ADIPOSOGENITAL DYSTROPHY

(FROEHLICH'S SYNDROME)

BY

KATHARINE HOWARD BAIRD

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF MEDICINE

UNIVERSITY OF WISCONSIN

1938

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INTRODUCTION

Adiposogenital Dystrophy is a very old and yet a relatively new disease. We have evidence that the condition existed in the old stone age and in ancient Egypt of 1400 B.C.[22][49] Still it was not until the beginning of the twentieth century that the syndrome became known in the medical literature. Babinski published his case report in 1900.[1] That of Froehlich, from whom the condition was to receive its name, was published independently in 1901.[21] True Bramwell in 1888 in his book on intracranial tumors had noted that tumors of the hypophysis were often associated with excessive development of subcutaneous fat, but this contribution attracted no attention and was overlooked until recently.[13] Just thirty years ago in 1908 Bartels introduced the name, adiposogenital dystrophy.[49] These past thirty years bringing with them the development of the new science of endocrinology, new knowledge of anatomy and physiology, especially that of the central nervous system, and great advances in biological chemistry, have done much to increase our understanding of the hypophysis. Yet, each discovery has only left further questions to be answered, and the problems of pituitary physiology and pathology are still far from solved.

ETIOLOGY

The first two reported cases of this syndrome, those of Babinski and Froehlich, were due to the same etiological agent, a craniopharyngioma. Froehlich's case, indeed, presented the typical picture of a brain tumors with headache and vomiting in addition to the localizing pituitary signs.[41] After Froehlich had called attention to the hypophysis as the site of pathology, numerous other lesions were discovered to give the same clinical picture. The morbid anatomy became so varied that the condition was recognized as a syndrome and not as a disease entity. Craniopharyngiomata remain as one of the chief causes of the full blown picture.[49] Chromophobe adenomata, neurofibromata, syphilis, and inflammatory conditions including basal meningitis, epidemic encephalitis, and poliomyelitis are also found to be etiological agents.[6,49] In addition external injury may sometimes cause the condition as in the famous case of Madelung's, where a bullet lodged in the sella turcica.[49] Congenital defects are also possible.[40] The majority of cases have no demonstrable etiological factor and are said to be purely "functional".[44] Indeed, many authors consider this type as <u>the</u> Froehlich type and refer to cases of known etiology as a "Froehlich-like picture" produced by the specific etiological agent.

PATHOLOGY

Of the two clinical findings which give the name to adiposogenital dystrophy, the genital dystrophy has proved the easier to study. Cushing's early work with dogs showed that the removal of the anterior pituitary in puppies gave a persistence of sexual infantilism while corresponding procedures in older animals gave regressive sexual changes.[12]

Later work done by Smith[56] and Cushing[13] in hypophysectomized animals, including studies with replacement therapy, have confirmed these early experiments. The specificity of the results was questioned when Smith included genital atrophy among the characteristic features of the syndrome produced by damage to the tuber cinereum.[55] This effect was explained by Cushing as being due to interference with blood or nerve supply to the gland or with the epithelial investment of the infundibulum.[13] "Hypothalamists" still exist, and no one will deny the importance of the nerve supply to the pituitary. However, the discovery of the specific gonadotropic hormones of the anterior pituitary have established the importance of that glandular organ in the regulation of sexual function. We can now say that sexual infantilism associated with pituitary pathology is due to the inactivation of the cells producing these gonadotropic hormones.[13,34]

Microscopically the picture is not so clear since it is not established which type of cell is responsible for the production of the gonadotropic hormones. The general concensus of opinion has been that the basophilic cells were the source of the gonadotropic hormones whereas the acidophilic cells produced the hormones responsible for growth.[17,14] However, it is the acidophilic cells which have been found to be increased in number in conditions in which there is a known excess of gonadotropic hormones in the blood, as in the castrate.[58] More detailed study may throw further light on this subject, although it is possible that there may be no specific type cell corresponding to each of the pituitary hormones.

The cause and nature of the obesity occurring in adiposogenital dystrophy has been the subject of many investigations, and the problem is still not solved. As early as 1888 Bramwell, in pointing out the

excessive development of subcutaneous fatty tissue associated with pituitary tumors, suggested that the obesity might be due not to the primary pituitary growth but to secondary effects in the surrounding nervous tissue.[13] The nerve pathways from the interbrain to the gland was discovered by Cajal in 1894.[13] Early experiments of Paulesco, Cushing, and Biedl seemed to prove that, in dogs, adiposogenital dystrophy was produced by the extirpation of the anterior pituitary.[6] Cushing believed that the condition was due to posterior lobe deficiency.[12] Blair Bell produced the syndrome by clipping the stalk without removing the anterior lobe, thereby concluding that the condition was due to interference with blood supply to the gland.[6] Aschner and Erdheim recognized the possibility of damage to the hypothalamus in their technique of hypophysectomy and suggested that obesity might be due to secondary changes in this region.[58,59] This was the first mention of the "adipositas cerebralis". The idea was taken up by other workers and finally by Smith who showed that subdiaphragmatic hypophysectomy without damage to the hypothalamus gave only inhibition of growth and sexual development without adiposity. Conversely injury to the tuber cinereum gave adiposity with little effect on growth or sexual development.[56] Attention was thus focused on the floor of the third ventricle with the dependent infundibulum and tuber cinereum. The most radical view is that it makes no difference whether or not the hypophysis is present as far as the development of obesity is concerned.[58] Cushing questions this view and thinks that obesity can exist without damage to the hypothamaus.[13] He points out the infrequency with which diabetes insipidus, tuberal polyuria, occurs in adiposogenital dystrophy as further evidence against the importance of tuberal injury. No argument has been advanced to answer this point. Neither has it ever been explained why

inhibition of growth does not occur along with the lack of sexual development in this syndrome.

The common method of considering obesity is to classify it as either exogenous or endogenous. The former term is used to describe the condition in which accumulation of fat occurs solely because the caloric intake exceeds physiological needs. The latter type of obesity is assumed to be due to an altered body metabolism. However, the recent trend is to emphasize the importance of excess food intake even in the cases of endogenous obesity.[33,42] Newburgh states that "perverted" appetite or a changed state so that a formerly normal appetite becomes too great is the fundamental cause of such obesity.[42] The usual dietary error is, of course, the intake of excess carbohydrate.[16] Bernhardt even claims that such cases respond perfectly satisfactorily to diet.[4] Other authors mention heredity as the important factor in obesity[2] and point to constitutional make-up as of great importance in influencing the pattern of fat distribution.[8]

Some of the physiological mechanism by which obesity is said to occur in adiposogenital dystrophy are listed here:

1. A lowered metabolic rate. This involves the thyrotropic hormone of the anterior pituitary.[38]

2. A changed carbohydrate metabolism. Glycogen may be deposited in the liver as occurs in overfeeding with altered intermediate metabolism in the liver.[38] The diabetogenic hormone of the anterior pituitary is indirectly involved.

3. A changed metabolism associated with sexual changes. This refers to the effect of puberty, pregnancy, and the involutional period on body build.[11] The gonadotropic hormones of the anterior pituitary are directly involved.

4. An abnormal salt and water metabolism. There is salt and water retention in obesity and in some respects the condition is the antithesis of diabetes insipidus.[38,53] This theory involves the hypothalamus where a center for salt and water regulation is known to lie.

5. A changed lipoid metabolism, Raab postulates a hormone "lipoitrin" an extract of the posterior lobe which is supposed to produce a fall in the blood fat.[46,58] The hormone acts on the fat metabolism center in the hypothalamus which in turn acts on the liver by way of the sympathetic nervous system. The fat is removed from the blood and used in the liver. In the obese patient the fat metabolism center is assumed to be unresponsive to the hormone. As a result the fat is not removed from the blood in the liver but is deposited in the tissues. The evidence for this theory is not yet accepted. However, it was early demonstrated that extracts of the posterior lobe could check the most striking symptoms produced by tuberal injury.[13]

CLASSIFICATION

There have been numerous attempts to classify pituitary disorder. Rowe divides the group into hypofunctional states in which all clinical and laboratory findings indicated a lowered functional level, a hyperfunction state in which just the reverse is true, and a dysfunctional state where there is a mixture of hyper and hypo function.[50] This last group includes

the Froehlich syndrome, although the picture here inclines more to the hypofunctional side.

Cushing classifies the syndromes as to whether or not they present signs of distortion of neighboring structures or signs of altered glandular activity.[12] Adiposogenital dystrophy commonly includes both with the glandular symptoms predominating.

Lambie divides the hypopituitary disorders into groups based on three factors which may be normal or subnormal. These are the growth, gonadal, and metabolic factors.[37] In Froehlich's syndrome the growth factor is said to be normal while the metabolic and gonadal factors are deficient. This classification is hardly adequate in view of our present knowledge of the physiology of the hypophysis.

Engelbach has three classes of endocrine dysfunction in his series, the pituitary, thyroid, and thyropituitary.[17] Adiposogenital dystrophy is a pituitary disorder but secondary hypothyroidism may complicate the picture. Gordon's classification is similar. He includes adiposogenital dystrophy in the group of primary hypopituitary disorders with secondary hypothyroidism.[31]

OCCURRENCE

Adiposogenital dystrophy has been described at all ages in both sexes. It is diagnosed most commonly in the preadolescent and adolescent male; less commonly in the female of this age since genital dystrophy is often not recognized until after the time of puberty in this sex. The youngest case reported is that of a thirty-five months old child.[17] There is a gradually increasing percentage of occurrence of the syndrome with

increasing age up to a peak age incidence of ten to twenty years.[17,51] The incidence among boys of high school age is about 2.5 per cent.[54,57] Gordon notes the tendency for the condition to occur following illness, trauma, or surgery in previously apparently normal children.[31] The obesity usually precedes the genital dystrophy or at least is noticed first.[9] Zondek thinks that the diagnosis of adiposogenital dystrophy is made too often in children just before puberty whose symptoms often tend to correct themselves spontaneously.[58] The condition also occurs rather frequently after pregnancy and at the involutional period.[51]

CLINICAL PICTURE

The typical girdle type of obesity in adiposogenital dystrophy has been described many times in the literature since the publication of Froehlich's original article. The fat deposits occur about the limb girdles, the hypogastric region above the mons veneris, over the hips and buttocks, in the thighs over the trochanters, and in the back in the subscapular region and over the vertebral prominences. The abdominal fat may be so heavy as to hang down and cover the external genitalia. In the male there is deposition of adipose tissue simulating mammary development and adding to the feminine contour of the figure. In the female the breasts may be pendulous but are poorly developed, there being much sub-mammary adipose tissue but little true glandular tissue. This typical distribution of fat may be masked by general obesity.[41, 59, 26, 31, 7]

Genital hypoplasia occurs in the juvenile age group. In the older patients lack of development or incomplete development of secondary sex characteristics is an added part of the picture. Cryptorchidism occurs

frequently. In three hundred eight cases Gordon found 60.1 per cent had simple genital hypoplasia, 17.4 per cent had bilateral cryptorchidism, and 15.7 per cent unilateral cryptorchidism.[30]

The stature may be increased or decreased in the Froehlich's syndrome. Engelbach states that there is rarely any abnormality of osseous development although unusual measurements may indicate previous hypo or hyper activity of the growth hormone.[17] Gordon gives the following percentages: 16 per cent average height, 50 per cent above average, and 34 per cent below average.[31] It has been pointed out by Loewenberg that these patients are usually larger than average in the juvenile period.[40] Bulger states that very frequently periods of accelerated growth occur but that when full development is reached the patients are seldom tall.[8] Gordon distinguishes between a short and a tall (Neurath-Cushing) type of Froehlich.[26]

In contrast to the girdle obesity the ankles and wrists are delicately formed with slender hands and feet. Spade-like hands and tapering fingers are typical.[24,40] Genu valgum may be found.[39] The joints are described as frail and loose and there is a tendency to muscular hypotonus.[38,59] The neck is short and chubby.[3] The face is round and small with delicate features. In contrast to the hypothyroid picture the teeth in the Froehlich patient are well formed and of good consistency. The upper central incisors tend to be large and the lateral ones small. In the short Froehlich the teeth are short and well spaced. In the tall form they are large and may be widely separated.[26,31,24]

The skin is delicate and transparent with a fine superficial capillary network. This rosy appearance combined with the small round face give the

characteristic "angelic" or "doll" face. In addition the skin is described as being like alabaster since it is cool and velvety with diminished perspiration.[24,3,49] There is often gross freckling of the exposed parts and the skin bruises easily.[15] The lips are typically projecting and plump.[3] The skin is hairless except for the scalp where the hair is abundant and silky.[3,49] Eyebrows and eyelashes are scant. The nails are small and lack crescents.[49]

The adult picture in adiposogenital dystrophy varies depending upon the time of onset of the condition. The juvenile Froehlich as he or she grows older continues to present the same picture although the skin tends to become wrinkled due to lack of supporting fibrous tissue.[49] When the condition develops in older patients, the genital dystrophy is shown by functional symptoms, impotence, loss of libido, amenorrhea, and sterility.[9] There may be atrophy of the genital organs with regressive changes toward a neuter type.[6] The obesity in this group is often marked with development of the "apron" of abdominal fat.

The development of the child with the Froehlich syndrome does not necessarily present a characteristic picture. Engelbach gives a decreased birth weight as typical in pituitary disorders.[17] Probably this occurs in cases where the growth hormone is involved. Gordon states that the birth weight is not significant but is usually between eight and nine pounds. There may then be a steady gain in weight, a drop to normal followed by a sudden increase following illness, or a sudden weight gain at the time of puberty.[31] He describes premature teething as occurring in 29.7 per cent of his cases.[28] Delayed talking and walking occur only when there is associated mental retardation.[28,29]

Concerning the mental status found in adiposogenital dystrophy there is fair agreement of opinion. That true mental retardation may occur is recognized by all. Gordon in a group of mentally retarded children with endocrine conditions found that adiposogenital dystrophy was the third most common endocrine disorder, childhood myxedema and hypothyroidism alone being more frequent.[26,27] Rowe states that this is the only pituitary disorder where mental retardation occurs.[51] Shapiro in his study of the syndromes in high school boys found that his patients were two or three years older than their classmates, although he states that many of the cases showed a belated but rapid mental development between the ages of twelve and sixteen.[54] In Levy's series of thirty-three cases only five were below normal in intelligence while eleven were normal and seventeen above normal.[39] Yet in Gordon's series of one hundred sixty-one cases only ninety-five were normal, forty were backward, and twenty-six definitely retarded. The average intelligence quotient was 75.1 with a range from 37 to 105.[28] However, the authors agree that in the Froehlich child the behavior is often more affected than the mentality. The children may appear to lack intelligence because of their inability to concentrate or cooperate. The "pituitary temper" is described by Goldzieher,[24] while Zondek emphasizes the indifference, constrained behaviour, indolence, and restricted emotional sphere.[59] Levy classes these patients as "submissive" in their adaptation to social life both with adults and with other children.[39] Taylor found the condition in an average of two per cent in his series of young delinquents.[57]

Other findings which have been described in the clinical picture of the syndrome are polyuria and polydipsia (diabetes insipidus),[26,31,51] epilepsy,[31,51] contracture of the visual fields,[51] otosclerosis,[51] keratoconus,[24]

presence of focal infection especially in the tonsils, constipation perhaps[51,] associated with the poor muscular tonus, a high frequency of gastro-[40,26] intestinal, liver and gall bladder disease, and the presence of allergic[48] manifestations.[24] In addition the obesity and genital dystrophy of the Froehlich syndrome are found in the Laurence-Moon-Biedl syndrome where they are combined with mental deficiency, retinitis pigmentosa or other retinal[49,47,10,45] abnormality, and polydactylism.

LABORATORY FINDINGS

The following laboratory findings have been reported in pituitary hypofunctional conditions including adiposogenital dystrophy. The more important findings are starred.

Blood morphology

Slightly decreased red blood cells and hemoglobin.[49]
Decreased polymorphonucleocytes[49]
Slight lymphocytosis[24,51,52]
Eosinophilia[24,51,52]
Decreased endothelial leukocytes.[52]

Blood chemistry

*Increased uric acid[31,24,51,52]
Increased chlorides[31]
Decreased fasting sugar[31,24,25]

Urinalysis

Increased volume (associated with diabetes insipidus)[52]
*Positive urobilinogen reaction[51,52]
Positive indican reaction[51,52]

Metabolic measurements

Lowered metabolic rate[24,40,49,31]
*High sugar tolerance[49,24,25,51,52]
*Low specific dynamic effect[23,31]
Decreased fat tolerance[24]
Salt and water retention[24,31]

Temperature, pulse, respiration and blood pressure

Temperature subnormal 49, or not affected.51

Pulse may be slow 51

Respiration

Lung volume normal or slightly decreased 52

Normal alveolar carbon dioxide tension 52

Blood pressure tendency to be low. 51,52

Endocrine

*Changes in the gonadotropic and estrogenic hormonal concentrations in blood and urine. 19,20

X-ray

*Enlarged or deformed sella 49,40

*Calcification in pituitary region (craniopharyngioma) 49

Normal osseous development 31

TREATMENT

Since knowledge of the endocrinology and pathology of this condition has been so recently acquired and is still so incomplete, it is not surprising that therapy as yet has not been particularly successful.

In cases where the symptoms are due to tumor relief can be obtained, temporarily at least, by surgical intervention. Eiselberg operated on Froehlich's original patient. The operation was followed by sexual development and reduction in obesity, although eventually the tumor proved fatal. 5

Medical treatment has followed two general lines. The first of these is diet which has been quite generally used although with varying success. Goldzieher states that diet alone will maintain the patient after organotherapy is stopped, while Gordon finds that the results are only temporary. 24 31 In a recent article Gray cites two cases of adiposogenital dystrophy cured by diet alone. 32 The diet prescribed is one high in protein and containing all necessary minerals and vitamins, but low in fat, carbohydrate, salt and water. A skimmed milk diet for two or three days a week

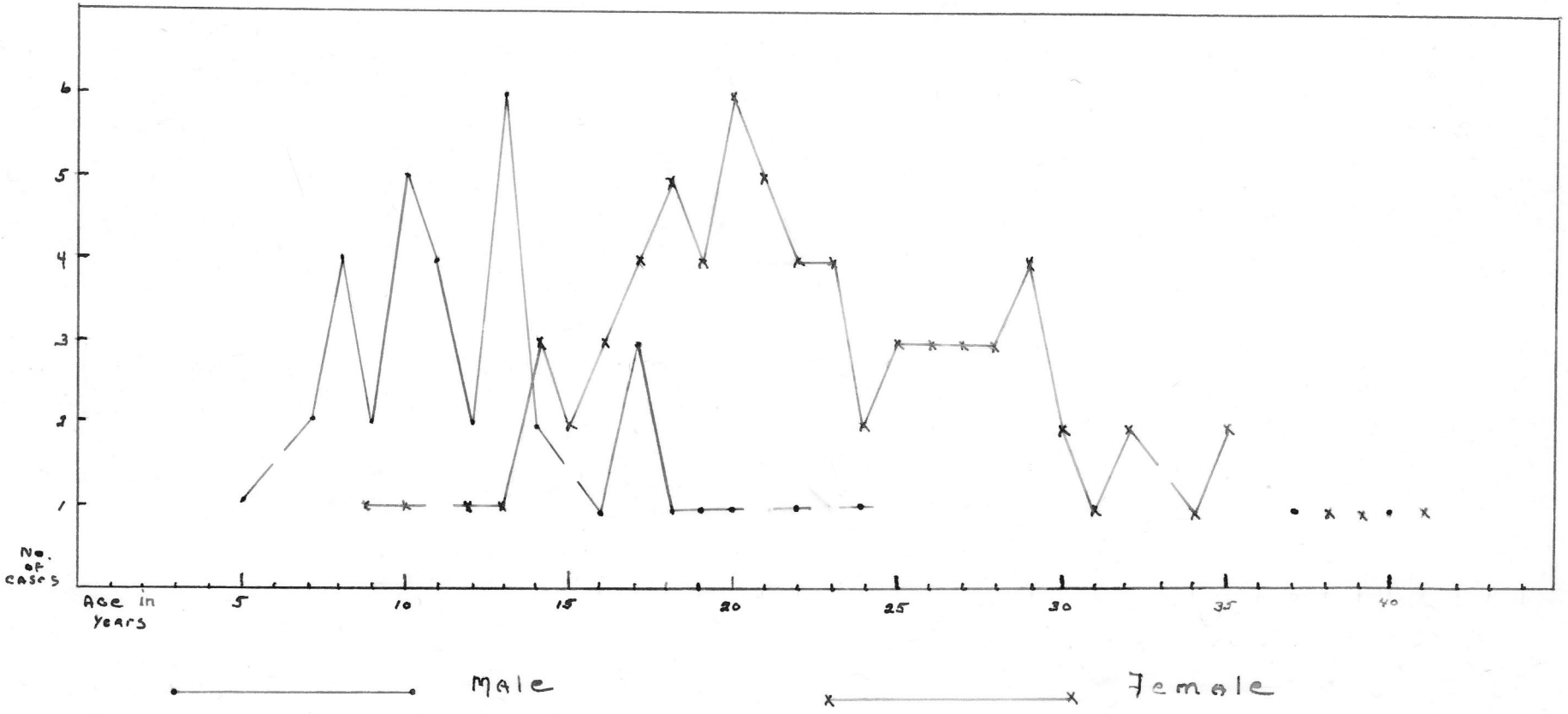
has even been advocated.[31] Exercise is, of course, prescribed together with the diet.[17,35,36,43,8]

The other method is organotherapy. Oral thyroid medication has long been used. Indeed, Froehlich tried it on his case.[41] Pituitary medication came later. For a time the use of this type of therapy was confused because of the failure of endocrinologists and clinicians to distinguish between true anterior pituitary preparations and the anterior pituitary-like preparations from pregnancy urine which were really placental substances. At present rapid progress is being made and specific anterior pituitary materials are available.[18] Novak advocates oral administration of pituitary, 60 to 100 grains, preferably combined with thyroid, 1½ to 2 grains daily.[44] Hypodermic injections of specific gonadotropic hormones seem a more logical approach and the ideal method is to correlate the therapy with studies of the hormonal concentration in the blood and urine.[19,20] This is especially true in the female whose sexual physiology is so definitely cyclic.

CASE ANALYSIS

The following data are presented from an analysis of one hundred twelve cases of adiposogenital dystrophy. The records were obtained from the Wisconsin General Hospital. The cases were selected from the index of the hospital records and from Dr. E. L. Sevringhaus' private file of pituitary cases. Most of the cases were under the care of Dr. Sevringhaus. Only cases which showed definite obesity and genital dystrophy were chosen. All cases showing these two symptoms were included regardless of other factors, age, sex, etc. Three cases of the Laurence-Moon-Biedl syndrome are also presented.

Age Incidence



OCCURRENCE

Of the one hundred twelve cases of adiposogenital dystrophy, thirty-nine were males and seventy-three were females. The age distribution is shown on the accompanying graph. The youngest case was that of a boy of five years, and the oldest that of a woman of forty-one years. The youngest female was nine and the oldest male forty. The graph shows clearly that the peak of incidence in the males is between the ages of 8 and 17 while that of the females is between 17 and 30. By incidence is meant the time the cases were seen in the hospital or came under the care of a doctor. It is impossible to make any statement about the actual age when patients first noticed symptoms of the condition since such information is usually lacking.

ETIOLOGY

A definite pituitary tumor was diagnosed in only one case, that of a woman of thirty-nine years. In three of themales and three of the females there was found abnormalities of the sella suggesting possible tumor growth. In two cases there was abnormality of the skull which was thought to be an etiological factor. The father of two of the cases was known to have syphilis involving the central nervous system, but neither child was ever found to have positive serology in blood or spinal fluid.

The following data were found relative to onset of the condition.

Males

Condition present since infancy..... 7
Definite time of onset before puberty - no known cause..... 8
Definite time of onset, before puberty, attributed to:
Appendectomy..... 2
Head injury..... 3
Scarlet fever..... 1

Cerebrospinal meningitis	1
Pertussis	4
Tonsillectomy and adenoidectomy	3
Septic hip	1
Mastoiditis	1
Onset at puberty	1
Onset after puberty	1
No data	2
Total	5
	39

Females

Condition present since infancy	9
Indefinite time of onset, before puberty	3
Definite time of onset, before puberty, no known cause	10
Onset at puberty	5
Onset after marriage	9
Onset after pregnancy	5
Onset after puberty, no known cause	10
Onset attributed to:	
Pneumonia in childhood	1
Tonsillectomy and adenoidectomy in childhood	1
Chicken pox in childhood	1
Appendectomy after puberty	1
Head injury after puberty	1
Measles, flu, and pneumonia after puberty	1
No data	16
Total	73

In addition there were four women whose symptoms became worse after marriage and three whose symptoms became worse after pregnancy.

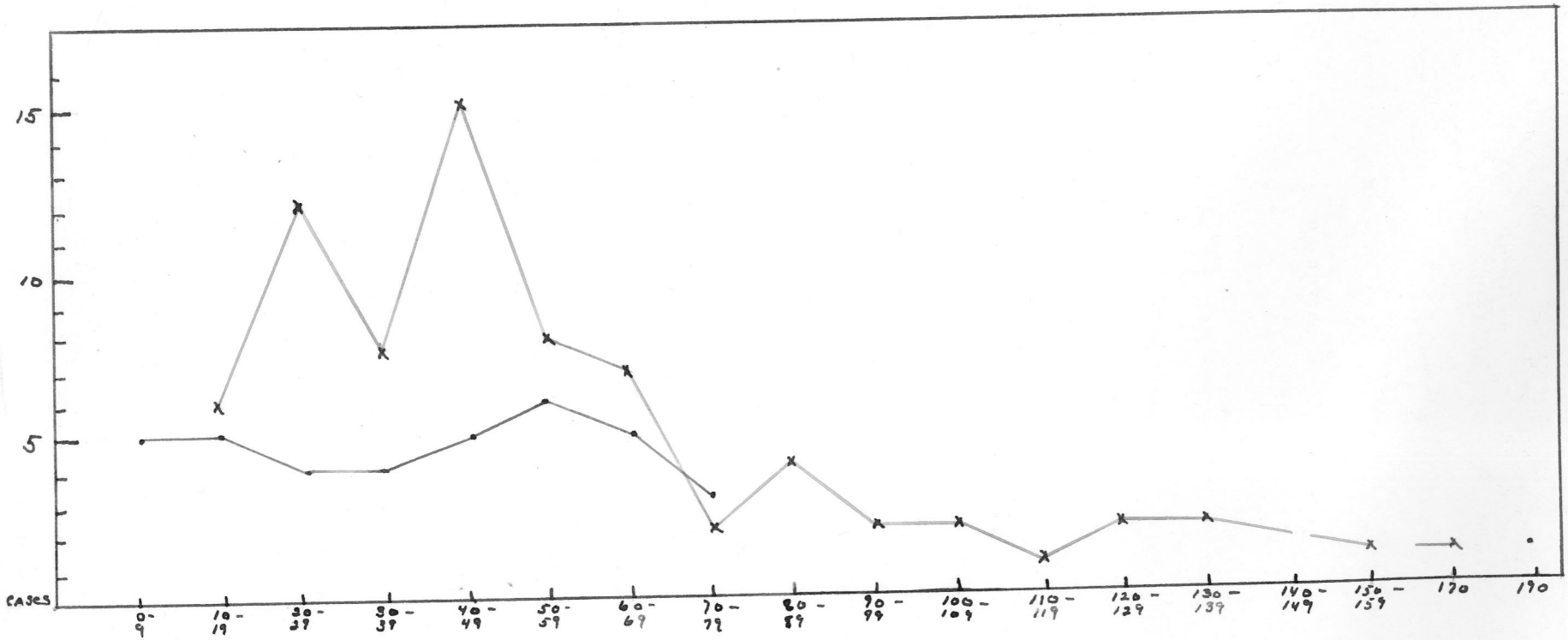
CLINICAL PICTURE

Obesity The amount of obesity is shown in the graph. The percentage overweight was calculated from the following formula.

$$\frac{\text{Actual weight} - \text{Normal weight}}{\text{Normal weight}}$$

The figures for normal weight were obtained from the Baldwin-Wood weight-height-age tables. Due to the great variation in the weight-height relationships no attempt was made to calculate the exact percentage of overweight, but this was expressed only as under ten per cent, between ten and

Obesity



Percent overweight

$$\frac{\text{Actual weight} - \text{normal weight}}{\text{Normal weight}}$$

males

females

twenty per cent, etc. The graph shows that the female patients tended to be more obese than the male although the highest percentage of overweight was that of one hundred ninety per cent found in a seven year old boy. Most of the patients were between ten and ninety per cent overweight. There was no relationship found between the percentage overweight and the age. In four of the men and one of the women a history of large appetite was obtained. One of the women had attacks of violent hunger, and another admitted a great craving for sweets.

Genital Dystrophy - the following data were found:

Males

Prepubertal	
Small and underdeveloped external genitalia	15
Small external genitalia with unilateral cryptorchidism	3
Small external genitalia with bilateral cryptorchidism	3
Pubertal	
Lack of secondary sex characteristics	4
Underdevelopment of secondary sex characteristics	9
Postpubertal	
Underdevelopment of secondary sex characteristics	4
Impotence	1
Total	39

Females

Prepubertal	
Impossible to make diagnosis	3
Pubertal	
Irregular menstruation	
Excessive flow	3
Scanty flow with periods of amenorrhea	13
Late menarche with irregular menses	2
Postpubertal	
Irregular menstruation	
Always irregular	18
Recently irregular	5
Sterility Complete, no pregnancies	15
Following pregnancies	9
Repeated abortion	3
Complete castration	1
Normal menstrual history (the pituitary tumor case)	1
Total	73

Of the forty-six women aged twenty or more, thirty-three were married and two others admitted having had sexual relations. Of the twenty-seven women listed above as sterile, twenty-three also gave a history of irregular menstruation with periods of amenorrhea.

Endometrial biopsies were done on twenty-five of the patients with the following results:

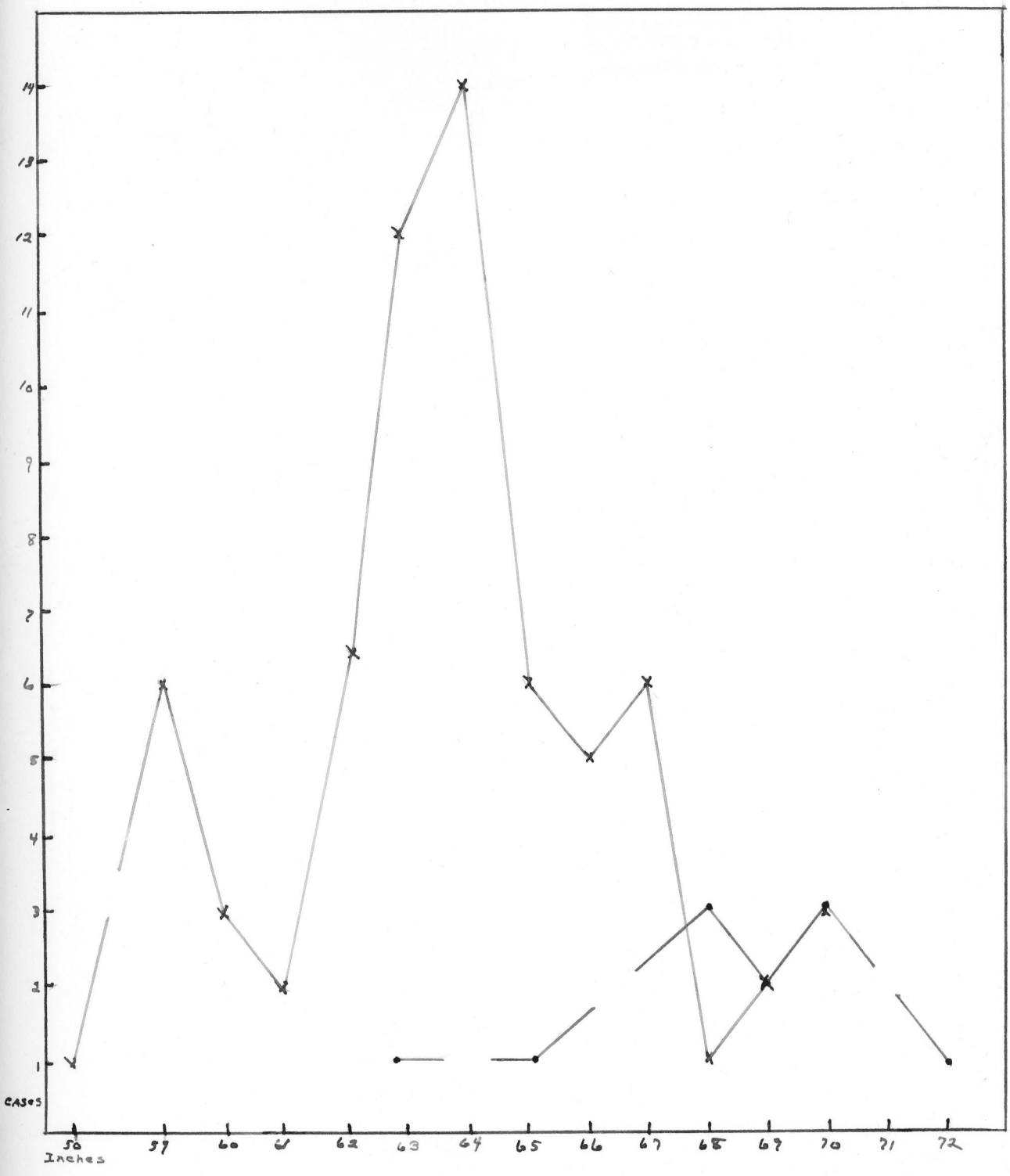
Normal corpus luteal effect	2
Normal follicular effect (no corpus luteal effect)	10
Slight corpus luteal effect	1
Poor follicular effect	7
Inactive endometrium	3
No endometrium	2
Total	25

This suggests that many were anovulatory bleeders.

Height. No significant changes in height were found to be characteristic in this series. Only one case was a true dwarf with a height of fifty inches at seventeen years. Two of the girls were diagnosed as gigants with the heights of sixty-nine and seventy inches respectively at the age of fourteen. In all a total of five females and four males were definitely of increased height, and six females and four males of decreased height. The accompanying graph shows the heights of all the cases sixteen years of age and over.

Mental. Complete studies were not done on all the patients. However, six of the boys had intelligence quotients definitely low (between 48 and 66). Institutionalization was recommended for two of these. Eight of the other boys were classified as "dull" or "retarded", and twelve of the girls were similarly classified. On the other hand, six girls and one boy were students at the University of Wisconsin.

Height



Cases Aged 16 And over

The following additional findings were noted:

Somnolence	9	
Headache	16	
Emotional instability	4	
Epilepsy grand mal	3	
Epilepsy petit mal	2	
Convulsions	2	
Nervousness and tremors	4	
Loss of pep and fatigue	4	
Behaviour problems	2	
Failing memory	1	
Deafness	2	
Psychosis	2	(one patient at Mendota Hospital)
Diabetes insipidus	6	
Pain in the abdomen	8	
Appendectomy performed	6	
Hirsuitism (in females)	8	
Abdominal striae	6	

FAMILY HISTORY

In the total of one hundred twelve cases the following pertinent findings were recorded about family history:

Obesity	23	
Diabetes	8	
Diabetes and obesity	7	
Goiter and obesity	1	
Syphilis in father	2	
Mental deficiency	2	
Small stature	1	
Tall stature	2	
Acromegaly	1	
Early menopause	1	
Hydrocephalic child	1	
Psychosis	1	
Four brothers died in infancy	1	
Three siblings "blue babies" died	1	
Three siblings deaf and dumb	1	(patient was deaf mute)

Three of the cases were adopted.

LABORATORY STUDIES

Sugar tolerance

Increased tolerance	5
Normal tolerance	15
Decreased tolerance	6

Basal Metabolic Rate

Above + 10	13
Between 0 and +10	24
Between 0 and -10	27
Below -10	8

THERAPY AND RESULTS

Diet and exercise were almost universally prescribed. Anterior pituitary gonad stimulating hormones were prescribed in most of the cases. Prephysin, 1 cc. hypodermically daily for five doses and then on alternate days for five more doses was advised for the women. The course was to be repeated with each menstrual period. Prephysin, 1 cc. hypodermically, daily to twice a week, was prescribed for the men. Thyroid medication was prescribed for the cases with persistently low basal metabolic rates.

The results in this series are not yet ready for study, but in general they seem to be encouraging although still not completely satisfactory. The lack of uniformity of results suggests that all factors involved in the development of the condition are not yet understood.

LAURENCE - MOON - BIEDL SYNDROME

Case I. The patient was a nine year old boy brought in for examination because he was backward in school. The backwardness had been noted ever since he started school. His history revealed that he had started teething at four months, had walked at thirteen months, and talked at eighteen months. He had always been fat, but marked obesity had developed at the age of seven. He had influenza at this age. Other significant facts were his inability to see weel, and the history of his having had a sixth finger removed from the left hand in infancy. Physical examination

showed an obese boy. His height was 44½ inches and his weight 105½ pounds. He was 45 pounds (75%) overweight for his height. Ophthalmoscopic examination showed temporal pallor, optic atrophy, and attenuation of the blood vessels. The external genitalia were infantile. Both testes were in the scrotum. The patient's intelligence quotient was found to be 72. His basal metabolic rate was not accurately obtained because of lack of cooperation. X-rays of the skull showed no abnormality of the sella.

Case 2. This patient was the older brother of Case 1. He was a sixteen year old obese boy whose eyesight was even poorer than his brother's and who had only been able to reach the second grade in school. Physical examination revealed unilateral cryptorchidism, small external genitalia, and only slight growth of pubic hair. The fundi were pale with narrowing of the arteries and veins and moderate papilledema. Height and weight figures were not available on this patient. He had a supernumerary finger on the right hand and a sixth toe on the left foot.

Case 3. The patient was a woman of thirty-one who entered the hospital with a chief complaint of poor vision. She had always had poor eyesight but thought that it had recently been getting worse. Significant in her history were the facts that she had had only one pregnancy which had terminated in an abortion, and that she had been born with six fingers and toes. The extra digits, stated to have been developed so far as the first joint, had been amputated from the hands. There was questionable consanguinity in the parents and a history of polydactylism in the family. A sister was known to have poor vision associated with some retinal abnormality. Physical examination revealed an obese woman. Her weight was

172 pounds for a height of 61 inches. This was 51 pounds above the normal weight, making her 43 per cent overweight. Ophthalmoscopic examination showed retinitis pigmentosa. Rudimentary sixth toes were present on the lateral aspects of both feet. The patient's intelligence quotient was found to be 58. Basal metabolic rate was +9 and +10, on two determinations. There was a decreased sugar tolerance.

The patient's sister was not examined, but the history suggests that she too may have presented the characteristics of the syndrome.

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Approved by

Elmer L. Severinghaus

Associate Professor of Medicine

Date

May 16, 1938.