

hospitals, losing valuable educational time in travelling and waiting. In 1951 a start had been made in providing physiotherapy in the schools, and by 1957 it was available in all the schools, together with speech therapy, and where a group of deaf cerebral-palsied children are gathered together a teacher of the deaf can visit them. In the old schools there is inadequate provision for these services, but in the new schools, built and building, the planning is excellent.

There are some children, too severely handicapped for the special schools of the London County Council, who may be at hospital schools or schools run by independent organizations and supported by the local education authorities, while others, about 60, receive teaching at home.

There has been a double change over the years, some handicapped children being received into the normal school community and others being drawn out of the home and the hospital into the special schools. Accordingly, it should not be assumed that all the decrease over the last 30 years is due to an improvement in the health of the child population. Much of the change is, however, due to just this. It is not that there are children with chorea or rickets in ordinary schools—there is no chorea, there is no rickets.

Summary

A survey was made in 1957 of the reasons given for admission of the 1,325 children in London's schools for the physically handicapped. The diagnoses were coded under the International Statistical Classification (W.H.O., 1957). 93 different conditions were recorded. The most common reason for admission was cerebral palsy (312), followed by poliomyelitis (240) and congenital heart disease (127).

This survey is compared with previous surveys made in 1928, when there were 4,061 children in these schools, and in 1951, when there were 1,657. The incidence of the main groups of diseases in these three surveys is examined.

The changes observed—the falling incidence of juvenile rheumatism and non-pulmonary tuberculosis, the rise of cerebral palsy—are discussed and the reasons for the general decline in the numbers in schools for the physically handicapped are examined.

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The Exhibition of Medical Records at the Royal College of Physicians of London (November 26 to December 12) covers nearly 400 years, from the end of the fifteenth to the middle of the nineteenth centuries. Among the many exhibits on view are the first ordinance book of the Fellowship of Surgeons (c. 1492-7) which contains the text of the Bye-laws of the unincorporated Fellowship of Surgeons of the City of London; and the Letters Patent incorporating the College of Physicians in London, granted in 1518. The earliest subscription book of the Archdeaconery of Chichester shows the subscription of Elizabeth Strudwicke, of Kirdford, who was licensed to practise as a surgeon in 1673; this is "probably one of the earliest examples of a female surgeon." Among the other 59 exhibits are the articles of agreement between David Irish, "prakticiner in physick," and Joseph Chitty, of Witleys, Surrey, to cure the latter's wife of "hipochondriak melancholy madness" for £5 down and a further £5 on completion of the cure. The catalogue of the exhibition (price 2s. 6d.), with an introduction by Mr. L. M. PAYNE, assistant librarian, Royal College of Physicians, gives further details.

REMITTENT INSULIN-INSENSITIVE DIABETES

BY

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Following total pancreatectomy the adult human requires about 60 units of insulin a day (Young, 1951), but this figure is probably less than the actual daily insulin secretion because the operation also presumably diminishes the production of glucagon—a hyperglycaemic hormone secreted by the alpha cells of the islets of Langerhans. Many diabetics actually require much more than 60 units of insulin daily to keep them in good health, and Bornstein and Lawrence (1951) and Bornstein (1953) have shown that some diabetics have normal serum insulin levels. In such cases diabetes is probably due to insulin insensitivity rather than to actual insulin deficiency *per se*, but the mechanism of this insensitivity is not yet clear. A number of hormones are known to counteract the hypoglycaemic effects of insulin, and it is possible that the endocrine secretions of the anterior pituitary, thyroid, and adrenal glands, and of the alpha cells of the pancreas, may each be involved to varying degrees in different cases. Several physiological and pathological processes are known to be associated with decreased insulin sensitivity, including puberty, pregnancy, thyrotoxicosis, infection, and metabolism in a high carbohydrate diet. In some cases, however, there seems to be no obvious cause for the observed fluctuations in insulin requirements.

A number of diabetics are seen in Singapore who exhibit this fluctuation to an extreme degree. Some of these patients require over 200 units of insulin daily for a period, though later their insulin requirements may fall to zero. The following eight cases are striking examples of this syndrome, and others have been observed.

Case 1. 720 Units of Insulin Daily. Over 3 Years' Complete Remission

A 52-year-old Malayalam taxi-driver was admitted to hospital on April 18, 1954, with a history of a cough for five months, and fever, polyuria, weakness, loss of weight, and excessive thirst for six weeks. He was found to be a diabetic with gross cavitating tuberculosis of the right upper lobe. His sputum contained acid-fast bacilli and his urine showed sugar and acetone. A glucose-tolerance test revealed a fasting blood sugar of 215 mg./100 ml., rising to 270, 332, 384, and 316 mg. at half-hourly intervals. Treatment was begun with streptomycin and isoniazid, and he was controlled on soluble insulin. The progress of his glycosuria and insulin administration is summarized in Fig. 1. It will be seen that ultimately 720 units of insulin were required daily to control his glycosuria. Later the insulin requirements fell away to zero, and on February 14, 1955, a glucose-tolerance test showed a fasting blood sugar of 83 mg./100 ml., rising to 120, 148, 170, and 154 mg. at half-hourly intervals. Meanwhile his pulmonary tuberculosis had also improved, and an arrangement that had been made in May, 1954, to fly him to London for a right upper lobectomy was cancelled. Anti-tuberculosis therapy was finally stopped on November 2, 1954, at which time his sputum was negative, his E.S.R. was 2 mm., and his chest x-ray film showed only mild residual fibrosis.

This patient has remained fit and well, and has never had a recurrence of his diabetes or tuberculosis. He has weathered a number of other infections, including influenza and gastro-enteritis, without any complication.

Case 2. 360 Units of Insulin Daily. 22 Months' Complete Remission

A slim Ceylonese jeweller aged 46 had a cough for nine months and was admitted to hospital on April 23, 1954, in pre-diabetic coma. He was found to have bilateral cavitating tuberculosis, and a glucose-tolerance test showed a fasting blood sugar of 181 mg./100 ml., rising to 217, 290, 385, and 363 mg. at half-hourly intervals. He was treated with insulin, streptomycin, isoniazid, and P.A.S. It was found that 360 units of insulin were required daily to control his diabetes, but after 12 days at this dosage his insulin requirements slowly began to fall, and insulin therapy was finally stopped on July 11. A glucose-tolerance test was then normal. His tuberculosis continued to improve and anti-tuberculous drugs were stopped on February 15, 1955. In May, 1956, he began to have increased thirst and polyuria, and found that he had glycosuria. He has since remained a fairly stable diabetic, and for the last year has been well controlled on tolbutamide.

Case 3. 360 Units of Insulin Daily. 27 Months' Complete Remission

A 24-year-old Indian housewife was well until August, 1954, when, in the 29th week of her first pregnancy, she noticed she had polyuria and felt very thirsty. Her urine was found to contain acetone and sugar, although at regular monthly checks these had previously been absent. A glucose-tolerance test showed a fasting blood sugar of 394 mg./100 ml., rising to 450, 455, 478, and 491 mg. at half-hourly intervals. She was admitted to hospital for stabilization on insulin, and for two weeks required 360 units of insulin daily. Yet over the course of 10 days her insulin requirements fell to zero. The baby appeared to be large, and so labour was induced at 34 weeks. During and following a normal delivery the patient's blood sugar remained within normal limits and the baby's fasting blood sugar after delivery was 52 mg./100 ml. The patient remained well and breast-fed her baby. She had no recurrence of diabetes, and regularly tested her urine without finding glycosuria until January, 1957. She was then in the seventh month of her second pregnancy and again had to have up to 360 units of insulin daily. Her insulin requirements fell just before parturition, but this time she has had to continue on a small daily dose of insulin.

Case 4. 400 Units of Insulin Daily. One Year's Complete Remission

A 52-year-old Chinese noticed the gradual onset of increased thirst, general weakness, and polyuria. He was found to have sugar and acetone in his urine. A glucose-tolerance test on January 7, 1954, showed a fasting blood sugar of 462 mg./100 ml., rising to 480, 512, 520, and 520 mg. at half-hourly intervals. The patient was 5 ft. 4 in. (163 cm.) tall and weighed 244 lb. (110.7 kg.). He was instructed to take a low carbohydrate slimming diet, and was stabilized on 400 units of insulin daily as an out-patient. His weight remained constant, and he was therefore admitted to hospital, and maintained on a slimming diet of 1,000 calories. There was an immediate reduction in his insulin requirements to 80 units a day, and as he lost weight his requirements gradually fell to zero. A glucose-tolerance test then showed a fasting blood sugar of 107 mg./100 ml., rising to 121, 148, 172, and 168 mg. at half-hourly intervals. He was discharged weighing 208 lb. (94.3 kg.) and kept at that weight for about a year. His weight then rose again and his diabetic symptoms recurred. He refused to slim again, and is now symptomatically controlled on tolbutamide.

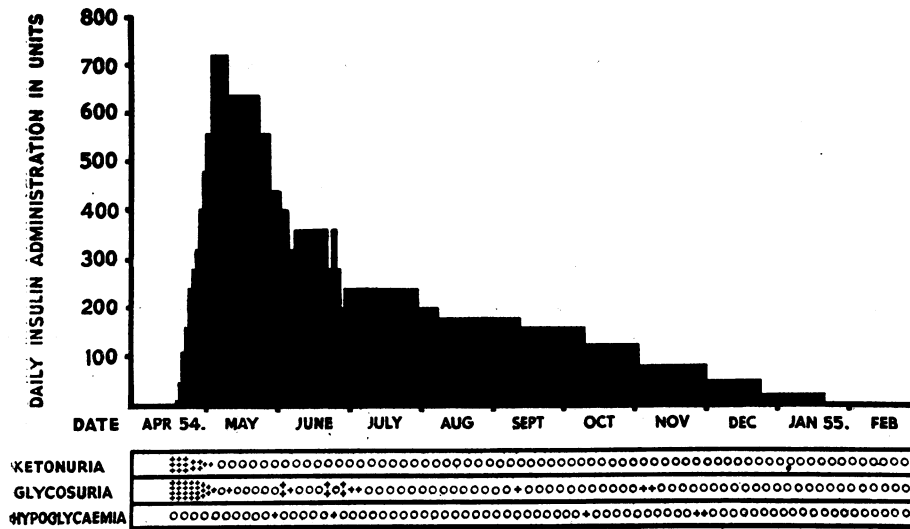


FIG. 1.—Insulin administration with related urinary findings and hypoglycaemic attacks (Case 1).

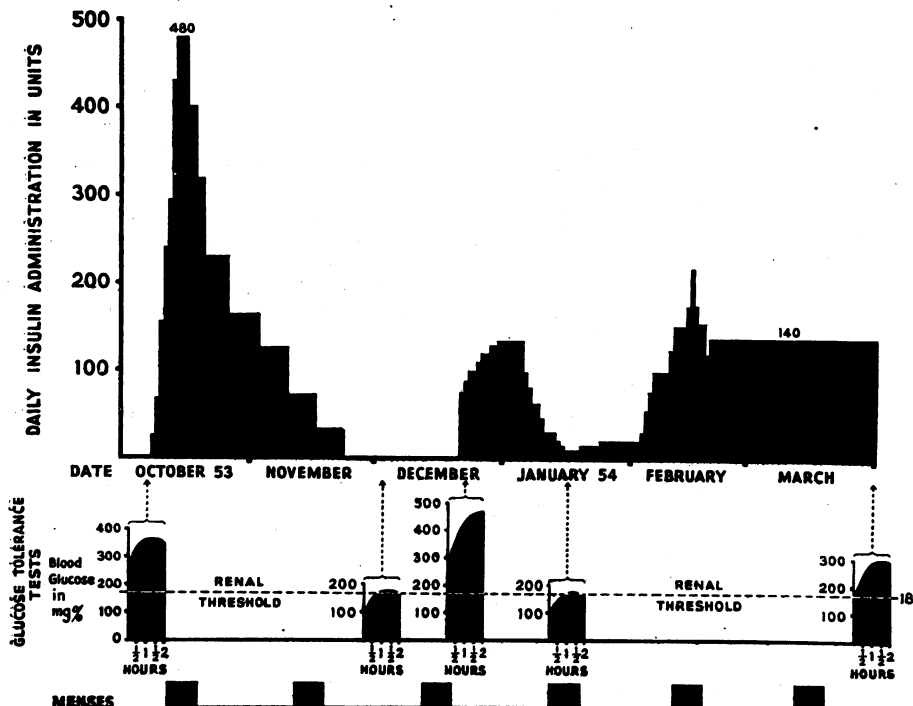


FIG. 2.—Insulin administration with related glucose-tolerance tests and menses (Case 7).

Case 5. 240 Units of Insulin Daily. 38 Months' Complete Remission

A 42-year-old Cantonese washerwoman presented with polydipsia, loss of weight, general weakness, pruritus vulvae, and polyuria in December, 1953. There was no evidence of infection. Her urine contained sugar and acetone, and a glucose-tolerance test showed a fasting blood sugar of 405 mg./100 ml., rising to 436, 472, 506, and 512 mg. at half-hourly intervals. She was controlled on insulin, and for five months her requirements remained stable at 240 units daily. She then suddenly began to have severe hypoglycaemic reactions and insulin administration was stopped. No glycosuria occurred, and six days after being well controlled on 240 units of insulin daily a glucose-tolerance test showed a fasting blood sugar of 88 mg./100 ml., rising to 121, 148, 164, and 160 mg. at half-hourly intervals. She remained well without treatment for 38 months, and periodic urine sugar tests were always negative. Then in September, 1957, she gradually developed diabetes again, and has since been well controlled on tolbutamide.

Case 6. 320 Units of Insulin Daily. Partial Remission

A slim 31-year-old Gurkha policeman had a sudden onset of increased thirst and polyuria associated with a common cold. He was found to have sugar and acetone in his urine, and a glucose-tolerance test showed a fasting blood sugar of 163 mg./100 ml., rising to 192, 232, 226, and 196 mg. at half-hourly intervals. His cold subsided in three days and he was stabilized on insulin, ultimately receiving 320 units daily for a period of 91 days. For no apparent reason his requirements then fell to 10 units a day and he was well controlled on this dose for six weeks. Eventually his requirements slowly rose to 240 units daily. He is now well controlled on tolbutamide.

Case 7. 480 Units of Insulin Daily. One Month's Complete Remission

A 16-year-old Franco-Pakistani schoolgirl noticed the onset of increased thirst and polyuria three weeks before she was admitted to hospital on October 6, 1953. She had no evidence of infection. Her menses began five years previously and were regular and normal. She had acetone and sugar in her urine, and a glucose-tolerance test showed a fasting blood sugar of 275 mg./100 ml., rising to 320, 370, 370, and 362 mg. at half-hourly intervals. The progress of her diabetes is summarized in Fig. 2. It will be seen that she required 480 units of insulin daily at one period, and later had two remissions before finally becoming a stable diabetic requiring 140 units of insulin a day. She has remained stable on this dosage, and is now a very fit student of economics in London. Her menses were not related to the fluctuations in her insulin requirements.

Case 8. 280 Units of Insulin Daily. Three Complete Remissions, One of Over 3 Years

A Dutch business man aged 63 was admitted to hospital in July, 1953, because of an acute exacerbation of gout. Although he had suffered from gout for 30 years he had apparently never been treated with colchicine. He was therefore tried on the drug and his gout quickly improved. However, he developed glycosuria, and a glucose-tolerance test showed a fasting blood sugar of 168 mg./100 ml., rising to 186, 224, 210, and 195 mg. at half-hourly intervals. His diabetes was controlled on 240 units of insulin a day, but after six weeks at this dosage his insulin requirements began to fall and insulin administration was stopped in November, 1953. His urine remained sugar-free until March, 1954, when, following another exacerbation of gout and subsequent colchicine therapy, he was again observed to develop diabetes. On this occasion he required 280 units of insulin daily for two weeks, and then his insulin requirements gradually fell and stabilized at 80 units daily. He then went to

South Africa for a holiday, and in August, 1954, apparently had a mild coronary thrombosis followed by a severe hypoglycaemic attack. A glucose-tolerance test was reported to be normal and his insulin administration was stopped. On returning to Singapore in September his urine was confirmed to be sugar-free. However, in November he again developed acute gout, took colchicine, and developed diabetes. A glucose-tolerance test on this occasion showed a fasting blood sugar of 176 mg./100 ml., rising to 195, 220, 224, and 210 mg. at half-hourly intervals. His diabetes was controlled on 80 units of insulin daily for five weeks, and then for the third time his insulin requirements fell to zero.

It was thought possible that his attacks of diabetes might be related to his colchicine therapy, and he was therefore started on probenecid. This has been successful, and since May, 1955, he has never had severe gout, insulin, or glycosuria.

Discussion

The eight diabetic cases described above each required over 200 units of insulin daily for more than seven consecutive days. In every case this period of insulin insensitivity was temporary, seven patients later having complete remissions, and one (Case 6) requiring only 10 units of insulin a day.

Diabetes mellitus insensitive or resistant to insulin is apparently uncommon in Europe and North America. In Joslin's very large experience of diabetes he records seeing up to 1952 only 20 patients who required over 200 units of insulin a day (Joslin, Root, White, and Marble, 1952); and Smelo (1948) found records of only 29 such cases in the world literature up to 1940, and another 25 cases in the subsequent English literature up to 1948. Yet in Singapore, I have observed 38 diabetics in the past five years who each required 200 or more units of insulin on at least four consecutive days, and it is not uncommon to find that diabetics here require over 100 units of insulin daily for long periods. The average insulin requirements of 165 diabetics in Singapore, selected only to exclude advanced pulmonary tuberculosis or incipient diabetic coma, was found to be 57.5 units a day (Tan and Wells, 1957), and, although no comparable figures are available, this seems likely to be higher than the average for diabetics in Britain. If this is so, one explanation may be that a higher proportion of the diabetics in Singapore fall into the older arteriosclerotic non-ketotic insulin-insensitive group, well described by Himsworth (1936) and Lawrence (1951).

To some extent the incidence of this type of diabetes may be genetically determined, as inferred by the findings of Lister, Nash, and Ledingham (1951). Another possible explanation is that most of those who developed insulin-sensitive ketotic diabetes in Singapore prior to 1945 died during the Japanese occupation because of the insulin shortage, producing a relative scarcity of this type of diabetic in Singapore at the present day. Conversely, the non-ketotic insulin-insensitive diabetics for whom insulin administration was not essential may actually have been benefited by the food shortages of the occupation which forced them to have restricted diets.

It has been suggested that the finding of insulin insensitivity may sometimes be false, owing to deterioration of the insulin used (Palmer, 1948). In the Tropics this possibility always has to be considered; but investigations in Singapore, including comparative assays in some of the cases reported above using insulin preparations specially flown here straight from the factories, have not shown any evidence of deterioration in the Singapore insulin stocks, even when these were at their recommended expiry dates.

Over-enthusiastic insulin administration may sometimes result in confusion between maximum insulin tolerances and optimum insulin requirements. It was the practice, however, in the management of the cases reported here, to keep the insulin administered so far as possible at the minimum which would adequately control the patient's glycosuria (cf. Fig. 1).

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.

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SEVERE INSULIN LIPODYSTROPHY AS A POSSIBLE CAUSE OF INSTABILITY IN DIABETICS

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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-