Remissions in diabetes of the duration and degree reported here appear to be rare in the literature, but Joslin *et al.* (1952) have commented that "remissions of the disease are common when the exciting cause for onset is removed and prompt aggressive treatment, soon after the onset of diabetes . . . is instituted." In Cases 1, 2, and 6 above, the exciting cause seems to have been infection. In Case 3 diabetes developed in the seventh month of pregnancy on two occasions, and in Case 8 the onset of diabetes seemed on three occasions to be related to episodes of gout treated with colchicine. In the remaining three cases, however, no exciting cause for the onset of diabetes was found.

Experience in Singapore certainly confirms that if diabetics are rapidly stabilized on soluble insulin, raising the total dose each day by one-fifth to one-third of the previous day's dose until no more than a trace of glycosuria is present, it is very common to find some degree of remission reflected by reduction in the daily insulin requirements. Such "aggressive" treatment inevitably results in occasional attacks of hypoglycaemia, but full insulin coma is rare if the insulin dosage is reduced at the first sign of hypoglycaemia and is thereafter kept at the minimum dose which controls the glycosuria. Where insulin is given hesitantly, the dosage being increased slowly, and particularly when full control of the glycosuria is never achieved, it is most unusual to obtain a remission. The chance of obtaining a complete remission seems worth the risk of an occasional hypoglycaemic attack, and personal experience of the latter is a valuable addition to a diabetic's education.

Experience with these cases, however, confirms that patients should be warned, "once a diabetic, always a diabetic." Although in the cases here reported there have been complete remissions for 38, 27, 22, and 12 months, all the patients have relapsed except Cases 1 and 8, who have had remissions of over three years. These two patients are still regularly testing their urines for sugar, despite naturally increasing optimism.

Before the introduction of carbutamide and tolbutamide, diabetics of the type reported here always presented difficult problems in management. In hospital it was possible to adhere to the "aggressive" scheme of treatment described, but when the patient was discharged the rapid fluctuation in insulin requirements still necessitated daily consultation and adjustment of the insulin dosage. In some cases the patients learnt to adjust their own dosages safely, and others telephoned for advice every morning before taking their insulin. There appeared to be no advantage in giving several injections of soluble insulin daily, and so, once they were over the severe phase in hospital, most of these patients gave themselves a single injection of protamine-zinc insulin each morning.

It is now apparent that many of these patients can be well controlled on tolbutamide instead of insulin, and the oral treatment has the great advantage that the dosage required seems to fluctuate only slowly and over a small range. Now that a high proportion of Singapore diabetics are receiving tolbutamide therapy it is unlikely that many more of these insulin-insensitive cases will be recognized here. A few diabetics, however, have been observed to have remissions while on tolbutamide, and it may be that they would have been insensitive to insulin.

Summary

A diabetic syndrome is described in Singapore, characterized by marked insulin insensitivity and periods of complete or partial remission. During these remissions the patients may sometimes remain fit and well, with no glucosuria for long periods, without insulin administration or any other treatment for diabetes. Eight examples of this syndrome are reported, and others have been observed. It is suggested that the insulin requirements of diabetics in Singapore tend to

be higher on average than those in Britain, and that this may be partly due to selective elimination of insulin-sensitive diabetics in Singapore during the Japanese occupation.

I am grateful to Professor G. A. Ransome for permission to publish the case reports of those patients who were admitted under his care.

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SEVERE INSULIN LIPODYSTROPHY AS A POSSIBLE CAUSE OF INSTABILITY IN DIABETICS

BY

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Abnormal reactions in subcutaneous fat to injections of insulin have been recorded since its discovery. Such reactions have been termed "lipodystrophy," and should not be confused with the so-called "insulin lumps" which usually result from improper injection technique. Lipodystrophic reactions have been classified thus:

(a) *Lipo-atrophy*—the usual type of abnormal reaction, the incidence varying from 33% (Yohalem and Pollack, 1949) to 55% (Paley, 1953) of an adult diabetic population receiving insulin.

(b) *Lipohypertrophy*—a less common complication in adult diabetics, the incidence ranging from 3 to 6.5%. An example of lipohypertrophy is shown in Fig. 1.

Joslin *et al.* (1952) state that insulin lipodystrophy is a harmless complication, since no important structures are damaged, and it is annoying solely on account of the cosmetic effect. Other workers believe that these lesions in the subcutaneous fat may influence the absorption of insulin. Lamar (1950) suggests that insulin "resistance" and increased insulin dosage are more frequent in atrophic lipodystrophies, apparently resulting from continuously impaired absorption. He suggested that "brittleness" is more frequent in the hypertrophic nodular type, where insulin absorption from one or more depots may at times be added to the current dose, with the production of severe hypoglycaemic symptoms.

At the diabetic clinic at Leeds General Infirmary a number of diabetic patients with severe lipo-atrophy have had great difficulty in finding a suitable subcutaneous site for insulin injections. Diabetic control has been poor, and on changing injections to a site where fat was normal, such as the abdomen or buttocks, they have experienced hypoglycaemic attacks. Clinically it appeared that the injected insulin was utilized more efficiently from the normal sites, but, as they were out-

patients at the time, all the factors influencing insulin absorption and utilization were not strictly controlled.

Diabetic patients exhibiting moderate to severe lipodystrophy as defined previously (Paley, 1953) were examined with respect to stability of diabetic control. Of 53 such patients, 28% were classed as unstable

FIG. 1.—Lipohypertrophy in Patient F. R.

(as defined by Fryers, Paley, and Tunbridge, 1954). The total incidence of unstable patients at the diabetic clinic at Leeds General Infirmary was 17%. Superficially it would appear that patients with lipodystrophy have a greater incidence of instability, but statistically the difference is not significant.

The evidence would suggest that lipo-atrophy is not a major cause of instability in diabetics, but in view of its frequency it seemed necessary to investigate whether it is a contributing factor. To test this hypothesis, six patients, each showing marked lipo-atrophic changes at the insulin injection sites and each a known unstable diabetic, were admitted to the diabetic annexe, Pinderfields General Hospital.

The disease had been present for more than five years in each patient, and they had been under careful supervision in the past.

Method

The patients, all females, were observed during an initial period lasting from 4 to 10 days. During this period they were maintained on their accustomed dose and type of insulin. No change was made in the site of injection, whether this had been into the atrophic or normal fat areas. No effort was made to improve the diabetic control during the study and there were no changes in insulin dosage. Although there was great variability in blood-sugar values observed, confirming the unstable nature of the disease, no hypoglycaemic attacks occurred, and there was no ketosis.

Diet and exercise were rigidly controlled. The insulin dosage was checked and insulin was injected by a nursing sister or a doctor. Times of meals and times at which blood sugar was measured were the same throughout the experiment. Capillary blood was used throughout for blood-sugar determinations, and was estimated by the method of Hagedorn and Jensen (Harrison, 1937).

Three anatomical regions for injection were selected—namely, (a) intramuscular, (b) normal fat, and (c) atrophic fat. Each patient received injections in each anatomical area for one week. The sequence of areas for injection was randomized according to the accompanying Table.

The blood sugar was estimated at 8 a.m., 11.30 a.m., 3.30 p.m., and 9 p.m.. The values were then analysed to demonstrate a difference in the time of day for the occurrence of high or of low blood sugars. This daily pattern of variations was obtained by plotting the mean deviation from the daily mean at specified times of the day for each patient from the three different anatomical sites.

The experimental design was described by Crump (1952) and further elaborated by Fryers *et al.* (1954) and Paley (1954). The statistical treatment is one of analysis of variance (Fisher, 1946).

Patient	Injection Site		
	1	2	3
E.P.	a	b	c
H.S.	b	c	a
D.B.	c	a	b
M.C.	a	c	b
M.B.	b	a	c
L.W.	=	b	c

Injection regions: (a) intramuscular, (b) normal fat, (c) atrophic fat.

Similarly, three female patients with severe lipohypertrophy were investigated under these experimental conditions. In this group, insulin injections were merely alternated at a week's interval between the hypertrophic areas and normal fat.

Results

Analysis of the blood-sugar estimations in the six female patients with lipo-atrophy shows no statistical difference at any time of the day for two patients, D.B. and L.W. (Chart for D.B. is shown in Fig. 2, A). Although significant differences in mean blood-sugar levels are encountered in the other four patients, no definite pattern of response emerges.

Thus a significant depression of blood sugar is observed at fasting level when patient E.P. receives the insulin into an atrophic area (Fig. 2, B); whilst a significant depression of mean blood-sugar levels is observed at 9 p.m. in patient M.C. when the results from both intramuscular injection and those from atrophic area are compared with the response from injection into normal fat (Fig. 2, C).

Conversely, a significant depression of mean blood sugars at 9 p.m. is observed in the normal and intramuscular sites when compared with the atrophic area for patient M.B. (Fig. 2, D). As if to emphasize the completely random nature of these results, patient H.S. shows a significant depression at 9 p.m., when the results from injections into normal fat are compared with intramuscular injection and also those into atrophic fat areas (Fig. 2, E).

When the results from the three patients with hypertrophic lipodystrophy are analysed two patients show no significant difference between the mean blood-sugar levels at any time of the day for injections into the hypertrophic and normal fat areas. The two curves for each patient are almost identical. Patient F.R., with severe hypertrophic lipodystrophy, was first maintained by injections into normal fat during the pre-investigation period; the first experimental area was also normal fat.

Although marked intra-daily variations of mean blood sugars were observed from injections in this site, no hypoglycaemic symptoms developed. The second experimental area was the hypertrophic fat. Here a significantly lower mean blood sugar was observed at fasting level with insulin injections into the hypertrophic areas, and slight hypoglycaemic symptoms were noted on the last two nights of the trial in this area (Fig. 3).

Discussion

Lipodystrophy has usually been considered a harmless complication of diabetes, and it was Lamar (1950) who first suggested that alterations in insulin absorption may be influenced by both atrophic and hypertrophic lipodystrophies at the sites of injection. Only scanty references to this topic can be found in the literature—those by Aubertin (1954) and Davis (1955)—although it appears to be a common clinical impression that insulin is "absorbed" more efficiently from normal fat than from an area showing lipodystrophy.

A direct comparison of a group of patients with severe lipodystrophy and a group with no lipodystrophy did show

FIG. 2.—Mean deviation from daily mean blood sugar for five patients.

FIG. 3.—Mean deviation from daily mean blood sugar for Patient F. R.

a higher incidence of instability in the former, though the difference was not statistically significant. Such an analysis, however, does not take into account all the factors associated with diabetic control, and in fact the result could be invalid.

Three sites for injection were selected—abnormal fat area, normal fat area, and intramuscular area. The intramuscular area was selected in order to see if there was a significant change in diabetic control, and, furthermore, in patients with severe atrophic sites it could then be recommended as a temporary alternative site for therapeutic insulin injections. Previous studies (Paley, 1953), and the present investigation, have shown no muscle atrophy to be present clinically in any of these patients. Lawrence (1928) stated that there was evidence that intramuscular injections of insulin may produce local necrosis.

Since unstable diabetic patients are subject to large and rapid swings of blood-sugar levels it seemed reasonable

to suppose that this experimental design could help to solve the problem of insulin absorption from lipodystrophic sites.

This study has shown that injection of insulin into atrophic fat sites does not appear to alter diabetic control and, similarly, that intramuscular injections of insulin do not cause an increased variation in blood-sugar levels. Instability in diabetic patients therefore appears to be entirely independent of the site of injection of the insulin.

Similarly, in the three patients with hypertrophic lipodystrophy no fixed pattern of blood-sugar levels emerged. In only one patient did a significantly lower blood-sugar level occur when insulin was injected into the hypertrophic area. If this effect is due, as Lamar (1950) suggests, to the occasional flooding of insulin from these hypertrophic depots, then it is surprising that this phenomenon occurred only once in the whole study. It is more likely that this solitary episode of hypoglycaemia was entirely independent of the site of insulin injection.

Summary

Six unstable diabetic patients with severe atrophic lipodystrophy and three patients with severe hypertrophic lipodystrophy were studied to ascertain whether insulin lipodystrophy was a factor in their instability.

The experimental design was an adaptation of one used in insulin therapeutic trials, and each patient acted as her own control.

No pattern of significant differences was observed in the blood-sugar curves obtained from different injection sites, and therefore lipodystrophy cannot be regarded as a cause of diabetic instability.

In view of the belief that intramuscular injections of insulin cause tissue necrosis, it is of interest that no untoward effects occurred from such injections given for four to seven days.

We thank Dr. J. Adler and his assistant for the blood-sugar estimations, and the ward sisters, dietitian, and patients for their willing co-operation in these trials. We also thank Professor R. E. Tunbridge for permission to study his patients.

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The considerable educational activities of the National Association for Mental Health are summarized in its latest Annual Report for the Year 1957-8. Its longest-established course is for school medical officers and is on the ascertainment of educationally subnormal children and mental defectives. Recent changes in the school health services and in the general approach to mental deficiency pointed "to a re-orientation of the course as a whole," but agreement on the precise nature of it in future has not yet been reached. Various refresher courses have also been held, and a new project was a residential course on "Mental Health in the Public Health Field." It was held in April this year, and was attended by ten medical officers of health from the north of England. Students who came from overseas to attend the courses included two from Malta and one from Trinidad who on returning to their own countries will set up entirely new services for the mentally handicapped. Courses for chaplains in mental and mental-deficiency hospitals were found to be useful in enabling doctors and chaplains to discuss problems of concern to both.

CONTAMINATION OF OPERATING-THEATRE AIR WITH *CL. TETANI*

BY

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Cases of post-operative tetanus have been attributed by Robinson, McLeod, and Downie (1946) and by Sevitt (1949) to dust-borne contamination. Both reports imply that such contamination of dust was probably exceptional, in one hospital because of its nearness to grazing pastures, in the other because of the use of plaster hair in repairs to the theatre suite; and in both reports it is suggested that these risks would be reduced by improvements in theatre hygiene, including the use of plenum ventilation with filtered air.

A recent study in this hospital (Lowbury and Lilly, 1958) has shown that *Clostridium welchii* could be isolated from the air at most times, and that these organisms are apparently carried into the hospital with outdoor air; a plenum-ventilated dressing station showed significantly smaller numbers of *Cl. welchii*. In this paper we report a study on the incidence of airborne *Clostridium tetani*. It shows that small numbers of *Cl. tetani* could be found usually in the street and often in the exhaust-ventilated theatres; but none were found in a dressing station which was plenum-ventilated with filtered air. A simple technique for the recognition of toxigenic *Cl. tetani* is described. Some results of examination of dust, soil, faeces, and burns for *Cl. tetani* are also reported.

Methods

Sampling

Bacterial samples from air were collected with a large slit sampler (Bourdillon, Lidwell, and Thomas, 1948), and sometimes also by settle plates, on to nutrient gelatin (20%), which was then melted at 37° C. and distributed into bottles of cooked-meat broth. These, in most of the tests, were heated at 65° C. for 30 minutes before incubation; in later tests the gelatin itself was heated before addition to the cooked-meat broth. After four days' incubation and again after 12 days' incubation at 37° C., Gram-stained films of the cultures in cooked-meat broth were carefully examined for terminal spore-bearing bacilli. When these were present the culture was examined by the methods described below for the presence of *Cl. tetani*.

Samples of faeces and soil were inoculated in cooked-meat broth, which was heated at 80° C. for 10 minutes before incubation. Road dirt, hospital dust, and burn swabs were inoculated in cooked-meat broth, which was heated at 65° C. for 30 minutes before incubation. Gram-stained films were examined, as above, after four days' and after 12 days' incubation.

Isolation and Recognition of *Cl. tetani*

Cultures in cooked-meat broth showing terminal spore-bearing bacilli were subcultured by wire loop to the water of condensation in Fildes (1925) slopes. After anaerobic incubation in a Mackintosh and Fildes jar for 48 hours, the slopes were examined with a hand lens. If a characteristic fine filamentous swarming edge of growth was present, it was subcultured to a second Fildes slope; swarming