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Endocrinopathy in the etiology of obesity

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by

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ENDOCRINE OBESITY

Introduction

The movies with their Marlene Dietrichs and Jean Harlows have made the public figure-conscious. People in all walks of life, from the young coed to the elderly spinster, are doing their utmost to make their figures approximate that of their favorite movie heroine. Even wives are attempting to make the husbands' figure look like that of some Greek god swaggering across the silver screen. We all love the fat W. C. Fields and Oliver Hardy, but they make the fat person rediculous, a thing to be laughed at.

Easy methods to reduce fill our newspaper and magazine advertising columns and crowd our radio programs. Reduce-your-weight methods embrace everything from marvelous physical culture schemes to belts and harmless "little pills". Hollywood diets have been all the rage and have prevented many a person from enjoying one of the great pleasures of life, that of sitting down to a nice appetizing dinner. It is safe, I believe, to say that millions of dollars annually are being wrung out of the gullible public by the promoters of the various ineffective and often harmful quackeries. But the public diets on, perfectly happy to pay for the expensive advertising programs of

these various concoctions, trying first one then another, with no relief, and frequently suffering actual harm.

Having been frequently embarrassed by having to say "I don't know" to questions of my friends who have obtained no relief even while under the care of a physician that I began to wonder if really very much was known about the treatment of obesity. If, as a result of this study, I am enabled to help fome of the miserable, self-conscious creatures, I will feel that my time has been well spent.

The importance of maintaining a normal weight is quite aptly pointed out by Nixon in his article "Obesity in Children" (51) in which he says, "We know that obese children are poorer surgical risks, that they are more prone to develop pneumonia and pulmonary complications, and that diabetes is a potentiality to be considered. Faulty posture, usually a lumbar lordosis, and various orthopedic abnormalities of the feet are aggravated or initiated by obesity. Fat children are the victims of continuous teasing, which in turn is apt to initiate a feeling of inferiority resulting in serious behavior problems. The esthetic value of a slim body, of prime importance to the young coed, is not the least consequential of all the reasons for maintaining normal weight in a child.".

Endocrinopathy as a Cause of Obesity

Much has been written both for and against endocrinopathy as a basis for obesity. One finds all gradations between absolute denial (50) and enthusiastic affirmation (14, 40, 43) of this mooted question. The literature is so well filled with evidence for both sides that it is difficult to weigh it to arrive at any accurate conclusions. My only attempt will be to present such evidence as I feel of value and leave it to the reader and further research to find the answer.

Newberg and Johnson (50), in their article "Endogenous Obesity--A Misconception" state that obesity is the result of an overabundant inflow of energy which is deposited as adipose tissue. This disproportion, they attribute to two general causes, namely: (1) human weaknesses, such as overindulgence and ignorance, and (2) a decrease in the requirements for energy, such as lessened activity or lowering of the basal metabolic rate for any reason. This, however, merely states the immediate cause of the obesity (a symptom) but not the fundamental causes underlying the increased appetite that leads to overindulgence, the lessened activity, or the lowered basal metabolic rate.

Silver and Bauer (57) say that obesity is practically always congenital or hereditary, explaining it as an inherent tendency of certain individual tissues to store fat. As an example of this they point out that a pedicle skin graft taken from the abdomen where there is usually a fairly heavy layer of fat and transplanted onto the dorsum of the hand where there is rarely any fat continues to maintain a good layer of fatty tissue. They also maintain that an increased appetite does not produce obesity but that an inherent tendency of the individual to store food in the form of fat causes him to have an excess appetite. As an example of this they cite a report on acromegaly (55) in which the authors showed how they had produced acromegaly in a dog by the injection of anterior pituitary extract. The dog thus treated grew much larger than the control and showed a marked increase in appetite. Silver and Bauer used this to show that the dog ate more because he was growing, not that he grew because he ate more. Grant that as true, I can still not see how they hope to prove anything by it. The dog did not grow because of any inherent tendency , he grew because he was receiving an abnormal amount of the anterior pituitary hormones. Thus, the endocrine cause for disturbances in the production of fat is more firmly established. However, this acromegalic dog was not in the least bit obese. To quote from the article itself, "Whereas the control

animal had a normal panniculus, in the dog which was given the injections there was an almost complete absence of subcutaneous and omental fat; only a few brownish shreds appeared here and there".

The positive side of the question has the advantage of a greater number of proponents. Some of them are quite conservative, as Christie (8) who states that not more than ten percent of all obesities are of endocrine origin. Others are a bit more emphatic in their stand for the endocrines. Lisser (40) insists that the shape and bulk of the human body is governed principally by the thyroid, pituitary and gonads. Engelbach (19) attempts to evaluate obesity as one of the most important diagnostic signs of ductless gland disorders. He belittles the idea that obesity,as a rule, is due to overindulgence, lack of exercise, etc. "Admitting that such causes do have some bearing upon certain cases, the fallacies of these deductions are soon proved by careful observation of a series of obese and emaciated patients.....The simple experiment of inquiring into the amount and kind of diet taken by a majority of obese individuals proves that, from the force of habit, acquired by many years of self-treatment, their intake actually is smaller and more deficient of carbohydrate foods than thatof the individual of average weight."

The balance of evidence seems to be in favor of the endocrinopathies. For that reason, and for the sake of simplicity, I shall present the various types of obesity as separate endocrinic entities.

Classification

The classification of endocrine obesity may be taken up from several different angles. Some authors (8, 20, 63) divide adiposity into three divisions according to the age of the patient at the onset of the condition: (a) Infantile adiposity, (b) Juvenile adiposity, and (c) Adult adiposity. Another method is to classify it according to the distribution of the fat. As will be seen later, disturbances of the various glands produce more or less typical distributions. This method, however, is rather uncertain. Still another classification is one based on the gland or glands involved. This one is the most commonly used and by far the simplest. For that reason, it is the one that will be followed in this paper.

The Pituitary Types of Obesity

The Pituitary gland is probably the most important of the ductless glands because of the wide range of influence it seems to exert both before birth and during the various stages after birth (43). To this gland three types of obesity are attributed, namely, Froehlich's syndrome or adiposogenital dystrophy, Dercum's disease or adiposis dolorosa, and Cushing's basophile hyperpituitarism. Lisser (41) classifies all three under the common heading of Froehlich's syndrome. He divides it into six types:

1. The childhood form (of two types): a, with skeletal undergrowth (Lorain type): b, with normal skeletal growth or overgrowth (Brissaud type).
2. The adolescent type.
3. The adult type.
4. Hypopituitarism with acromegaly (Neurath-Cushing type).
5. Adiposis dolorosa (Dercum's disease).
6. Dystrophia adiposogenitalis with atypical retinitis pigmentosa and mental deficiency (Lawrence-Biedel syndrome).

Since Froelich, in 1901, first described his epoch-making syndrome, much work has been done to prove or disprove the connection of the pituitary body to obesity. Cushing (11) was able to produce this syndrome in dogs by removing the anterior lobe of the hypophysis. He therefore concluded that it was due to hypofunction of the anterior lobe, but at the same time, he would not deny that the posterior lobe might also play a part.

Later Smith (58, 59), after a series of experiments on rats, produced evidence that he could remove the hypophysis entirely without producing obesity. This he attributed to the fact that he carefully avoided any injury to the tuber cinereum. Then, by leaving the pituitary gland undisturbed, he was able to produce a typical "pituitary" type or obesity by slightly injuring the tuber cinereum. Thus the relationship of the pituitary to the production of obesity was severely questioned. Then on the other hand, Reichert (56) reported that adipose tissue, especially in the groin, of a hypophysectomized dog, definitely disappeared during the first two weeks after beginning pituitary transplants.

The question was not settled with the findings of either Smith or Reichert. Strength was added, however, to the pituitary viewpoint when Anselmino and Hoffmann (1) in 1931, reported the occurence of a substance in the

in the anterior lobe which causes a rise of the acetone bodies in the blood. It has been found that under physiologic conditions the substance occurs (in the blood) only when fat is burned. From this and other facts the authors concluded that this substance had a regulatory function in the fat metabolism. These facts are: primarily the occurence of the substance in the blood only when fat is burned, not under other conditions; secondly, the well known connection of acetone bodies with fat combustion or transformation; and finally, the old clinical observation of a connection of the anterior lobe with certain forms of obesity.

Experimental work seems to challenge the complicity of the hypophysis itself to conditions that have long been called hypophyseal adiposity. On the one hand, adiposity does not result from discrete injury to the hypophysis or its removal, and on the other hand, we have seen the invariable production of adiposity by slight injury to brain areas adjacent to the hypophysis. Still, we have the results of Cushing (11) and others (24) who claim to have obtained results therapeutically following the administration of hypophyseal substance.

Absolute proof of the activity of the pituitary gland is as yet lacking. There are certain types of obesity, however, which are commonly attributed to it. For convenience I will describe them as pituitary obesities, keeping

in mind, of course, the element of doubt and the possibilities of what further researches may disclose.

Froehlich's Syndrome

Adiposogenital dystrophy was first described by Froehlich in 1901. It is a fairly clear-cut symptom complex, very common at puberty, and not at all uncommon in later life; though many early examples lose the characteristics in the later years of adolescence (18). Beck (4) Defines it as a condition due to underfunction of the hypophysis, characterized by obesity, genital hypoplasia, and faulty skeletal development; associated with nervous and mental symptoms which are either the direct result of deficient secretion or dependent upon local or general intracranial pressure.

Etiology

The etiology of Froehlich's syndrome includes a very wide range of factors. It is easy to understand how practically anything could upset the delicate balance of the endocrine system. Thus it is not remarkable that so many people are suffering from disorders of this type, but that not more are affected. Beck (4) lists very completely the possible etiological factors. It is from him that I am taking most of the following material. It is unnec-

essary in most instances to discuss to any extent these factors so I will but list them giving explanations only where they appear necessary.

1. Predisposing factors:
   a. Heredity - It is frequently noted that one or both parents of these patients are obese, or that there is a brother or sister showing the same syndrome.
   b. Congenital hypopituitarism - Under this may be grouped, first, developmental abnormalities, either osseous, influencing the size and shape of the sella turcica, or glandular through embryonic defect in which the pituitary is imperfectly developed; and second, congenital syphilis.
2. Trauma - This is demonstrated by Madlung's case, so often quoted, in which a bullet lodged in the sella turcica of a nine year old girl and produced the typical syndrome of adiposogenital dystrophy.
3. Alterations in physical epochs - This grouping includes puberty in both sexes, and menstruation, pregnancy, lactation, and the climacteric in the female.
4. Infections - Both severe and chronic infections play an important role. It is a common observation that the obesity first makes its appearance after some severe infection, notably typhoid and rheumatic fever.
5. New growth - This may be in the form of a simple hyper-

plasia, as it is caused in cases of multiple pregnancies, or in the form of a true neoplasm. The following varieties of hypophyseal lesions have been encountered, namely, adenoma, glioma, maningioma, metastatic carcinoma, adenocarcinoma, teratoma, sarcoma, angioma, cystoma, lipoma, chondroma, and fibroma; other lesions include gumma, tubercles, embolism, hydrocephalus, etc. (4)

Symptoms

The two striking symptoms emphasized by Froehlich in his original report (42) are obesity and genital hypoplasia. These symptoms naturally vary somewhat depending upon the sex and age at which the condition first manifests itself.

Obesity - The obesity is characteristically deposited about the hips, thighs, mons, and lower abdomen - girdle obesity - with the extremities notably unaffected (4, 5). The hands and feet are distinctly free from fat deposits in practically all cases, giving them a small, delicate appearance in contrast to the unusually bulky body. The mammae are also frequently involved. In a case of a man thirty-four years of age, reported by Loewenberg (43), the mammary glands are described as large and pendulous, resembling those of a mature woman. In early life the tendency is toword a more general adiposus. After puberty

there is more variation in form and figure of body. In a large group of cases, especially in women, there is an enormous preponderance of fat localized in the above mentioned areas in otherwise normally developed individuals. These deposites often appear as huge masses of folds over the buttocks and thighs with an apron of fat (panniculus adiposus) over the lower abdomen (4). It is distinctly a girdle type of obesity, with the greater proportion of the adiposity spread from the navel down to about the middle of the thighs, and over the mons veneris (2).

The peculiar distribution of the fat gives to the males a marked feminine appearance. The resemblance of this distribution to that produced frequently by castration is more than coincidental, as will be seen under the discussion of gonadal obesities.

Diagnosis

The diagnosis of dystrophia adiposogenitalis ordinarily is not difficult. The triad upon which the syndrome is based consists of obesity, skeletal undergrowth, and hypogenitalism. To complete the clinical picture alterations in the sella turcica and neighborhood symptoms, including distortion of the visual fields should also be added. As to the alterations in the sella turcica, these may be enlargement and distortion as

produced by tumor growth in or around it or a diminution in size. In quite a number of cases,however, there is no noticeable change in the outline of the sella turcica (4). Notice should also be taken of the physiological age of the patient.

A complete differential diagnosis will be taken up at the end of this section on pituitary obesities.

Adiposis Dolorosa

Adiposis dolorosa is a syndrome of symptoms associated with fat metabolism. It is characterized by four cardinal symptoms, (1) adiposity, (2) pain and tenderness of the fatty tissues, (3) asthenia and (4) psychic disturbances,(44). To this may be added bullae or ulcers on the extremities (25). It was first described by Dercum in 1892. In his original paper he described three cases of the disease with the griss pathological findings of two of them, both of which had abnormal thyroid glands. Thus he was led to the conclusion that the disease was the result of a dysthyriodism. In 1902, Dercum and Mc Carthy (17) reported another case which revealed a pituitary gland enclosed in a calcareous layer between it and the dura and composed mostly of a tumor of eosinophilic cells. The thyroid in this case was perfectly

Normal. Dercum and McCarthy thus concluded that the pituitary body bore some relation, though perhaps indirectly, with a fat-producing or fat-destroying function, a relationship which up to that time, had not been considered.

Cushing (12), in 1912, was the first to question the rationale of calling the disease a clinical entity. He felt that the syndrome covered too many conditions to be classed as such. In his opinion many of the cases of adiposis dolorosa could not actually be called examples of disturbed metabolism secondary to disease of the ductless glands. Wilson (68), in 1933, agreed with Cushing that this is not a clinical entity. This is shown by the fact, he believed, that there have been no findings consistent in all of the cases reported. "It seems more reasonable to assume that the condition is one of either simple obesity or lipomatosis associated with neurosis or neurasthenia, and that the pathological conditions that have come to autopsy were incidental." As has already been mentioned, Loewenberg (42) classifies it as merely another type of Froehlich's syndrome.

Etiology

Regarding the etiology of this syndrome as a whole, most authors are content to call it a polyglandular syn-

drome without going any further to explain it. Dercum (16), in one of his earliest papers expressed his belief that it was due entirely to a thyriod disturbance. Later, however, he accepted the pituitary gland as probably the main etiological factor, but, to quote his words, "the fact that the thyroid gland has been found diseased in all cases cannot but be of significance" (17). Other writers since then have expressed much the same view but attributed the changes in the other endocrine glands as a result of pituitary changes (25) Waldorp,(64) on the other hand, attributed the obesity to perturbations in the trophic diencephalic centers. In conjunction with this view I might again mention the recent works of P. E. Smith (58, 59) regarding the production of obesity following slight injury to the tuber cinereum. Winkelman and Eckel (71), in1925, reviewed the necropsy findings of the fifteen cases in the literature up to that time. Their findings are quite interesting: in only two of the cases were there no definite changes in the ductless glands. Of the eleven patients in whom the pituitary body body had been examined, eight showed definite alterations; the thyriod was abnormal in twelve cases; the sex glands were pathologic in nine cases; the suprarenal in three, and the pancreas in two.

With the variability of the number of glands and the individual glands involved, it is easy to see why many of the authors refuse to accept this condition as a clinical entity. In the light of our present knowlege, it is impossible to assign Dercum's syndrome to any definite cause or series of causes except to say that the most commonly accepted theory is that it is a polyglandular syndrome.

Symptoms

Obesity - The obesity of this syndrome is highly variable, both in form and distribution. Diffuse deposits may involve a single portion or the greater part of one extremity. It may involve only a single small area, may be symmetrical, or it may be almost universal. The face, hands, and feet are characteristically free from fat, although even these regions have been invaded in rare instances. Many cases have been reported in which the fatty deposits were described as nodular, lobulated, feeling like a bundle of worms or like a varicocele (6, 16). The nodular masses may be encapsulated, single, multiple, or symmetrical (44).

As a general rule the obesity seems to involve the trunk only, resembling in this respect the adiposity of Froehlich's syndrome. The distribution may be about either

the pelvic or the pectoral girdle, or both. Lyon (44) reports a case in which the fat is distributed only to the thorax, neck, and upper arms. On the back it hangs in large, pendulous folds. The lower half of the trunk, the legs, and the forearms are remarkably free of fat, appearing emaciated. Other cases described in the same article show the distribution involving the entire body except head, hands and feet or involving only the thighs or the upper arms.

The fat is not limited only to the subcutaneous tissues. In the two cases that came to autopsy in Dercum's first series fatty changes in the heart and fatty infiltration of the liver were reported in both (16). Foote et al (25) in their case found fatty infiltration of the myocardium, fatty invasion fron the epicardium; fatty invasion of the liver; and they reported the omentum as moderately adipose and the mesenteric vessles imbedded in lines of fatty tissue. On the other hand, other cases have been reported (71) in which the mesentery, omentum, heart, pancreas, and liver were "only slightly fatty". Thus one might conclude that the internal distribution of the fat faries very much like the subcutaneous distribution.

The pain in the fatty masses may vary from tenderness

on pressure to violent attacts of spontaneous pain which have been described "as though a dog were tearing the flesh from the body" (68). There have been cases reported in which there was no pain, although all the other cardinal symptoms were present (25). The larger proportion of the cases, however, have definite pain on pressure or spontaneously (17, 68, 71).

The exact cause of the pain is not clear. Some ascribe it to peripheral neuritis of the nerves in the fatty masses and report finding this condition to substantiate their claims (6,71). Foote et al (25) reported finding the fat and nerves perfectly normal on microscopical examination. Waldorp (64) ascribes the pain to either a lesion of the optic thalamus in the brain or to a peripheral neuritis. Wilson (68) makes no attempt to explain the pain in the fatty nodules, although he does suggest that pain in the abdominal wall may be due to stretching of the nerves that supply it. As yet no satisfactory explanation of this symptom has been offered.

The adipose tissue in these cases seems to show no special characteristics of its own. Some authors have reported it as being normal fat or resembling in structure a lipoma (25, 68). Burr (6) in reporting a case of this type described the gross appearance of the fat as re-

vealing a fibrous character, it being firmer than normal subcutaneous fat and showing here and there, in encapsulated areas, softer and less yellow in color. Microscopically there was a marked increase in connective tissue. An interesting report on the chemistry of the fat is given by a Dr. D.L.Edsal who compared fat from these tumor masses with free subcutaneous fat and omental fat.

	tumor masses	free subcut. fat	omental fat
Iodine value	71.53	70.03	69.18
Melting point	28.5 C	29 C	31.5 C
Acid value	4.4	2.0	1.2

The iodine numbers and the melting points are all about normal. The figures for the acid value are all rather low, but that for the tumor fat is more than twice as great as that of the other fats. It was hoped by the authors that a still higher value might have been obtained. This, they felt, would have offered some explanation of the pain.

One can not say that the fat of Dercum's disease differs in any great respect from normal fat. The differences that have been reported apparently might have been secondary changes, possibly circulatory in origin.

The other symptoms of Dercum's disease are the same as those of Froehlich's syndrome, with the exception that the nervous symptoms are more marked. These consist mostly of

visual disturbances such as changes in the visual fields and muscular imbalance (13, 65); nervous and mental disturbances such as lassitude, torpidity and drowsiness, states of excitement, depression, psychoneurosis, and even hallucinations (4). Other authors record also retarded mental development, epilepsy, severe headache, insomnia, somnolence, syncope, coma, vertigo, and tinnitus.

Diagnosis

The distribution of the fat in this disorder is the same as that in Froehlich's syndrome. The main differential factor is the pain in the fatty masses, although this is sometimes also seen in cases of Froehlich's syndrome. Dercum's disease is also accompanied, not infrequently, by genital hypoplasia, like that in the other condition. Differentiation between these two conditions seems to be more a matter of degree than of specificity.

Basophilism

In 1932, Cushing (14) retrieved from the waste-basket group of "polyglandular" syndromes a condition which he designated as pituitary basophilism. This syndrome he described as comprised of seven characteristic features:

1. Rapidly acquired, peculiarly disposed, and frequently painful adiposity confined to face, neck, and trunk, the expremities being spared.

2. A tendency toword kyphosis.

3. A sexual dystrophy shown by early amenorrhea in the females and ultimate functional impotence in the males.

4. An alteration in normal hirsutes shown by a tendency to hypertrichosis of face and trunk in all the females as well as the preadolescent males and probably the reverse in adult males,

5. A dusky or plethoric appearance of the skin with purplish lineae atrophicae.

6. Vascular hypertension - $\frac{230}{170}$ to $\frac{178}{100}$

7. A tendency to erythemia.

Later writers (9, 53) have added to this headaches, asthenia, fatigability, hyperglycemia, and albuminuria, intracranial signs with exophthalmos, diplopia, papilledema, dimness of vision, polyphagia, polydipsia, polyuria, and acrocyanosis.

This syndrome most frequently makes its appearance in young persons, the average age of onset being given as eighteen years (14, 53). The onset is most frequently manifested by a sudden cessation of menstruation. This

is followed by an increase in weight accompanied by a loss of hair from the scalp and increase in the amount of hair notably on the face and limbs. There is also a tendency for these patients to become round-shouldered in the course of a few months, which may be so marked as to cause a loss of two to three inches (5 to 7.5 c.m.) in height. The greater majority of the cases prove fatal in the course of about five years.

Etiology

When Cushing first described this condition (14) he attributed it to a primary hyperfunction of the basophilic element of the pituitary body, with secondary changes in other of the endocrine glands. Later authors (9, 53) have also born out this original contention. Cushing, however, does not give the entire credit for the obesity to the pituitary gland. He states (15) that the basophilic elements may not exercise their effects through the blood stream, but their product, possibly modified during its passage through the posterior lobe and stalk, may exercise a local effect, presumably stimulatory, on the diencephalic nuclei in whose neighborhood the veins carrying the anterior lobe secretions appear to disgorge their product. The obesity may be, therefore, a tuberal one. As Smith (58, 59) has shown

that obesity may be produced by slight injury to the tuber cinereum, so Cushing believes that on the basis of a tuberohypophyseal mechanism hyperactivated by secretory products from the pars intermedia a similar process is established which is the immediate cause of the obesity accompanying basophilic adenomas of the pituitary gland. This hypothesis is strengthened by the fact that many of the patients show varying degrees of polyuria and polydipsia.

The pathological findings at necropsy have shown a considerable degree of variation. The findings of pituitary adenomas have been most constant. These have varied in size from 2 to 3 m.m. in diameter to adenomas replacing almost a whole lobe of the pituitary gland. The adenomatous growths have been found most consistantly to be composed of basophilic cells. Pardee (53) believes that in the face of no adenomatous growth demonstrable, a simple hyperactivity of the basophilic cells is the cause of the milder, non-fatal degrees of this disease. Associated pathology in other glands, such as hyperplasia of the adrenals and atrophy of the ovaries or testicles, is often found.

Symptoms

Obesity - The most that can be said for this is that it is limited to the head and trunk, the extremities being spared. The face, the breasts, and the abdomen are the most common sites of the fatty deposites. This distribution may vary from a general adiposity to that resembling froehlish's syndrome. The obesity of the abdomen, instead of forming a flabby apron so frequently seen in the other types of pituitary obesity, resembles, with unusual frequency, a full term pregnancy. In several cases reported (14) the fatty deposites have been painful, resembling Dercum's adiposus dolorosa.

The other symptoms have already been listed under Cushing's description.

Differential Diagnosis of Pituitary Obesities

	Froehlich's	Dercum's	Cushing's
Obesity	girdle no pain	girdle painful nodular	Head and trunk often painful
Genital	hypoplasia	hypoplasia	hypoplasia
Skeletal	undergrowth Sella altered	undergrowth sella altered	osteoporosis sella usually unaltered
Nervous	psychic disturbances visual disturb.	marked psychic disturbances	no change
Miscell.		bullae and ulcers on extremities	striae atrophicae on abd., & extremities

Thyroidal Obesity

That the thyriod gland bears a relationship to certain types of obesity is an almost universally accepted fact. It is common knowlege that hypothyriodism is accompanied by an increase in weight.

Thyroxin, the secretion of the thyriod gland, has a stimulating effect upon the metabolism. Hence a deficiency of this substance causes a lowering of the metabolic rate. This lowering of the nasal metabolism has been used to explain the obesity on the basis of a lessened output of energy. In 1921, Mellanby and Mellanby (J. Physiol. 55:vii-viii) found that a great amount of fat in the diet produced a hyperplasia of the thyroid gland. From this it may be concluded that there is some direct relationship between this gland and fat metabolism. According to Croti (10) this is because of a lipase that is formed in the thyroid.

Etiology

Thyriodal obesity can be divided into two main groups; physiological and pathological.

(1) Physiological group.

(a) Puberty and adolescence - This form is usually transient and associated with some swelling of the gland. It iccurs as a result of functional strain upon the thyriod which therefore undergoes varying degrees of hypertrophic

or colloid swelling. The basal metabolic rate is almost invariably low, from -10% to -30%. The weight increase may vary between ten and forty or more pounds above the average normal.

(b) Obesity after parturition - This condition is brought on by an exhaustion of the thyroid because of the recent strain made upon it by the recent pregnancy.

(c) Obesity after convalescence - This type is frequently seen following convalescence from some severe infectious disease such as typhoid fever and pneumonia. This too is a condition of exhaustion from the recent strain of the infection.

(d) Abdominable obesity - This is the "bay window" type seen occuring in middle age and early senility. It is attributed to thyroid atrophy resulting from 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 for weight increase. The obesity may be out of proportion to the metabolic findings, as these may be but little below normal.

(2) Pathological types of thyroidal obesity.

(a) Postoperative - This is simply a case of hypothyroidism from an insufficient amount of gland tissue.

Operative removal or X-ray treatments are the basis for this lack of sufficient tissue.

(b) Thyroidal obesity following administration of iodine - A case of this type is reported in which there was a recurrence of symptoms of thyrotoxicosis following thyroidectomy. The patient was given iodine and the basal metabolic rate dropped to minus twenty- eight and minus thirty. Then by stopping the thyroid the physician was able to bring the B.M.R. up to a minus fourteen (28).

Symptoms

Obesity - The distribution of the fat in the so-called thyroid obesity differs markedly from the pituitary types previously described. It is a smooth, universal distribution of subdermal infiltration with cervical fat pads in the supraclavicular region and padding of the hands and feet on their dorsal surfaces (22). The entire body is involved. The face is full, "moon-faced". The trunk is uniformly covered with an even layer of adipose tissue. The extremities are obese to their tips in contradistinction to the slender hands and forearms and feet and ankles of the pituitary obesities. Masterman-Wood (48) describes completely this distribution in one paragraph: "The distribution of fat is generalized with peculiarly marked focal excesses. These excesses are

obvious in the conformation of the face with its swollen lips and cheeks, puffy eyelids, underhanging secondary chins, and immensly thickened neck. The supra-clavicular hollows are completely obliterated, and upon both supra-scapular regions are large prominens. The arms are gross and the fingers and backs of the hands are puffy. The breasts and abdomen are very fat, while the elephantine legs terminate in feet and toes swollen and puffy on their dorsal aspect".

Other symptoms - The signs and symptoms of hypothyroidism are dependent upon a lowered metabolism. The skin is dry, and cold with a tendency to thickening and scaling. Skin eruptions, usually eczematous in character, are quite common. The hair is coarse, dry, and brittle and frequently is lost to a considerable degree. There may result an almost complete alopecia. The eyebrows and the eyelashes are also scant. The nails are coarse and brittle. The heart rate and the blood pressure are low (39). These patients also have a low sugar tolerance. Cachexia is as frequent in these patients as is obesity. A low basal metabolism is the most commonly accepted sign of thyroid deficiency. Hurxthal (33), however, lists also suprarenal deficiency and hypophyseal deficiency as causing a lowered metabolism. Thus, as he states, not all cases of obesity with a lowered metabolic rate can be

called hypothyroidism. As a criterion in the differential diagnosis between these three factors he makes use of the blood cholesterol, which has been shown to be increased in cases of hypothyroidism (47).

Adrenal Obesity

McKinlay and Fisher (46), in 1926, demonstrated that there was some relationship between the adrenals and fat metabolism. Goldzieher (27), again in 1927, obtained the same findings, He showed that there was a decrease in blood cholesterol in experimental animals following the injection of extracts of adrenal cortex. Later, in 1934, he showed there was also a marked increase in the weight of animals thus treated. This he interpreted as the effect of a lipoid fixing (lipopexic) activity of the hormone.

The role of the adrenals in obesity is further demonstrated by the extreme loss of fat that occurs in conditions of suprarenal insufficiency and the fact that patients suffering with thes condition gain markedly in weight on cortical hormone preparations (52).

Etiology

The obesity occasioned by a disturbance in the adrenals

is perhaps less often recognized andtunderstood than that of any other group. This obesity is always associated with a disturbance of the cortex which may be caused by either a diffuse hyperplasia or a neoplasm, (27, 38). Three cases reported by Walters, Wilder and Kepler disclosed adeno-carcinoma in two of the cases and an adenoma in the other (66) Koster et al (38) report a case in which they found no tumor but simply a hyperplasia of both suprarenal glands. One was approximately three times normal size and the other was still larger. After removal of the larger of the two glands the patient lost a total of 145 pounds in a period of about eseven months.

Symptoms

The pathological changes in the adrenal cortex produce three different syndromes depending on the age of the individual at the time of their development. If the lesion occurs during intrauterine life, there is a disturbance in sexual development causing hermaphroditism in a large number of cases. When the pathological changes begin early in infancy, precocious sexual development results. This type is by far more common in the female, and is very often associated with obesity, excepting when the adrenal cortex is the seat of malignant neoplasm. The third type develops during adult life and is

accompanied by obesity, changes in the secondary sexual characteristics toword the male line, such as hirsutism, thickening of the skin, and changes in the voice. Amenorrgea of variable duration is a concomitant feature (38).

Obesity - The obesity affects mostly the face, neck, trunk, arms, and thighs. The abdomen, buttacks, and breasts are common sites of fatty deposites. The forearms and hands, and the legs and feet are characteristically not involved, (7, 38, 66).

Other symptoms - This condition appearing in the female causes a change in the secondary sexual characteristics. This is shown by a hairy growth on the face, especially the upper lip, the arms and legs, and the chest. The crines pubis is often of the masculine type, extending up to the umbilicus in some cases. Other changes toword the masculine type are a thick skin frequently marred by acne and comedones, voice changes - the voice becomes deep - and virilism. Some patients demonstrate a remarkable strength. One case is reported, however, in which the patient complained of weakness.

There is frequently a precocious sexual development in those cases appearing before or during adolesence.

Small children two years of age may have an adult development of the external genitalia. Hypertension and hyperglycemia and hypocholesteremia are also common findings (35, 38, 66).

Gonadal Obesity

We have all seen the practical application of castration as it is used in agriculture to fatten stock animals. The boar and the steer, after castration, increase their market value considerably by their increase in weight. Pezard (54), working with chickens, found that periabdominal fat in castrated cocks averaged somewhere between 90 and 150 grams, while in the normal fowl of the same type it weighed between 10 and 60 grams. The effects of castration in the human have been studied and published by Walter Koch (37) during his residence among the castrated sect of Skopzies in Roumania. The skopzies are a religious sect living in Russia and Roumania whose religion prescribes that male members be castrated. (How they manage to propagate their cult is beyond me.) Koch described four types of Skopze: (1) the ordinary type with long extrenities; (2) the type of gigantism; (3) the type with acromegaly, and (4) a type with hypophyseal obesity. The type seems to depend upon the age at which the castration was carried out.

Castration in the female is frequently encountered following pelvic inflammatory conditions which necessitate surgical removal of the ovaries. The menopause is, in effect a physiological castration. It is generally recognized that obesity usually, but not invariably, follows such operative procedures (49). According to Wintz (cited by 49) 40% of menopausal women become more or less obese.

Etiology

Testicular insufficiency may result from trauma; from disease such as syphilis, gonorrhea, orchitis following mumps, scarletina, measles, or pneumonia. It may be secondary to primary disease of some other ductless gland, e.g., of the pituitary body in dystrophia adiposogenitalis. Malignant tumors of the testes may also destroy or necessitate the surgical removal of the testicles (2, 21).

In the female, ovarian insufficiency may be produced by removal of the ovaries at operation. It may be secondary to a primary impairment of other ductless glands, e.g., hypo- or hyperthyroidism, or pituitary disfunction in adiposogenital dystrophy. Insufficiency of the medulla of the adrenals is also given as a cause. Ovarian atrophy following the menopause is the most common

cause (21, 36, 49).

Symptoms

The symptoms of hypogonadism depend not only upon the degree of hypofunction of the glands, but also, to some extent, upon the sex of the individual, the age at the onset, and the degree to which other ductless glands are disturbed. Hypogonadism in the male produces a change in the distribution of the hair about the body, a change toword the female type of distribution. The hair of the arms, legs, and chest is absent or very scanty. The crines pubis assumes a female configuration. Lanugo hairs take the place of the mature hair on the face (2, 45, 62).

The psychosexual conditions of individuals who have been castrated early in life clearly show an absence of sexual power. There is impotence and loss of libido and energy. There is a decrease in the size of the genitalia in the adult, while in the preadolescent they remain infantile.

Mentally, castrates are inferior to normal individuals. They are also nervous and excitable. Following castration many men complain of hot flashes followed by sweats (45, 62).

The voice in early castrates retains its timbre of youth at about the age of puberty. This factor was frequently utelized during the middle ages to maintain tenor voices for the singing of God's praises.

The symptoms of castration in the female are essentially the same as those in the male with one exception, in the human female libido is usually not influenced, in fact it is occasionally even accentuated.

The disposition of the fat is the same in both sexes. Characteristically it is deposited in the trochanteric regions (35). In uncomplicated complete hypogonadism the panniculus adiposus is confined to the iliac crest, mons, and upper and outer third of the thigh, which includes an area extending from just below the lateral margin of the iliac crest to an approximately equivalent distance below the great trochanter with its peak opposite the latter bony prominence (48). The lower abdomen is also a favorite site of the fatty deposites (45, 62) as well as the outer ends of the upper eyelids. The similarity between this type of obesity to that of Froehlich's and Dercum's syndromes has already been discussed.

Pancreatic Obesity

Another possible endocrine factor in the production of obesity is hyperinsulinemia. With an increased production of insulin the blood sugar drops. The patient then complains of such symptoms as weakness, trembling, dizziness, severe hunger or pain in the pit of the stomach. These symptoms are relieved only by eating. Thus a vicious cycle is established which consists of hunger - eating - relief - hunger - eating and so on until the patient becomes obese (31, 49). Besides the increased ingestion of food there is the increased carbohydrate metabolism aided by the abnormal amount of insulin. Considering the protein-saving value of carbohydrates, one can readily see how obesity could be the result of such a cycle.

Etiology

The causes of pancreatic hypoglycemia involve considerable discussion of the physiology of the pancreas and also of the other endocrine glands as well. Without going to too great length, I shall endeavor to but list the possible causes with only a brief discussion of them.

Simple hyperplasia of the islets of Langerhans resulting in an increased secretion of insulin has been

suggested as a cause (30). Along with this might be mentioned tumors of the pancreas. Simple adenomas of the island tissue, according to Smith and Seibel (60) are not as uncommon as the small number of cases reported would lead one to believe. They report five cases of proven adenomas associated with hypoglycemia. It is their belief that the tumor cells do not respond to the normal controling mechanism for the production of insulin. Tumors of the acinous portion might also play a part in causing hypersecretion of the islands. Epstein and Rosenthal (23), in 1925, showed that there was a relationship between trypsin and insulin; that the trypsin neutralizes the insulin. Hence if a tumor were large enough to destroy the trypsin-producing tissue, or by blocking the larger ducts, impair its activity, this portion of the insulin regulating system might be disturbed with a resultant hyperinsulinism. Other factors causing a blocking of the ducts, such as a chronic pancreatitis or inflammation of the ampulla of Vater, would produce the same effect.

Some authors attribute this disturbance to overstimulation by dietary excesses (69, 70). Many of these patients are found to have been on a distinctly high carbohydrate diet previous to the onset of their symptoms.

This, of course, might have been merely one manifestation of a mild hypoglycemia existing for a period of years before it became marked enough to produce alarming symptoms. However, if it is accepted as a fact that faulty diets predispose to the infections that play a part in the etiology of pancreatitis, sugar-saturated, vitamine-starved Americans, i.e., those who live largely on white flour bread, white potatoes, white rice, lean meats, sugar-saturated coffee, and sugar-laden desserts, with candy and soft drinks between meals, would seem to be prone to become victims of pancreatic disorders, including hyperinsulinism and diabetes (29, 31).

Symptoms

The symptoms of this condition are essentially those of insulin shock, sometimes seen in deabetics after they have received too much insulin. Characteristically the attact comes on several hours after meals, as during the night or in early monning before breakfast. Physical labor or exercise between meals will shorten the interval. A sensation of weakness associated with a feeling of hunger is usually the first complaint. Then follows a feeling of anxiousness and a sensation of inward trembling. This latter begins in the extremities and passes on into the body. Excitability and slight emotional

disturbances are next seen. Sweating, tachycardia, blurring of vision, and diplopia develop. Incoordination is seen as the patient attempts to drink or to rub his hands over his eyes in an endeavor to clear his vision. Motor aphasia, tremors, mental confusion, and disorientation are next in order. Then convulsions, not unlike epilepsy set in. They gradually subside and the patient passes into a state of coma unless carbohydrate is given, but many pass off at any stage depending upon some autonomic mechanism that releases stored-up glycogen to raise the blood-sugar concentration (32).

Not all cases of hyperinsulinemia are associated with obesity. In fact a large portion are distinctly emaciated or cachectic. I am able to find reports of several cases which showed an increase in weight (32, 69, 70), but nowhere have I found any description of the obesity. One author (70) states that the configuration of his patient was not that usually found in pituitary obesity. However, judging from the fact that this obesity is primarily the result of overeating, I feel that I am safe in assuming that there would be no definite or characteristic distribution of the fat. Then too, the distribution would certainly vary with the other endocrine glands that might also be disturbed.

Conclusions

1. It is important that the general practitioner understand the pathological physiology of obesity, that he may establish more effective pherapeutic measures.

2. While there is still much to be said, the balance of evidence seems to be in favor of certain of the endocrinopathies as etiological factors in the production of obesity.

3. Due to the close proximity of the tuber cinereum to the hypophysis and the evidence that there is a relationship of the tuber to obesity, there is some question as to the actual relationship of the hypophysis. Still, there is evidence that it plays an active role from the fact that results have been obtained therapeutically with the administration of hypophyseal extracts.

4. Froehlich's syndrome and Dercum's disease may be but different degrees of the same condition. Cushing's basophilism, however, is evidently a separate entity.

5. Adiposogenital dystrophy, or Froehlich's syndrome is a condition due to under function of the hypophysis, characterized by obesity, genital hypoplasia, and faulty skeletal development; associated with nervous and mental symptoms which are either the direct result

of deficient secretion of dependent upon local or general intracranial pressure.

6. Dercum's disease is quite like an exaggerated picture of Froehlich's syndrome; pain in the fat is occasionally seen in the latter, while it is a constant finding in the former, and the nervous symptoms in Dercum's disease are the same as in Froehlichs syndrome, only of a more marked degree.

7. Cushing's basophilism is always associated with an adenoma of basophile cells of the pituitary body. This is the only one of the pituitary obesities with a constant pathological finding.

8. The obesity of pituitary origin is characteristically a girdle obesity, involving either the pelvic or pectoral girdles, or both. The extremities are rarely, if ever, involved.

9. Thyroidal obesity is peculiar to itself. It is a smooth, universal distribution of subdermal infiltration with cervical fat pads in the supraclavicular region and padding of the hands and feet on their dorsal surfaces.

lo. The thyroid is much less often a cause of obesity

than the literature on the subject would indicate. Hypothyroidism may cause cachexia as well as obesity. A diagnosis of thyroidal obesity cannot be made on the finding of a lowered basal metabolism rate alone. It has been shown that hypophyseal and suprarenal deficiencies also occasionally cause a lowered metabolism.

11. Hyperactivity of the adrenal cortex is another cause of obesity. This type affects mostly the face, neck, trunk, arms, and thighs, also the abdomen, buttocks, and breasts.

12. Hypogonadism resulting from trauma, disease, surgical removal, or physiological atrophy of the gonads is a common cause. The distribution is typically inter-trochanteric.

13. Hyperinsulinemia produces obesity by causing an increased appetite and by increasing the sugar metabolism. The literature is peculiarly devoid of any description of the distribution if the fat in these cases.

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