LIPODYSTROPHY

BY

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One of the earliest descriptions of lipodystrophy was given in 1885 by Weir Mitchell. He reported the case of a girl aged 12 who had lost all fat from the upper half of the body while the parts below the waist were unaffected. More than twenty years later Barraquer (1906) reported a similar case. Pic and Gardère (1909) described a patient with fat atrophy of the face and upper part of the body in association with fat increase over the pelvis and legs. Simons (1911) introduced the term "progressive lipodystrophy," and since then the disorder has sometimes been referred to as Barraquer–Simons disease. As the fat loss so typically affects only the upper half of the body, Gerhartz (1916) suggested that the condition should be called "lipodystrophia progressiva superior." Parkes Weber (1916) drew attention to the fact, however, that lipodystrophy was not progressive, since, after fat had been lost from the typical areas, there was no tendency to involvement of the lower half of the body, in which, on the contrary, abnormal accumulation of fat might occur, particularly in women of middle age. Marañón and Soler (1926) suggested the term "cephalo-thoracic lipodystrophia."

While the typical clinical picture of lipodystrophy is one of great loss of fat from the upper part of the body, producing a characteristic facies and abnormal prominence of muscle such as to give in women an appearance of masculinity, there are certain exceptions. A few cases are reported (Smith, 1930; Horton and Emmett, 1932; Bigler, 1939) in which the lipodystrophy affected the legs, the upper half of the body remaining normal. Moreover, a recognized form of the disorder is that described by Laignel-Lavastine and Viard (1912) in which the fat atrophy in the upper half is of less degree than in the classical type and may appear after adiposity of the lower half, always a prominent feature in this type, has developed. This state may be regarded as intermediate between typical lipodystrophy and the relatively common condition in which adiposity affects only the lower half of the body, the upper half remaining normal. This latter condition, in which there is no fat atrophy, appears as a characteristically feminine tendency and is often superimposed on the typical case of lipodystrophy. It cannot be regarded as a form of lipodystrophy, since this term is used to define a clinical state characterized by fat atrophy and in which adiposity of the lower part is not an essential feature. Nevertheless such cases have been so regarded by some authors. Christiansen (1922), referring to 15 cases seen by him, divided them into two groups, one showing the fat atrophy of the upper part of the body, the other occurring particularly in women about the menopause in whom the only abnormality was obesity confined to the lower part of the body. It would appear that in the latter group the diagnosis of lipodystrophy is unjustifiable, although it seems probable that some other observers have included such cases in their series, as, for example, Marañón and Cascos (1930), who mention 50 "mild cases," without giving details.

Aetiology

More than 100 cases of lipodystrophy have been reported. Parmalee (1948), reviewing the literature, found 95, and several cases have since been recorded. Examination of the case histories which have been published reveals that certain other features have often occurred in association with lipodystrophy. In the accompanying Table 74 of these cases, together with three new cases reported below, are summarized in order to show such additional characteristics. The sex of the patient is also shown, together with the age at the onset of the disorder when this has been recorded.

Summary of Reports of 77 Cases of Lipodystrophy

Author	No. of Cases		Age at Onset			Psychological Symptoms	Thyroid	Glycosuria
	F	M	Under 10	10–20	Over 20			
Weir Mitchell (1885)	1		1				?	
Osler (1895)	1		1					
Barraquer (1906)	1			1				
Campbell (1907)	1		1					
Pic and Gardère (1909)	1					1		
Simons (1911)	1			1			1	
Laignel-Lavastine and Viard (1912)	1				1		1	
Feer (1915)	2		2				1	
Gerhartz (1916)		1	1			1		
Herrman (1916)	1		1					
Parkes Weber (1916)	2		1	1		1		
Bossert-Rollett (1918)	1		1			1		
Spear (1918)	1		1			1		
Weber and Gunewardene (1919)	1		1					
Langmead (1920)	1		1					
Kraus (1921)	1		1					
Mirallié and Fortineau (1921)	1				1	1		
Smith (1921)	1			1			1	
Christiansen (1922)	1			1				
Irving (1922)		1	1					
Strauch (1922)	1			1		1	1	
Boston (1923)	2			2		1		
Reuben, Zamkin, and Fox (1924)	2	2	4			1	1	
Watson and Ritchie (1924)	4		2	1	1	1		1
Wolff and Ehrenclou (1927)	1				1	1		
Ziegler and Prout (1928)	2					1		1
Zieg'er (1928)	5	2	1	3	1	7	5	3
Bilderback (1929)	1		1					
Currier and Davis (1930)	1				1	1		
Marañón and Cascos (1930)	2		1	1			1	1
Smith (1930)	1				1	1		1
Weber and Bode (1930)	1		1					
Capper (1932)	1	1	2			1		
Cockayne (1932)	1		1					
Hartson (1933)		2	2					
Cohen and Eis (1934)	2				2	2	2	1
Zondek (1935)	1			1				
Bigler (1939)	1		1					
Hansen and McQuarrie (1940)		1	1					1
Harris and Reiser (1940)		1	1					1
Patton (1945)	1		1					
Crosfill (1946)	1			1				1
Lawrence (1946)	1				1		1	1
Richardson (1946)	1				1			
Baxter *et al.* (1948)	3			3				
Igersheimer (1948)		1	1					
Barraquer Ferré (1949)	1		1			1	1	
Warin and Ingram (1950)	1	1	1		1	2		1
Otto (1951)	1		1					
Williams and Kelsey (1951)	1	1	2					
Present series	3		1	1	1	3		2
	63	14	40	19	13	30	16	15

The disease occurs much more often in the female subject than in the male; 63 (81.8%) were of the former sex. It begins most commonly in the early years of life. The onset was observed prior to the age of 10 in 40 (55.5%) cases, and in 19 (26.5%) between the ages of 10 and 20. It is noted that of the 14 male patients 12 (85.7%) developed the disease before the age of 10.

The aetiology of the disease is obscure, and various suggestions regarding its cause have been made. Several cases appeared to follow measles, but, as Bilderback (1929) pointed out, this is such a common infection in childhood that any relationship may well be coincidental. Other infections have been noted to occur before the onset of lipodystrophy, and Harris and Reiser (1940), reporting a case beginning in a child after a prophylactic injection of tetanus antitoxin, suggested the possibility that infection might act by affecting the central nervous system. Weber and Bode (1930) thought that lipodystrophy should be classed with the congenital developmental dystrophies, and Igersheimer (1948) has postulated congenital derangement of mesenchyme, a view regarded as "the most plausible" by Williams and Kelsey (1951). Weber (1932) contrasted the condition with Cushing's disease and suggested the possibility of hypofunction of pituitary basophils. Wolff and Ehrenclou (1927) were of the opinion that lipodystrophy was to be regarded as part of a congenital autonomic imbalance resulting from deranged central trophic control. In the view of Barraquer Ferré (1949) the essential lesion is in the hypothalamus, usually a hereditary degenerative process, perhaps accelerated in some cases by psychic trauma, and leading secondarily to hyperthyroidism, but also possibly developing as the result of a pathological lesion—"encephalitic, hormonal, metabolic, etc."—of that part of the brain.

In considering the cause of lipodystrophy it is necessary to take account of the disorders so often found in association with it. As Warin and Ingram (1950) have pointed out, endocrine or nervous disorders occur too frequently to be regarded merely as coincidental. Some authors have found that patients become nervous as a result of the embarrassment caused by their facial appearance. Such cases, in which nervous symptoms may be regarded as purely secondary, have been excluded so far as possible in the present review, yet it will be seen from the Table that 30 (39%) patients were reported as showing some psychological disturbance. Of the cases previously reported, the onset of the disease in three patients followed quickly on a severe fright in childhood. Nineteen were regarded as psychoneurotic, nervous, or emotionally unstable. Asthma or other psychosomatic disorder was present in three cases, one patient was reported sexually frigid, while in another there was a strong family history of neurosis. Parkes Weber (1913) observed that neurotic phenomena may usher in the disease, and Christiansen (1922) found that patients complained of vague neurotic symptoms and showed a tendency to profound depression. Ziegler and Prout (1928), inquiring into the neuropsychiatric aspects of lipodystrophy, reviewed 82 cases from the literature. They noted in eight cases a pronounced nervous or mental disturbance which might or might not have been due to worry about their appearance, concern about which, on the part of either the patient or friends, was present in another 32 in the series. They concluded that there was no psychiatric symptom-complex common to lipodystrophy, and no conclusive evidence that the integrity of the nervous system was affected. On the other hand, Cohen and Eis (1934) remarked on the frequency of the occurrence of nervous symptoms both in young and in adult patients, and noted that the latter were particularly prone to develop hyperthyroidism.

Thyroid dysfunction, varying from hyperplasia of the gland to thyrotoxicosis with auricular fibrillation, was observed in 16 (21%) patients. In addition to these the early case reported by Weir Mitchell suffered from "free perspiration," which may have been attributable to hyperthyroidism. Thyroidectomy was performed in three cases without benefit (Ziegler, 1928; Cohen and Eis, 1934; Lawrence, 1946), while in another temporary improvement after operation was soon followed by relapse. Lawrence's patient, who never exhibited any signs of Graves's disease, showed a remarkably high B.M.R., which continued to be raised after operation, even when she developed hypothyroid symptoms requiring thyroid for their relief. It was suggested that the high rate of metabolism was more akin to the increase found in leukaemia, and that possibly the histological changes in the thyroid might be secondary. Marañón and Soler (1926), who do not give reports of individual patients (hence not included in the Table), state that 8 out of 10 of their cases suffered from hyperthyroidism, while Marañón and Cascos (1930), referring to a large series of cases of lipodystrophy, note its occurrence "especially in hyperthyroid women." Christiansen (1922) reported that 2 of his 15 cases suffered from myxoedema.

In a large proportion of cases disturbance of carbohydrate metabolism has been reported. Eight patients were found to have diabetes, although in several this was mild; another had a high fasting blood sugar; and another had impairment of glucose tolerance. In addition to these, one patient showed a "lag" curve and two were reported to have renal glycosuria. In the remarkable case described by Lawrence, diabetes and lipodystrophy were associated with gross hepatomegaly, marked insulin resistance, and little tendency to develop ketosis. Two other cases of similar nature have been recorded (Ziegler, 1928; Hansen and McQuarrie, 1940), but in none other is there mention of liver enlargement. MacNeal (1947), however, states that hepatomegaly often accompanies progressive lipodystrophy in children. In most cases diabetes was noted within 10 years after the beginning of the fat loss, but in Lawrence's patient the diabetes preceded it. On the other hand, lipodystrophy may be present for long periods without evidence of diabetes developing. In approximately one-fifth of the cases reviewed lipodystrophy had persisted from 15 to 29 years, but in only two of these was diabetes noted.

Menstrual function seems to have been undisturbed in most cases. Hypertrichosis may occur (Boston, 1923; Reuben *et al.*, 1924), but, despite the appearance of masculinity often mentioned, no abnormality of distribution of pubic hair has been reported.

Three cases are described below. These show the typical features of lipodystrophy together with certain other characteristics less commonly encountered.

Case 1

This patient was a married woman aged 52. Loss of fat of the face began at the age of 25, and was first observed soon after she had had a severe fright. Fire had broken out in her home and, unable to get downstairs, she had to escape by jumping out of a window. The face was first involved, but gradually in the next two years the neck, arms, and upper trunk became thin. The lower part of the body remained normal until after the age of 40, when she started to gain much weight round the buttocks and thighs. She gave no history of illness prior to the onset of lipodystrophy. She was married at the age of 22, and has had two children. The first was born when she was 23, and the second when she was 28. Menstrual periods were regular until they ceased three years ago. She was concerned

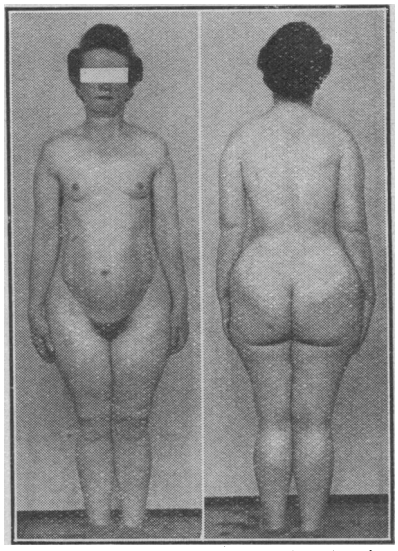

FIG. 1.—Case 1. Photographs showing thinness of face, lack of adipose tissue in arms and trunk, and pronounced adiposity of buttocks and thighs.

about the obesity below the waist, but did not seem ever to have been disturbed by the emaciated condition of her face. She had no other complaint, but on examination she was found to have severe glycosuria, and it transpired that she had experienced thirst for some months.

The thinness of the face was very striking, the complete absence of fat showing up the musculature, and there was general lack of adipose tissue in the arms and trunk. Below the waist the adiposity of buttocks and thighs was very pronounced (Fig. 1). The liver was enlarged 3 in. (7.5 cm.) below the costal margin. A glucose-tolerance test showed a fasting blood sugar of 242 mg. per 100 ml., rising to 392 mg. at one hour, and falling to 298 mg. at two hours. Glucose-insulin tolerance test (6.2 units of insulin intravenously with 52 g. of glucose orally) gave the following results: fasting blood sugar, 259 mg. per 100 ml.; 20 minutes after insulin, 283 mg.; 30 minutes, 313 mg.; 45 minutes, 307 mg.; 60 minutes, 343 mg.; 90 minutes, 303 mg.; 120 minutes, 243 mg. This indicated a moderate but not complete insulin-resistance.

On a restricted diet she has lost 9 lb. (4 kg.) and the circumference round the hips has diminished by 4 in. (10 cm.). On this diet the glycosuria has been kept under control.

Case 2

A single woman aged 37 lost her mother when she was aged 8 and is said to have been greatly upset by the bereavement. Soon afterwards she became thin, first in the face and later in the arms, and was taken to the doctor by her grandmother, who feared that the emaciation was due to serious illness. The patient herself did not worry about this condition, and when told she was thin would point to her legs, which remained normal. After the initial loss of fat in the upper part of the body she remained unchanged for years. Recently she has been gaining weight, but this has all been "from the waist downwards." Menstruation began at age 14 and has been regular and normal. There have been no diabetic symptoms. In October, 1950, she experienced a choking sensation and became emotionally disturbed, weeping with little provocation. She was thought to be suffering from hyperthyroidism and was given methylthiouracil by her doctor, but although this had been taken for some months it appeared to have had little effect on her symptoms.

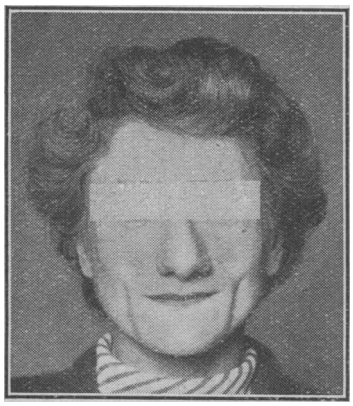

FIG. 2.—Case 2. Photograph showing absence of fat on face.

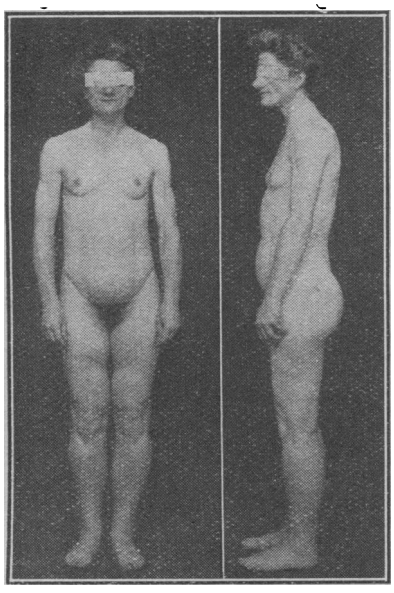

FIG. 3.—Case 2. Photographs showing absence of fat on face, neck, arms, and upper part of trunk, and adipose tissue below the waist slightly greater than normal.

Examination showed complete absence of fat on face, neck, arms, and the upper part of the trunk (Figs. 2 and 3). Below the waist, adipose tissue was slightly greater than normal. The absence of fat gave an appearance of muscularity, and even suggested masculinity. There was rather excessive growth of hair on the legs and slight upward extension of pubic hair. The pulse rate was normal and blood pressure 140/90. There was no palpable enlargement of the thyroid, but the B.M.R. was increased (+28, +37, +11, +19). Total plasma cholesterol was above normal (283 mg. per 100 ml.). The liver was enlarged 2 in. (5 cm.) below the costal margin. There was slight glycosuria. Glucose-tolerance tests gave the following results: fasting blood sugar (venous blood), 94 mg. per 100 ml.; 30 minutes after glucose, 101 mg.; 45 minutes, 125 mg.; 60 minutes, 146 mg.; 90 minutes, 176 mg.; 120 minutes, 139 mg. The fasting urine contained no sugar; there was a yellow reduction of Benedict's reagent after the test. The glucose-tolerance test was repeated after the administration of 6.1 units of insulin intravenously with the following results: fasting blood sugar (venous blood), 89 mg. per 100 ml.; 30 minutes after glucose, 102 mg.; 45 minutes, 157 mg.; 60 minutes, 180 mg.; 90 minutes, 184 mg.; 120 minutes, 136 mg. The curves are virtually identical and appear to indicate insulin resistance. Liver-function tests gave no evidence of disturbed function.

Case 3

A girl aged 18 started to put on weight eight months previously, and has gained 2 st. (12.7 kg.). All the increase of adipose tissue has been below the waist. Her buttocks and thighs have increased markedly. She stated that her arms had become thinner, but there was no obvious fat loss in the upper half of the body. Relative to the lower part of the body, however, this appeared thin. Clinical examination revealed no other abnormality. The thyroid was not enlarged and evidence of hyperthyroidism was not present. There was no glycosuria, and a glucose-tolerance test showed no abnormality. Menstruation was normal. Since the age of 14 she has had evidence of vasomotor disorder, her hands tending to swell and become blue, and she has been troubled with chilblains on her legs from that age. During the past year there has been very considerable emotional conflict with her father.

Discussion

The first two cases are typical examples of lipodystrophy and show the characteristic feature—almost complete loss of fat from the upper half of the body. Gross adiposity of the lower parts developed in the first case, but not until many years after the upper half had become thin, while in the second case the lower half of the body is only slightly fatter than normal. In contrast with these the third case showed rapidly developing adiposity below the waist with only slight evidence of thinning of the upper half of the body, and is of the type of Laignel-Lavastine and Viard.

The frequent association of lipodystrophy with emotional disturbance is borne out in the present cases. In the first the onset of the disorder followed sudden severe fright, a happening that has been noted previously, but thereafter no signs of emotional instability were evident. In the other two patients psychoneurotic symptoms were present. Attention has been drawn elsewhere (Murray, 1950) to the importance of emotional disturbance in continuing thyrotoxicosis, and this may explain the frequent development of thyroid dysfunction in the adult suffering from lipodystrophy. As mentioned above, thyroidectomy was performed in some cases without benefit. In Case 2 of the present series the B.M.R. was persistently raised and had not been influenced by the administration of methylthiouracil, and the patient was not considered to be suffering from thyrotoxicosis. This is comparable to the findings in Lawrence's (1946) case, although in the latter the elevation of the B.M.R. was much greater. Certainly in the former there was no indication for thyroidectomy, and had this been performed it seems probable that it would have been as unavailing as

in the cases previously reported. In this and similar cases some stimulus other than the thyrotrophic may be postulated as the cause of the raised B.M.R. Szego and White (1949) showed in mice that the growth hormone of the anterior pituitary caused an acceleration of fat metabolism with mobilization from depots and intense fatty infiltration of liver, and it is conceivable that such a factor as this may be involved. It would seem that the disturbance of thyroid function in these cases may arise from altered activity of the hypothalamus, in which, according to Barraquer Ferré, lies the essential lesion of lipodystrophy.

The impairment of glucose tolerance, often mentioned in case reports of lipodystrophy, may in some instances have been associated with hyperthyroidism. None of the cases of the present series were, however, of this nature, but two had glycosuria. Case 1 must be regarded as frankly, and Case 2 potentially, diabetic. Both patients had enlarged livers and were insulin-resistant. Similar findings are obtained in the obese type of diabetic in whom liver enlargement is not uncommonly present, and in whom, as Bearn, Billing, and Sherlock (1951) have demonstrated, insulin-resistance and fatty changes in the liver are found. Lawrence (1951), discussing that form of diabetes occurring in association with disturbance of fat storage, subdivided this into lipoatrophic and lipoplethoric types. "Lipoplethora" of the lower half of the body is often found in cases of lipodystrophy. If difficulty in fat storage is, as Lawrence suggests, the primary cause of the diabetes of the obese it is surprising that diabetes has not been much more commonly found in patients suffering from lipodystrophy.

In Case 1 the obesity of the lower half of the body was so great that, had there been no lipodystrophy in the upper parts, she would have been regarded simply as of the common type of obese diabetic. It is impossible to say whether inability to deposit fat in the upper half of the body resulted in diabetes becoming manifest earlier than would otherwise have been the case. Moreover, the factors involved in the production of the great enlargement of liver are unexplained. However, in Case 2 there was no obesity. Fat deposition below the waist had increased but was not excessive. Carbohydrate tolerance was impaired, but to a degree insufficient for a definite diagnosis of diabetes. But even at this stage there was considerable hepatomegaly. As already noted, liver enlargement was a prominent feature in three cases of lipodystrophy with diabetes previously reported. It seems probable that disturbance of liver function resulting in hepatomegaly may be associated with abnormalities of storage in fat depots, and that this may play an essential part in the development of insulin-resistant diabetes.

Summary

Three cases of lipodystrophy are reported. Two presented the classical features of the disorder, while the third was of the type described by Laignel-Lavastine and Viard, in which the loss of fat from the upper part of the body is slight but obesity below the waist is pronounced.

While the essential characteristic of lipodystrophy is fat atrophy, obesity of the lower part of the body is commonly found in association with it, developing particularly in women of middle age. Obesity affecting only the lower parts of the body appears to be a not uncommon feminine tendency. This may be a disorder akin to lipodystrophy; in the latter there is a loss of fat from the upper half of the body, and in the former failure to increase the fat deposits in these parts. The Laignel-Lavastine and Viard type of lipodystrophy may be regarded as a state intermediate between these two.

In a large number of cases of lipodystrophy there is a history of emotional disturbance which may or may not be persistent. It seems probable that it is on this account that thyroid dysfunction, evidence of which was found in 21% of recorded cases, is so apt to occur.

In the two cases reported which showed remarkable fat atrophy there was glycosuria, hepatomegaly, and insulin-resistance, but only in very few recorded cases of lipodystrophy have similar findings been observed. Since the essential feature of lipodystrophy is disturbance of fat storage it would be expected that if this was a cause of diabetes the latter disorder would be more commonly found in association with it. Attention is drawn to the liver enlargement in these cases and in others previously reported, and it is suggested that disturbance of liver function in association with abnormality of fat storage is an important factor in the production of glycosuria.

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The Royal College of Obstetricians and Gynaecologists has now issued its Annual Report for 1951. During the year 130 candidates passed the examination for Membership, and 325 the examination for the Diploma of the College. Twenty-one Members were admitted to the Fellowship during the year. The *Journal of Obstetrics and Gynaecology of the British Empire* is now owned by the College. A committee has been appointed to watch over the affairs of the journal, and Professor James Young remains in the editorial chair.