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LIPOATROPHIC DIABETES*

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Lawrence (1951) enumerated certain types of human diabetes; one of these is clearly associated with disturbance of fat storage. When this is excessive he referred to the condition as lipoplethoric diabetes. This is, of course, one of the commonest forms of the disorder and occurs particularly characteristically in the middle-aged obese woman. He introduced the term lipoatrophic diabetes to describe that rare form of the disease when it appears in association with lipodystrophy resulting in widespread disappearance of subcutaneous fat. His description of a remarkable case of a young woman who was under his care is well known. In his original paper (Lawrence, 1946) he referred also to two cases of a similar nature which had been previously reported by Ziegler (1928) and by Hanson and McQuarrie (1940). In these cases, as in lipodystrophy generally, the very striking loss of fat from the face and upper part of the body gives the patient a characteristic emaciated facies. No amount of feeding ever leads to fat deposition in those parts from which it has disappeared. In the three cases referred to it has been suggested that this difficulty in fat deposition was in some way associated with the appearance of diabetes.

A review of published reports of lipodystrophy, however, shows that this disorder is not associated with diabetes as commonly as might therefore be imagined. I have reviewed the reports of 74 cases published by 50 different authors and have reported other 3 cases observed by myself (Murray, 1952). As there has been some confusion about the application of the term lipodystrophy it is necessary to stress that this diagnosis is permissible only when the patient shows evidence of fat atrophy. In the great majority of cases fat disappears from the face, arms and trunk to the waist, the lower parts of the body being not affected. The condition was at one time referred to as progressive lipodystrophy; but, as Parkes Weber (1916) pointed out, the fat atrophy,

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having become virtually complete in the upper half of the body, does not tend to progress to the lower parts. Thus the term cephalo-thoracic lipodystrophy has been suggested as preferable, but since very rare cases have been reported in which the lower rather than the upper half of the body has been involved, even this is not entirely satisfactory. The disorder has also been referred to as Barraquer-Simon's disease, but, as is not uncommon with the use of eponyms, this is invidious, since an excellent description was given many years earlier that that of either of these authors, by Weir Mitchell (1885). In some subjects of lipodystrophy, great obesity may develop later in the buttock and legs ; this occurs particularly in women about to menopause. But this tendency to obesity below the waist without involving the upper parts of the body is a not uncommon female characteristic and when this occurs in a lipodystrophic patient it must be regarded as a feature superimposed upon, and not part of, the syndrome. There is, however, an intermediate state where obesity of the lower half of the body develops early and the loss of fat in the upper half is less pronounced, certainly in the initial stages. This is the type of lipodystrophy described by Laignel-Lavastine and Viard (1912). This review includes only cases in which definite loss of fat has been reported.

TABLE 1.
Summary of reports by 51 authors on 77 cases of lipodystrophy.

Number of Cases		Age at onset*			Associated disorders		
Male	Female	Under 10	10-20	Over 20	Psychol. Symptoms	Thyroid	Glycosuria
63 (82%)	14 (18%)	40 (55%)	19 (26.5%)	13 (18%)	30 (39%)	16 (20.8%)	15 (19.5%)

* In 5 cases age at onset is not reported.

As is shown in Table 1 lipodystrophy is predominately a disorder of the female sex and its onset is generally in early life. The cause of the disease is obscure but there is much to support the view of Barraquer-Ferré (1949) that it is attributable to changes in the hypothalmus. It is of interest to notice how frequently certain other disorders have appeared in association with lipodystrophy. Various forms of emotional disturbance or psychosomatic disease are reported in 39 per cent. Thyroid dysfunction, varying in degree from slight hyperplasia of the gland to flagrant thyrotoxicosis, was observed in over 20 per cent of cases. Glysosuria was noted in almost the same proportion. The type of the glycosuria varied. In 3 of the 15 cases in whom this was observed it was of innocent nature, in 3 it was apparently mild and associated with hyperthyroidism, while the remaining 9 were reported as diabetic. Half of these latter

ERRATA

Vol. 33, page 474, Table 1, should read as follows:

Number of Cases	
Female	Male
63 (82%)	14 (18%)

cases are stated to have been 'mildly diabetic'; in the remaining 5 diabetes was associated with enlargement of the liver. It is to this latter group that I wish to draw particular attention.

TABLE 2.
Nature of glycosuria reported in 15 cases of lipodystrophy.

	Number of cases
Renal	1
'Alimentary'	1
'Lag curve'	1
With hyperthyroidism	3
Diabetic (mild)	4
Diabetic with hepatomegaly ..	5*
Total	15

* Of these patients, one underwent thyroidectomy without benefit and two others had increased B.M.R. but were not considered hyperthyroid.

Hepatomegaly is frequently to be found in the lipoplethoric diabetic. Difficulty of palpation through an obese abdominal wall may account for this not being recognised as frequently as it probably occurs. In these cases fatty infiltration of the liver has been demonstrated (Bearn *et al.*, 1951). A much greater degree of liver enlargement was a feature of the case described by Lawrence as lipoatrophic diabetes, and also of the other two cases he cited from previous literature. No other cases have so far been reported, and it is these together with two others who have been under my care that comprise the group of 5 showing lipodystrophy, diabetes and hepatomegaly. A description of the cases observed by myself has been given elsewhere (Murray, 1952), but briefly the essential details are as follows.

Case 1. Female, married, aged 52. She commenced to lose fat from the face when she was 25 and within two years face, arms, and upper trunk had become extremely thin, while the lower part of the body below the waist remained normal. She appears to have had no concern about this, but after the age of 40 she started to put on weight round the hips and buttocks and this adiposity increased until it became extreme. When first seen about a year ago she had been experiencing excessive thirst for some months but had no other significant complaint. She was found to have severe glycosuria. A glucose tolerance test showed a fasting blood sugar of 242 mg.%, rising 392 mg.% one hour after glucose, and falling to 298 mg.% at two hours. Glucose insulin tolerance test (6.2 units of insulin intravenously with 52 g. glucose orally) gave the following results :—fasting blood sugar, 259 mg.% ; after insulin—20 minutes 283 mg.%, 30 minutes 313 mg.%, 45 minutes 307 mg.%, 60 minutes 343 mg.%, 90 minutes 303 mg.%, 120 minutes 243 mg.%. These showed her to be definitely diabetic, and indicated moderate, if incomplete, insulin-resistance. The liver was enlarged three inches below the costal margin. There was no thyroid

enlargement and no evidence of hyperthyroidism. On a restricted diet she lost weight, the circumferance round the hips diminished, and glycosuria was brought under control.

Case 2. Female, aged 38, single. About the age of 8 she developed lipodystrophy but despite the emaciated appearance of the upper half of the body, below the waist she remained normal. In recent years she has gained a little in weight, but this has all been ' from the waist downwards,' but there is nothing to suggest adiposity. Two years ago she became emotionally disturbed and was thought to be suffering from hyperthyroidism. The doctor prescribed methyl-thiouracil and this was taken for some months but appeared to have no effect and was eventually abandoned. The thyroid was not enlarged, the pulse rate was normal, but B.M.R. was increased (+28%). The liver was enlarged two inches below the costal margin. There was slight glycosuria. Glucose tolerance test showed fasting blood sugar within normal limits, and a curve rising somewhat above the normal values for venous blood, and failing to fall normally two hours after glucose. The fasting specimen of urine was sugar free, but after the glucose tolerance test this gave a yellow reduction of Benedict's reagent. A glucose insulin tolerance test gave a virtually identical result, and it was taken to indicate complete insulin resistance. Glucose tolerance test repeated 16 months later, showed some deterioration in tolerance. Thus, on 25th January, 1951, from a fasting level of 94 mg.% the blood sugar rose to 176 mg.% at 90 minutes and fell to 139 mg.% at 120 minutes. After 50 g. glucose orally and 6.1 units of insulin intravenously, the blood sugar rose to 180 mg.% and 184 mg.% at 60 and 90 minutes respectively, falling to 136 mg.% at 120 minutes. On 20th May, 1952, the fasting blood sugar level was found to be 118 mg.% and the glucose tolerance curve rose to 207 mg.% and 233 mg.% at 45 and 60 minutes, and fell through 204 mg.%, 172 mg.% and 136 mg.% at 60, 90 and 120 minutes respectively. She has never had diabetic symptoms and with ordinary diet glycosuria is slight and intermittent.

COMMENT.

The first patient is certainly a classical example of lipodystrophy. She remained in the same condition for many years and then developed gross obesity of the lower half of the body and with this she became diabetic. The clinical features would justify the diagnosis of lipoatrophic diabetes. On the other hand it seems possible that had it not been for lipodystrophy and the resulting impossibility of fat deposition in the upper half of the body she might have become generally obese, and when glycosuria was discovered she would then have been regarded as of the lipoplethoric type of diabetic. In the latter type liver enlargement is a common feature, although generally not to the extent encountered in this patient. Despite the very marked lipodystrophy present in this patient she might be more correctly classified as an example of lipoplethoric diabetes.

The second patient is also an undoubted example of lipodystrophy, but who has not, as yet at least, developed obesity of buttocks and legs. She is only potentially diabetic but she has an enlarged liver. She is insulin resistant, and although without other evidence of hyperthyroidism the B.M.R. is raised and unaffected by the administration of antithyroid drugs. She shows, in fact, all the features of lipoatrophic diabetes as described by Lawrence, although of much milder degree than in his case. There has been no alteration in her condition in the past 18 months but it seems probable that if the condition were to progress it would be in the direction of a more severe form of lipoatrophic diabetes. Perhaps

significant in this respect is the raised B.M.R. as this is a feature which has been noted in all these cases. (In Lawrence's case thyroidectomy was performed, after which definite evidence of hypothyroidism became manifest, but the B.M.R. remained high.) In another few years, when she reaches the menopause, it is conceivable that obesity of the lower half of the body may develop and she would then resemble more closely the first case I have described.

Another interesting case has been described very recently by Professor A. V. Neale of Bristol who has kindly given me permission to mention it. The details have not yet been published and the case is not included in the summarized review above. The patient is a girl aged 15 years with typical lipodystrophy who also has an enlarged liver. When first seen, glycosuria was slight, glucose tolerance test showed a slight 'lag curve,' and plasma cholesterol was normal. Liver biopsy demonstrated the presence of fatty degeneration. Within 6 months the glucose tolerance test showed a marked diabetic curve with a fasting sugar of 300 mg.%, cholesterol was much increased, there was definite lipaemia, and she showed remarkable insulin resistance. The B.M.R. was + 45 per cent, but there was no evidence of thyroid enlargement. The condition of this patient when first examined seems to have been very similar to that of the second patient I have just described. While in the latter the condition remains stationary, in the former this progressed rapidly until she now presents the fully developed clinical picture of this very rare disorder, lipoatrophic diabetes.

As regards the tendency for diabetes to appear in association with them, there seems to be a similarity between the two extremes of abnormal fat deposition, lipodystrophy and obesity. Lipodystrophy may develop and persist for many years and the patient never becomes diabetic. A patient may become obese and remain so throughout life without developing diabetes. But, some lipodystrophic patients develop enlargement of the liver and it is only in such cases that lipoatrophic diabetes may ensue. With the development of fatty infiltration and, frequently, enlargement of the liver the obese patient may become a diabetic of the lipoplethoric type. Furthermore, as exemplified by my first case, diabetes developing in a patient the subject of lipodystrophy who subsequently becomes grossly obese in the lower half of the body and is found to have hepatomegaly, might be classified as either a lipoatrophic or a lipoplethoric diabetic. It thus appears that an important feature in the progress from either lipodystrophy or obesity to diabetes, either lipoatrophic or lipoplethoric, is this enlargement of the liver, a characteristic particularly marked in the former type. A feature, so far unexplained, which tends to differentiate these two types, is the occurrence in lipoatrophic diabetes of a raised basal metabolic rate seemingly independent of hyperthyroidism.

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