. It regards this tendency as congenital and hereditary although, like many other congenital factors, it may not become evident for many years after birth.

If we locate the genesis of obesity in a constitutional tendency of the tissues of certain people to store fat then we can understand a disturbed balance between energy intake and expenditure as a necessary sequel of this almost irresistible

tendency. We can also understand those cases of obesity, common in the experience of everyone, where in spite of rigorous diet and exercise, we are unable to reduce the fat from the areas where it is most obvious. We know of patients who suffer from a severe grade of inanition and even emaciation without any effect on the fat deposits that we would most like to influence.

The authors conclude: "The concept of constitutional obesity regards the lipophilia of the tissues as the basis and cause of the metabolic disturbance. It does not deny that obese patients are on a positive energy balance. It explains this perversion of metabolism as the result of a congenital factor, already present in the fertilized ovum, that destines the organism to accumulate fat. Obesity is not the result of over-eating, but over-eating may be an inescapable consequence of an inborn tendency to obesity".[64]

XIX Central Nervous System Control

But what is the nature of this "inborn tendency" which is so inescapable? And what did Barker mean by speaking of an "infrapsychic regulation"? These and other vague phrases have appeared in this paper and have purposely been left unexplained because they are parts of the newest and in many ways the most attractive theory of the etiology of obesity--the theory of central nervous system regulation and control.

It is common knowledge that the body weight of many normal adult persons remains fairly constant for many years in spite

of the fact that both the caloric intake and output vary extensively under everyday conditions.[22] We also know that the vast majority of us are over-nourished, but of normal weight. An example of this will prove the point. Diabetic patients who have been educated in the management of their diets, weigh their food and take enough calories to supply their basal metabolism plus a fifty per cent. additional supply. The addition is intended to cover the increment to the basal energy exchange from exertion. These patients keep well and strong on such a regime and maintain their weights. In the case of a man of average stature, such a diet will reach 2400 calories, not more. On the other hand, the consumption of food by the help, nurses and physicians in the University Hospital averages 3,000 calories of food per individual. There is a discrepancy here of 600 calories a day. If the diabetic can maintain his weight, and work, on 2400 calories, the interne and nurse could certainly do the same. Therefore, the overfed nurses and physicians should be adding to their weight at the rate of about forty pounds a year. Actually, they are not doing so, for with few exceptions they are remaining thin.

It is also a common observation that periods of incidental loss or gain of weight in normal persons--due to disease, undue strain, or inactivity--are followed by periods in which the weight is more or less automatically restored to the previous level. Furthermore we know from clinical and experimental evidence[60] that such persons can be easily made to lose

or gain weight by artificial means--such as starvation and increased exercise, or overfeeding and limited exercise--but that these alterations from the normal weight will stop and restoration of the previous weight will follow as soon as the subjects are not interfered with in their instinctive eating and exercising habits, if the loss or gain of weight did not exceed certain limits.[60]

In these same respects obese persons show the following behavior:

(1). The body weight of obese persons is usually considerably above the normal average. But overweight is evidently neither a necessary nor a pathognomonic characteristic in obesity. There are obese persons who are not overweight, and there are overweight persons who are not obese.[60] The first group might be called "masked obesity" and comprises persons who maintain a normal or slightly over-normal weight by artificial means, that is, by living on a restricted diet and forced exercise, resisting constantly their natural eating and exercise impulses. These persons in spite of their normal weight, must be classified as masked obesity for the same reason as diabetics, as has been said above. As soon as the voluntary or artificial restriction as to diet and exercise is removed these normal weight obese persons will immediately gain weight, thereby demonstrating the presence of the anomaly.

The second group might be referred to as "pseudo-obesity" and comprises overweight persons who are not essentially obese.[60] These persons became overweight because of forced overeating

and limited exercise. That they are normal persons is manifested by the fact that as soon as they live again according to their instinctive habits they lose their excess weight in a short time. These persons may manifest all the clinical symptoms of obesity, but from the pathologic point of view must be distinguished from essential obesity. To classify such normal persons in the stage of overweight as obese would be as incorrect as to classify the polyuria of the beer drinker as diabetes insipidus, or the high temperature caused by a high frequency current as fever.

(2). It is a common view that obese persons are characterized by a "tendency to gain weight". By this is meant the gain of weight following even occasional overeating or inactivity in these persons, and the constant attention which is necessary to prevent further fat deposition. Rony believes that this statement needs an important correction, and develops his argument thus:

All obese persons have gained weight over a more or less extended period of their life. There is, however, a limit to the gain in weight even in extreme cases. Clinical observations show that after a high body weight is reached which is individual and which may be moderately, markedly, or extremely high, a phase is entered in which the high body weight is maintained practically automatically. There is a period in which the tendency to gain weight is very marked--it may be called the dynamic phase of obesity--and there is a period in which there is no tendency to gain weight, which might be called the static phase.[60]

It is frequently observed that obese persons who find themselves unable to prevent further gain at say 180 pounds maintain with ease their body weight at 220 pounds. No tendency to gain is present at this time and at this weight. But if the weight of this person is reduced by restricted diet considerably below 220 pounds, the tendency to gain immediately reappears. It seems then that the tendency to gain weight is not a characteristic of obesity in general, but only of one of its phases, the dynamic phase. The dynamic phase may be of short duration and represents the period in which the body weight of the obese person is below his individual abnormally high level.

(3). Another common observation is the resistance of the obese to loss of weight. By this is meant that the response of obese persons to low caloric diets and forced exercise would be different from that of normal persons inasmuch as the loss in weight would be smaller in proportion than the calculated caloric deficit, or that it would be accompanied by subjective symptoms of discomfort much more marked than in the normal person.[60]

As to the objective response there is no doubt that any obese person will lose body fat on a low caloric diet exactly according to the caloric deficit, if proper supervision insures the strict observance of the diet.[81] The loss in weight is of course not a true index of the loss in body fat, because the weight also includes the changing water content of the body.[22] The loss of body fat is accompanied in some cases by increased water elimination, in other cases by water retention; thus the

scale may show an amazing loss of weight in one case and little or no loss of weight in another on the same low caloric diet,, although the actual loss of body fat might have been the same.[75] If the fluctuations of the water equilibrium are determined and calculated, it can be shown that the loss in body fat corresponds in every instance exactly to the calculated caloric deficit.[52]

Neither is the subjective resistance of obese persons to continued low caloric diets in any way different from that of normal persons. It is true that a number of obese persons find it difficult to follow dietary restrictions; they soon complain of hunger, weakness, dizziness, restlessness, headaches, insomnia, etc. But many obese persons have no difficulties on such a regime. We observe similar differences in response to caloric underfeeding in normal weight persons; some of them can stand it remarkably well for a long time, others are quite distressed. The peculiar feature of obesity is only that symptoms of caloric underfeeding may appear at a stage when their body fat content is still well above the average normal. Apparently the obese is just as sensitive to reduction in his abnormally high body fat content as the normal is to reduction in his normal body fat content.[60]

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

this regulating mechanism is govered by the existing fat content of the body--a mechanism that might be compared to the body heat or pH governing mechanism.[11] In the healthy person of average weight this body fat controlling mechanism automatically tends to maintain a weight which is normal for the person's age, sex and height.

The normal fat content of the body represents the zero point, the normal level, or threshold of the mechanism controlling fat deposition. Factors disturbing fat deposition set the regulatory mechanism to work, resulting in change of appetite or in muscular activity--and possibly other factors concerned with the caloric intake and output--and these changes will restore the normal fat content if not interfered with. This mechanism is probably set at a certain level genetically, and may be changed or influenced by hormonal or nervous influences.[2]

In obesity the level of the fat regulating mechanism is represented by an abnormally high fat content of the body. The operation of the regulatory mechanism in obesity is no less efficient than in normal persons; it is adjusted only at a different level. The mechanism tends to maintain the "abnormal" level in obesity just as rigorously as the normal fat level is maintained in normal persons.[60] Indicental or artificial changes brought to bear on the mechanism in obesity will call forth just as efficient operation of the mechanism as occurs in normal persons, so that it is as difficult to influence permanently the body weight of the obese subject as it is the normal weight one.

This discussion seems to indicate that other factors than caloric intake and output may operate in the body which are concerned in the etiology of obesity and that an inbalance of caloric intake and output is secondary to a more prime cause.

Assuming for the moment, then, that there is a prime cause, how can this cause be discovered? There is extensive evidence to show that the cause is purely endocrine, but we have already seen that there is a marked difference of opinion on this matter. Rony[59] believes that this quarrel arises from the fact that in adults the interpretation of the symptomatology and the determination of the glands involved is purely a matter of opinion, and even in the presence of manifest and unquestioned endocrine disorders the proof of their etiological relationship to obesity is open to question.

Both these difficulties are materially reduced when one concentrates his attention on the juvenile age, which provides a highly sensitive test period for glandular influences due to the known marked effects of the glands on the somatic, sexual and mental development. In the developmental period the endocrine disorders, especially of the pituitary and sex glands and to some extent of other glands are relatively easily recognized and readily identified, whereas in adult life the influence of these glands on the development has waned. Rony[59] believes that "results reached in an analysis of juvenile obesity are essentially applicable to adult obesity also". An outline of his work follows:

From the study of 50 cases of obesity in childhood, two

features draw attention. One is that some endocrine abnormality was found in 44 cases, 88 per cent. of the total. This high incidence of abnormal findings in juvenile obesity is the more striking since only comparatively simple tests were employed in this study. The second feature is that the abnormalities found in this series comprise variations from the normal in both directions. Thus there are cases with accelerated and others with delayed somatic development; cases with sexual infantilism and others with precocious puberty; the sugar tolerance is abnormally high in some cases, and abnormally low in others. Furthermore, all possible combinations of these variations exist in certain of these cases. What is the significance of these anomalies as to the etiology of obesity?

(1). It cannot be simply chance coincidence; these anomalies are much too frequent to support this possibility.

(2). Direct etiological relationship can hardly exist for the following reasons: in the first place none of these different types of anomalies was found in every case. Disturbances of the pituitary-gonad system were the most frequent, but even these were entirely missing in 34 per cent. of the cases. Furthermore, in 12 percent. of the cases no abnormality whatsoever was found. Finally, and most peculiarly, the anomalies found represent deviations from the normal in both directions inasmuch as in some cases hypofunction and in others hyperfunction was found.

(3). The endocrine, metabolic and mental abnormalities may be but indicators of the presence of some other disturbance common to all cases, this latter being the direct cause of the obesity.

The nature and location of this common disturbance must then be such that it should be likely to occur simultaneously with any of the anomalies found without itself being caused by them.

There is experimental evidence that the hypothalamus contains structures instrumental in fat deposition. Smith has shown that the whole pituitary gland can be removed in rats without definite effect on weight if care is taken not to injure the adjacent brain tissue; however, if the tuber cinereum is destroyed, extreme adiposity will follow. Rony[59] suggests, then, that the body fat level of normal persons is maintained by the operation of a regulatory mechanism which is chiefly of nervous nature.

In analogy with heat regulation, an automatic reserve fat regulation must exist with a nervous center which controls the primitive impulses for caloric intake (appetite) and caloric output (muscle activity) as well as all other factors of the caloric equilibrium. Furthermore, in obesity, due to some disturbance in this central control, the regulatory mechanism is adjusted to an abnormally high body fat level, although it operates with normal efficiency. In view of the experimental evidence mentioned above, it is suggested that the center of this regulatory mechanism is located in the hypothalamus. Such a center would naturally have close embryological, anatomical and possibly functional relations with the pituitary gland, with other metabolic centers in the midbrain and certain structures of the brain. It would be likely that a simultaneous occurrence of disturbances of some or all of these structures may take place

frequently without one necessarily causing the other.

On this basis, Rony's[59] interpretation of his findings in juvenile obesity is offered: subjects of juvenile obesity which are otherwise entirely normal--12 per cent. in his series--are due to a developmental anomaly limited strictly to the reserve fat regulating center, resulting in disturbance of the primitive impulses for caloric intake and output with a shifting of the body fat level and without glandular or metabolic changes. If the developmental anomaly also includes related structures in or near to the hypothalamus, then the various "pathological" forms of obesity will result, such as those with pituitary or cortical manifestations or with abnormal basal metabolism or abnormal carbohydrate tolerance. Neither of these anomalies has causative relation to the obesity. They signify only the involvement of symptom-producing areas in addition to the disturbance of the otherwise "silent" fat reserve center.

Along the same line, Wilder tells us that among the cases of adiposogenital dystrophy that have come to necropsy, the lesions found in the majority were not of the pituitary body, but of the diencephalon. In a recent review of post-mortem examinations in 149 such cases, Leschke[42] found in 21 that the hypophysis alone seemed to be involved; in all the others clear evidence of injury to the diencephalon was present. Wilder questions whether participation of the tuber cinereum and other adjacent parts of the diencephalon has ever been ruled out with certainty in cases of this kind.

Another strong piece of evidence favoring the idea of a central fat regulatory center located in the hypothalamic region is the large number of cases of obesity which have developed so promptly on the heels of an attack of lethargic encephalitis. This disease attacks by preference the mesencephalon and diencephalon. It almost never affects the hypophysis.[81] Eaves and Croll[23] who present two cases of post-encephalitic obesity make the following statements: "There is as yet no good evidence of the importance of a pituitary hormone to obesity. The supporters of the possible hypophyseal origin of obesity regard the condition as due to a deficiency of hormone, but there is a difference of opinion as to which lobe of the pituitary is affected. If the posterior lobe is responsible, it is difficult to understand why obesity is not more commonly associated with diabetes insipidus." In neither of their two cases was the anterior lobe particularly abnormal, but in both there were alterations in the hypothalamic region.

Moncrieff[50] cites two cases of obesity following chorea. These cases like those cited above began to develop abruptly after an acute disease involving the central nervous system, and Moncrieff feels that the excessive weight was caused by inflammatory changes in the region of the pituitary body and adjacent parts of the brain.

Barker[2], Bernhardt[11], Silver and Bauer[64] and Wilder[91], as well as many others have also noted the incidence of obesity as a complication of encephalitis, and attribute some etiological relationship to it.

Even in the absence of a known lesion, Wilder[81] thinks that the similarity of the symptoms between an unknown case and a known case of cerebral adiposity warrants the diagnosis of cerebral obesity in the former. Thus, a tendency to good-natured cheerfulness is observed among both groups of patients, also a certain childishness or effeminacy; the intelligence may be weakened, unusual sleepiness and inattentiveness may be noted, also lack of energy and amenorrhea. Joe of the "Pickwick Papers" might now be called a case of diencephalic obesity, but there is no proving it, and the identical clinical picture may be seen when all diagnostic methods fail to provide any evidence of organic disease of either the hypophysis or the brain. In other words, types of obesity are not so characteristic as to permit sharp differentiation, and if organic lesions of the diencephalon are responsible for some, it is entirely probable that functional disturbances of the same centers account for others.[81] The same argument holds here as with diabetes insipidus, in which organic lesions are often missing.

Finally, two more pieces of evidence for the central nervous system control of obesity may be mentioned. (1). The fatness of the lower half of the body, with marked absence of fat in the upper half,[2] and (2). the fatness of one lateral half of the body with leanness of the opposite side, the so-called unilateral obesity. Barker[2] and Beck[4] report cases of the second type, as does Macnab.[45]

Barker summarizes the neural concept of obesity very clearly: "The principal neural regulatory centers lie in the dien-

cephalon and are made up of a number of adjacent areas (in the hypothalamus) that govern hunger, thirst, heat-formation, and carbohydrate-, fat-, salt- and water-metabolism; these centers are kept labile by the integrity of the cerebral hemispheres, and they exert their influence upon the fat cells through vegetative paths that run downward through the axis of the nervous system and through the peripheral nerves (cerebro-spinal and sympathetic) to the fat cells."

XX Case Reports

Case 1. Adiposogenital pituitarism in the male. Quoted from Engelbach.[24]

"History.--Male, 15 years 10 months. Chief complaints: (1) Marked obesity, weight 205 lb. (2) Underdevelopment of genital organs with absence of libido. (3) Mental depression. (4) Constipation and nycturia. Duration: Eight years.

"Course: Patient's gain in weight began at the age of seven following a mild attack of measles. Following this gain of weight patient states that he became drowsy and went to sleep easily. He also noted that he perspired very much more than previously. Coincidentaly, his scalp hair began to grow rapidly, necessitating its being cut every two weeks. His appetite became voracious, and he had a craving for meats and sweets. He also had attacks of dull pain in the precordial region, and for a number of years had nycturia which has recently decreased. The gain in weight was universal, but was particularly excessive about the thighs and abdomen. In the last few years he noted that his genitalia were not developing. He admits brooding about this to such an extent that he is moody and despondent.

"Complaints referable to other systems were occasional headaches, dull, precordial pain, and dyspnea on effort. In addition to his inordinate appetite with craving for meats and sweets, he had at variable intervals a polydipsia at which times he required large amounts of water. Associated with his general condition is a moderate degree of constipation. Intermittent

complaints of his special senses was a 'feeling of weakness' of eyes, vague pain in the left ear, inability to breathe well through the nose, occasional sore throat, and tonsillitis.

"Personal: His weight was 7½ pounds at birth, 105 pounds at ten years, 175 pounds at fourteen, and 205 pounds at fifteen years and nine months. His early intelligence was rated as good, and at the age of fifteen he had finished the third year of high school. Measles at seven as noted above. Intermittent fever at the age of twelve. No other infections, intoxications, operations, or injuries. One cup of coffee daily and no tobacco or alcohol.

"Family: Father is 6 feet tall and weighs 300 pounds. Has 'kidney trouble'. Mother is 5 ft. 6 in. tall and weighs 160 lb. 'Has heart trouble'. (Remainder essentially negative).

"Examination:General.--Marked universal adiposity with some localization in the mammae, mons, and girdle regions. Mammae especially large. Very slight amount of hair on the face, axillae, and about pubis. Hair on the head is very thick and of a coarse texture. Hands normal size and shape. Fingers slightly wide, red. Size of shoe is nine. Chloasma along the angles of the superior maxilla. Marked aplasia of the external genitalia. Temperament psychoneurotic, fairly well controlled. Hyperesthesia over the entire body. Pulse 80, temp. 98.8.

"Regional.--(Positive signs): Head small compared to rest of body. Eyes, ears and nose negative. Mouth: Upper incisors enlarged and separated. Right upper incisors twisted outward and forward. Canines small, separated from incisors. Lower

frontal incisors malplaced behind the line of occlusion of the bicuspids. Marked irregularity in position of the posterior upper and lowers. Many posterior teeth have filled small cavities. Neck, chest, and lungs: negative. Heart: Very slight systolic murmur disappearing on inspiration at the apex and base. Pulse slow, blood-pressure 140/80. Abdomen and Viscera: With exception of marked hyperesthesia, negative. Extremities and reflexes: Normal with exception of adiposity and hyperesthesia. Genitalia: Infantile. Length of the penis one inch. Length of the testicle one-half to three quarters of an inch. Very small amount of hair but decided mons padding.

"Laboratory: Blood: Normal. Wassermann negative. Sugar tolerance increased. Fasting, 54 mg. per cent. First hour 132 mg. per cent. Second hour 68 mg. per cent. BMR: -18 per cent. Test unsatisfactory owing to the marked nervousness of the patient resulting in restlessness and irregular respiration. Test not controlled.

"Roentenographic: Sella: Normal size and shape, plate also shows that the sphenoid sinus is clear. Shows nonerupted molar teeth, one above and one below. Hand: Osseous development normal.

"Diagnosis.--Adiposogenital pituitarism. Recommendations: (1) Replacement of anterior lobe substance orally and hypodermically. (2) Replacement of pituitrin hypodermically.

"Course and Therapeutic Reaction.--.....After a year his weight gradually was reduced from 205 to 149 lb. Other symptoms such as headache and the mammary and girdle adiposity disappeared,

leaving linea stria about these regions. Marked padding around the mons and epigastrium was much diminished but not entirely absent. The hips, formerly convex, were now concave although a slight trochanteric pad remained. Stature, formerly suggestive of feminism, was now distinctly masculine.....There was a marked development of the genitalia, especially the penis, and decided growth of hair about the mons, axillae, and face. Libido had developed and he had a nocturnal emission on the average of once a week. His psychic reactions disappeared and his mental attitude changed entirely."

Case 2. Obesity following chorea. Quoted from Moncrieff.[50]

"Girl age 10 years, 8 months. This child was admitted to hospital in October, 1930, with her third attack of acute chorea in two years, and was then transferred to a special rheumatism convalescent home. On discharge at the age of 10 years in November, 1931, she weighed 65½ lb., the normal for her age being 64 lb. Examined at that time she presented the appearance of a normal child, the heart being unaffected. She returned to an ordinary school and led an ordinary life. During the next few months she began to put on weight at a great rate. By July, 1932, she weighed 89 lb. a gain of nearly 24 lb. in eight months. X-ray examination of the pituitary fossa showed no abnormality and a sugar tolerance examination was normal.

"Discussion: It is significant that the adiposity did not develop during prolonged rest in a convalescent home, but only when, the disease process being over, the child returned to ordinary life. The girl is not near enough to puberty to

explain the increase in weight by the well-recognized tendency to adiposity occurring at this period of development."

Case 3. Obesity and hyperthyroidism. Quoted from Rony.[60]

"A woman 48 years old who was always overweight. She weighed 225 pounds in 1925. A year later she developed a toxic adenoma with a basal metabolic rate of plus 46 per cent; her weight was then 146 pounds. Thyroidectomy in October, 1926, was followed by marked improvement. In August, 1927, her weight was 207 pounds, pulse 66 and basal metabolic rate minus 0.6 per cent. In January, 1928, she again compalined of nervousness, palpitation of the heart, increased perspiration, etc.; a recurrence of the adenoma was found, the pulse was 108 and the basal metabolic rate was plus 60 per cent. Her weight was still 207 pounds. During the following eight months the basal metabolic rates varied between plus 60 per cent. and plus 73 per cent. Her weight was still between 200 and 212 pounds. Operation was refused by the patient."

This case is cited to uphold the claim made by Rony that obesity may exist independently of the endocrine glands, and that even a high metabolic rate is not incompatible with the obese state.

Case 4. Neuropituitary syndrome with obesity. Quoted from Engelbach.[24]

"Male, 18 years. Chief complaints: (1) polyuria, polydipsia and polyphagia. (2) Attacks of headache. (3) Obesity. Duration: Polyuria and obesity since birth; headache three years.

"Course: The onset of the overweight was noted from birth.

Weight at that time was 9 lb. though delivery was normal. Increase was rapid furing the first year. Polyuria was also noted during the first year of life. Enuresis, urgent, passed urine frequently as often as every half-hour. The increase in weight was constant, with gradual progression to 190 lb. at the age of 17. Polyuria has been present throughout life and associated with dryness of the mouth, polydipsia, and inordinate appetite. Nycturia has been present as often as one to two hours during the night. Enuresis has continued throughout life. Has a constant thirst, night and day, drinking enormous quantities of liquid. Three years ago he began to have severe attacks of headache. These are described as being so intense that he has been unable to talk from eight to ten hours.....

"Past and Personal.--With the exception of diphtheria, from which he made a rapid recovery without change in the course of his polyuria or obesity, he has been exceptionally free from all infections and injuries. His sleep is broken on account of the polyuria. Appetite, ravenous; bowels, regular. Libido and potency normal.

"Family.--Paternal history of diabetes. Maternal history of endocrinopathy.

"Examination: General.--Adiposogenital type. Marked pectoral and pelvic girdle adiposity with distinct genu valgum. Posterior cervical, supraclavicular, and mons padding with marked abdominal obesity. Hypoplasia of the external genitalia and feminine hair distribution. Hands short and broad, tendency to clubbing of the terminal phalanges...Slight increase in hair

growth over lower extremities and chin. Temperature 97.6° F.

"Regional: (Positive signs): Head pituitary type. Small in proportion to body. Eyes: Palpebral slits narrowed. Fullness of upper lids, with pads over the zygoma, bilaterally. Mouth: Upper lateral incisors small. Neck: Submental adiposity. Thyroid not palpable. Heart: B.P. 124/80. Genitalia: Penis and testicles very small. Feminine hair distribution over mons. Reflexes: Normal.

"Laboratory: Urine: Two 24-hour specimens: 9,720 cc. to 11,220 cc. Sp. Gr. 1.005 to 1.007. Free from sediment. Sugar positive in both specimens. Single specimen: Negative, including blood sugar. P.S.P.: 54 per cent. 300 cc. of urine passed during two hours. Blood: Normal. Wassermann negative. Blood sugar: 83 mg. per cent. Serum calcium: 10.5 mg. per cent. N.P.N.: 27.7 mg. per cent. B.M.R.: -10 per cent.....

"Roentgenologic: Head, elbow, foot, shoulder, knee, and pelvis: Normal ossification. Thymus: Suspect shadow indicating possible enlargement. Fused hilus shodaows of the lung.

"Diagnosis.--Adiposogenital pituitarism associated with glycosuria and polyuria. Recommendations: (1) Pituitrin intramuscularly daily, increased to tolerance as shown by intestinal reaction. (2) Antuitrin intramuscularly 1 c.c. to the tolerant headache dose. Pituitary substance grains 10 after meals. (3) Reduced carbohydrate diet."

Case 5. Obesity with, but not caused by, endocrine disorder. Quoted from Silver and Bauer.[64]

"The patient, a housekeeper, aged forty-seven years, has

suffered from progressive obesity since a thyroidectomy, which she underwent in 1923.

"The patient's mother died of pulmonary tuberculosis. Seven siblings died as children. Father alive and well.

"The patient was quite well until the outbreak of the World War. The unrest caused by the hostilities and the death of a brother at the front occasioned the patient great uneasiness. It was later noted that her eyes had become prominent and that a goiter had appeared. She began to suffer from palpitation and involuntary twitchings. She sought the clinic of Professor Mannaberg, where the diagnosis of hyperthyroidism was made. At this time the patient was of normal stature and weighed 50 kg.

"At that time, 1921, Mannaberg was investigating the effect of radiation of the ovaries on the progress of Graves' disease. The patient was radiated and became amenorrheic, but the course of the Graves' disease was uninfluenced.

"In 1923 a partial thyroidectomy was performed in the clinic of von Eiselsberg. The course of the patient was uneventful, and she was discharged from the clinic in September, weighing 49 kg.

"Since 1923 the patient has been growing progressively more obese, and now weighs over 100 kg., an increase of more than 100 per cent. of her former weight.

"The amenorrhea that followed the Roentgen treatment was complete for one year. After this the menses returned, at first irregularly, but later they became quite normal under ovarian therapy.

"Physical examination reveals a considerable obesity. There is a residual exophthalmos and some enlargement of the parotid glands, as is not uncommon in obesity. The pulse rate averages 90 per minute. Blood pressure readings have varied between 170 systolic and 95 diastolic and 130 systolic and 80 diastolic. The hemoglobin is 94 per cent and the red cell count 5,124,000; whites 7300; polymorphonuclear, 59 per cent.; lymphocytes, 33 per cent.; monocytes 4 per cent.; eosinophiles 1 per cent.; mast cells 3 per cent.; blood sugar 120 mgm. per cent.; Roentgen ray of the sella turcica normal; basal metabolic rate is -3. The general physical examination reveals nothing else of significance.

"Discussion.--A careful analysis of the cause of obesity in this case reveals the dangers encountered in studying obesity accompanied by disorders in endocrine function.

"In the case cited above it is the obvious tendency to associate the obesity with either the thyroid or the ovaries, as each of these glands has shown a distinct abnormality. However, an analysis of the clinical picture shows that no causal relationship can be established between either of these glands and the obesity. That we are not dealing with a post-operative hypothyroidism is shown by the absence of any of the signs of this condition. The skin is normal, moist and warm and the patient perspires freely. The pulse rate is 90 per minute and the temperature and basal metabolic rate are normal...There is, then, no evidence to make one believe that the obesity that followed the thyroidectomy was caused by it.

"Similarly, we can find no firm basis upon which a diagnosis of hypogonadal obesity can be established. The amenorrhea that resulted from the Roentgen treatment began in 1921, and it was not until 1923 that the patient became obese, and now that the ovarian function is reestablished, as manifested by the return of menstruation, the patient's obesity continues unchecked. In addition, the genitalia show no evidence of abnormality clinically, so there is no evidence upon which a diagnosis of hypogonadal obesity can be based.....

"The case presented shows no abnormal pituitary function; the growth, hair distribution, libido and genitals are normal and there are no evidences of a pituitary tumor.

"As in so many other cases of obesity, the key to the understanding of this case lay in a study of the family and an appreciation of the constitutional, familial nature of the affection. A sister of the patient weighs 83 kg., although rather short. This sister has a daughter who weighs 80 kg. at 17 years of age. This occurrence of obesity in sister and niece is certainly more than coincidence. The sister has no thyroid or ovarian disturbance, eats at a different table and yet develops an obesity of the same character and distribution of the patient who has had so many endocrine disorders. The thing they have in common is not an inherited excessive appetite, but a constitutional tendency to obesity which is also manifest in the succeeding generation.

Case 6. Post-encephalitic obesity. Quoted from Eaves and Croll.[23]

"G.F.G., a man, aged 31 at death, had an attack of "influenza" in December, 1925, and had double vision occasionally. He came to the South Yorkshire Hospital in July, 1926, very depressed and in a Parkinsonian condition and unable to walk. He had occasional epileptic fits, but had been subject to epilepsy since the age of 19.

"His weight increased progressively from 7st.8 lb. in July, 1926, to 10st.7lb. in September.

"He died in February, 1928, two days after contracting erysipelas.

"The pituitary.--A large amount of colloid could be seen between the anterior and posterior lobes. The pituitary was of rather unusual form, being elongated in an antero-posterior direction. The anterior lobe was congested, a fair number of acidophiles was present, but the cells were unusually discrete. The large mass of colloid showed variations in its staining properties in different areas. At the junction of the pars intermedia and pars nervosa and in the latter, was a group of cells rather similar to mucous acini. Possibly these had nothing to to with the encephalitic condition, as a similar appearance has been seen by the writers in the case of another epileptic. The fibers of the pars nervosa were unusually widely separated."

For discussion of this case, see above, part XIX.

XXI Summary

1. Heredity plays a part in the etiology of obesity. Probably the inheritance of fat-forming habits is the largest factor.

2. Certain races have obese tendencies, occasioned by the demands of their environment.

3. There are ages at which adiposity is more likely to develop, as the result of both endocrine and environmental influences.

4. Climate regulates minor degrees of obesity and leanness.

5. There are more obese females than males. This is true from infancy to old age, and probably is due to the fact that women lead more inactive lives and are subject to more endocrine disturbances.

6. Occupation has very little, if any influence on obesity.

7. Corpulence may be caused by exogenous or endogenous factors. Some authors say both, some deny the existence of one or the other form.

8. Endocrine dysfunction per se is not accepted by many authorities as an etiological factor in obesity.

9. The basal metabolism is normal in most cases of obesity. However, the basal metabolic ratio is greatly increased.

10. There is no evidence of caloric economy in the muscle activity of the obese, so this is not an etiological agent.

11. Generally speaking, the obese do not over-eat or under-exercise. If these were etiological factors, the wonder would be that we do not all get fat.

12. Although thought for a while that the specific dynamic action of foods is decreased in all cases of obesity, later work has shown that this is not true.

13. "Negative phases" in the metabolism of the obese may account for excessive weight on the basis of an energy-sparing mechanism. This theory cannot be accepted, however, until confirmatory experiments have been made.

14. That normal persons have a "luxus consumption" whereby excessive nourishment is burned up, and that in obese individuals this is lacking, is another theory of the cause of embonpoint. This must be more widely demonstrated, however, before it can be accepted.

15. There is some evidence pointing to an exaggerated tendency of the tissues to store fat. This concept of lipophilia has not been accepted by most authorities.

16. That obesity is the result of the aberration of a fat regulatory mechanism in the central nervous system is the newest and most widely accepted theory. This mechanism may be compared with that controlling body temperature. It has been located in the hypothalamus.

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