evidence which suggests that patients with meningo-encephalitis give rise to cases of meningo-encephalitis or that meningo-encephalitis cases are caused by a "separate" neurotropic strain. The prevalence of mumps meningo-encephalitis in Northern Ireland in 1958 may have been due to a mumps virus of increased neurotropism, or may simply have been the reflection of a large epidemic of mumps and an available viral diagnostic laboratory whereby infection of the C.N.S. with mumps virus could be differentiated from non-paralytic poliomyelitis and other causes of aseptic meningitis and encephalitis.

Summary

The clinical, laboratory, and epidemiological features of 50 cases of mumps meningo-encephalitis are described. 39 of these occurred during 1958, when there was a mumps epidemic in Northern Ireland. The diagnosis in all cases was confirmed by complement-fixation tests using V (viral) and S (soluble) antigens. The C.S.F. findings in 36 cases are presented. Males were more commonly affected than females, and 84% of the cases occurred in children under 15 years of age.

The principal clinical features were fever, headache, neck rigidity, and vomiting with or without salivary-gland involvement, which occurred in only 54% of the cases. About one-third of the patients showed signs of encephalitis, one of which was of the post-infective type.

The peak incidence of mumps meningo-encephalitis occurred in the late spring and early summer months, and there was no difference in the seasonal incidence of mumps meningo-encephalitis with parotitis and mumps meningo-encephalitis without parotitis. Mumps virus infection appears to have been more readily transmitted by patients with parotitis than by patients without enlarged salivary glands.

A follow-up study of a number of patients was done, and the absence of serious sequelae in this series suggests that a good prognosis may usually be given in mumps meningo-encephalitis.

We wish to acknowledge the co-operation of many clinicians in the preparation of this paper and of the clinical pathologists who provided data on the C.S.F. In particular we would like to thank Drs. F. F. Kane, G. F. W. Tinsdale, and A. R. Crawford, of the Northern Ireland Fever Hospital, and Dr. S. N. Donaldson for their help, and Mr. J. J. McAlister, F.I.M.L.T., and Mr. D. C. Wilson, F.I.M.L.T., for technical assistance in the Virus Reference Laboratory, which is supported by the Northern Ireland Hospitals Authority. We thank Professor G. W. A. Dick for help in the preparation of this paper, and Dr. D. S. Dane for his valuable criticism.

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The Australian Director-General of Medical Services for the Army, Major-General W. D. REFSHAUGE, is to become Australia's Director-General of Health. The present permanent head of the Department of Health, Dr. A. J. METCALFE, will retire later this year. Major-General Refshauge, who is 47, is a graduate of Melbourne University, and is at present engaged in work for the Department of Defence.

SERUM INSULIN IN A CASE OF SEVERE DIABETES MELLITUS SHOWING REMISSION

BY

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Increasing interest has latterly been shown in cases of severe diabetes showing remission (Goadby, 1943; Harwood, 1957; Phillips, 1957; Peck, Kirtley, and Peck, 1958; Stutman and Hayes, 1959), and some recent correspondence in the *British Medical Journal* has emphasized that clinical remission in the more severe forms of the disease may be commoner than is perhaps realized (Waddell, 1959; Wolff, 1959; Paton, 1959).

Serum insulin studies in a case in which spontaneous remission took place from a state of severe diabetic ketosis are described below. While this case was less severe than some of those reported by the authors above, and even in clinical remission an impairment of glucose tolerance remained, observations on serum insulin and insulin antagonists have not hitherto been reported in this type of patient. In view of current interest in this aspect of diabetes, it seemed worth while to give a detailed account of these studies for the light they may throw on serum insulin in early diabetes.

Case Report

A married professional man, aged 33, attended the out-patient department in May, 1959, with a one-month history of increasing thirst, polyuria, and lassitude, and during this time his weight had decreased from 9 st. 7 lb. to 8 st. 11 lb. (60.3 to 55.8 kg.). Until this period he had been well, without significant earlier illness, nor was there any family history of diabetes. Detailed examination did not reveal any abnormal physical findings, apart from evidence of early dehydration, though his breath smelt strongly of acetone. Intercurrent infection appeared to be absent. The urine then contained over 2% of sugar and gave a strong positive ferric-chloride reaction for acetoacetic acid. The blood-sugar at the time of examination was 352 mg./100 ml. The patient was admitted for stabilization of his diabetes, and after an uneventful period in hospital was discharged on a dose of 20 units of soluble insulin in the morning, 14 units in the evening, and a suitable diet containing 200 g. of carbohydrate.

After severe hypoglycaemia his insulin dosage was reduced to 12 units in the morning and 10 units in the evening and he was instructed to reduce the dosage still further if hypoglycaemia continued. In July, 1959, as a result of increasingly severe hypoglycaemic episodes, he was taken off insulin entirely, and has remained without insulin until the time of writing (January, 1960). During this period he has remained symptom-free, with blood-sugars, taken at an afternoon clinic which he was attending at six-weekly intervals, ranging from 84 to 134 mg./100 ml. His weight has increased to and has remained at 9 st. 4 lb. (59 kg.). An oral glucose-tolerance test, performed in September, 1959, was, however, definitely diabetic in type. Thus, after 50 g. of glucose the blood-sugar rose from a fasting level of 125 mg. to 177 mg./100 ml. at half an hour, and 245 mg. at one hour, falling to 217 mg. at two hours after the glucose. It is clear, therefore, that diabetes in this patient remains quiescent, and that remission is in no sense complete.

Methods

Serum Samples.—Samples of blood were drawn from an antecubital vein into a clean dry syringe. After allowing

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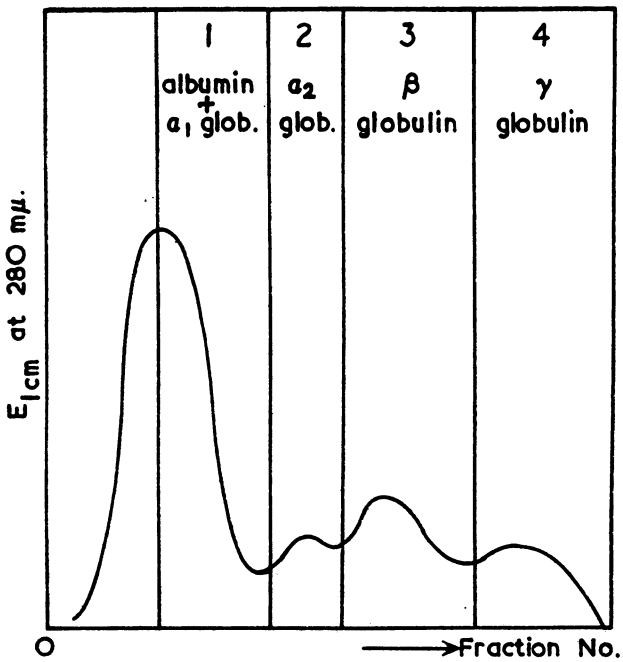
the blood to clot, the serum was separated from the cells by centrifugation. A sample of blood was obtained for investigation when the patient was admitted during ketosis, before the inception of insulin therapy, and a further sample two months after the cessation of insulin injections, in the phase of remission.

Determination of Insulin Activity.—The insulin activity of serum samples was investigated by determining the effects of serum on the glucose uptake of the isolated rat diaphragm *in vitro*, employing methods previously described (Randle, 1954, 1956). In these experiments serum was diluted 1:4 with bicarbonate-buffered saline (Gey and Gey, 1936) so as to give a final glucose concentration in the incubation medium for diaphragms of 250 mg./100 ml. Glucose uptake was calculated as milligrams of glucose disappearing from the medium/g. of wet diaphragm/hour of incubation. Mean uptakes of glucose for each group of hemidiaphragms in the test were calculated and the significance of differences between means was determined by calculating "t." Reference to tables (Fisher and Yates, 1943) enabled "P," the probability that such differences were due to chance, to be determined.

Fractionation of Serum Proteins.—Serum proteins derived from blood taken during ketosis were fractionated by zone electrophoresis on columns of treated cellulose, by methods already described (Randle and Taylor, 1958a). The concentration of protein in the eluate from such columns was determined by measuring the optical density of 4-ml. portions of the eluate at 280 mμ in a Beckman spectrophotometer. The pattern of serum-protein fractions obtained in this way is shown diagrammatically in the Chart. Fractions



Subdivision of protein fractions after zone electrophoresis of serum taken during ketosis. (For further details, see text.)

were pooled, as shown, so as to yield four main subfractions. These have been designated an albumin and α_1-globulin fraction, an α_2-globulin fraction, a β-globulin fraction, and a γ-globulin fraction. Such pooled fractions were dialysed against distilled water, lyophilized, and the freeze-dried material dissolved in buffered glucose, to correspond with 50% serum, in order to test on the diaphragm for insulin activity.

Results

In Table I are shown the effects of the patient's whole serum on the glucose uptake of the isolated rat diaphragm. Serum taken during the phase of ketosis appears to be without effect on glucose uptake, though a statistically significant effect due to the serum taken in remission is seen. Reasons have been given elsewhere for regarding the effects of whole serum on glucose uptake of the rat diaphragm as due entirely to insulin (Taylor and Randle, 1959), and it is clear that during remission the patient's serum contained endogenous insulin, probably in considerable quantity.

The absence of a stimulatory effect on glucose uptake due to serum taken during ketosis does not, however, mean that there is no insulin present, since the effects of insulin, under these circumstances, might be nullified by insulin antagonists. In an attempt to separate insulin from such antagonists, serum proteins were fractionated by zone electrophoresis, and the resultant fractions also tested for their effects on the glucose uptake of rat diaphragm. These results are shown in Table II. Stimulatory effects on

TABLE I.—*Effect of Patient's Serum on Glucose Uptake of Isolated Rat Diaphragm in Vitro*

Source of Serum Sample	Addition to Medium	Glucose Uptake. Mean ± S.E.M. (mg. Glucose/g. Wet Diaphragm/hr. Incubation)	Significance of Differences between Means (P)
During ketosis ..	None	3·4 ± 0·27 (5)	<0·6>0·5
	Serum	3·6 ± 0·21 (5)	
,, remission ..	None	2·5 ± 0·25 (5)	<0·02>0·01
	Serum	3·6 ± 0·23 (6)	

Serum was tested as 25% serum, in bicarbonate-buffered glucos e (see text).
Number of observations is given in parenthesis after each mean .

TABLE II.—*Effect of Protein Fractions of Serum, Taken During Ketosis, on Glucose Uptake of Isolated Rat Diaphragm in Vitro*

Addition to Medium	Glucose Uptake. Mean ± S.E.M. (mg. Glucose/g. Wet Diaphragm/hr. Incubation)	Significance of Differences between Means (P)
None	(a) 3·6 ± 0·22 (6)	(b–a)<0·2 >0·1
Fraction 1 (albumin + α_1-globulin)	(b) 4·3 ± 0·34 (5)	(a–c)<0·2 >0·1
,, 2 (α_2-globulin)	(c) 3·2 ± 0·18 (5)	(b–c)<0·02>0·01
None	(a) 2·8 ± 0·23 (5)	(b–a)<0·02>0·01
Fraction 3 (β-globulin)	(b) 3·9 ± 0·23 (5)	(c–a)<0·01>0·001
,, 4 (γ-globulin)	(c) 5·3 ± 0·21 (5)	

Fractions, which were prepared by zone electrophoresis, are as defined by the chart.
Each main subfraction was dissolved in a volume of buffer so as to correspond with 50% serum.
Number of observations is given in parenthesis after each mean.

glucose uptake are seen both due to the albumin-α_1 fraction and due to the β- and γ-globulins. Evidence has been presented that both these effects are due to insulin (Randle and Taylor, 1958b). It is concluded, therefore, that, even in ketosis, insulin is present in this patient's serum.

A small though not statistically significant inhibition of glucose uptake was observed due to the α_2-globulins. This effect, which may have been reduced by insulin contamination from neighbouring fractions, is referred to below.

Discussion

In view of the almost complete remission seen in this patient, the detection of insulin even during ketosis is not perhaps surprising. By contrast, Baird and Bornstein (1957, 1959) have reported that some young severe diabetics exhibited no demonstrable insulin in their serum when this was extracted by an acid-butanol type of method. It is to be presumed that these patients represent a further stage in the progression of the disease, in which the pancreatic supplies of insulin have become exhausted (cf. Wrenshall, Bogoch, and Ritchie, 1952).

Nevertheless, the possibility remains that many severe young diabetics possess adequate quantities of circulating insulin, at least in the early stages of the disease, before a state of "absolute diabetes" (Lawrence, 1951) has become established. This conclusion is also suggested by the histological studies of

Maclean and Ogilvie (1959) on the pancreases of diabetics dying within eight weeks of the onset of the disease. In such individuals these workers showed that islet tissue might be normal or hyperplastic, in contrast to that obtained from subjects dying many months or years after onset, in whom islet-cell volume was diminished.

The results presented in this paper also support the view that in diabetic ketosis there is present a circulating insulin antagonist. Many other workers have presented evidence for the presence of such antagonists in the blood of uncontrolled human diabetics (Vallance-Owen, Hurlock, and Please, 1955; Baird and Bornstein, 1957; Vallance-Owen, Dennes, and Campbell, 1958; Field, Tietze, and Stetten, 1957), though the precise identity of such substances is at present uncertain. In this connexion the small degree of inhibition of glucose uptake due to the α_2-globulins of this patient is of interest. Similar effects due to the α_2-globulins of normal human serum, whether these were prepared by cold ethanol fractionation (Taylor, Vargas, and Randle, 1959) or by column electrophoresis of serum proteins (Randle and Taylor, 1958a), have also been reported. Though it is at present uncertain to what extent this last factor is of importance in human diabetes, evidence is accumulating that it may be pituitary-dependent (Taylor, Randle, and Vargas, 1960). If this is so, then growth hormone may well be implicated in some way in the genesis of human diabetes in giving rise to such a substance which opposes the action of insulin, as Young (1951) has suggested. Similar considerations would also apply to the albumin antagonist of Vallance-Owen, Dennes, and Campbell (1958), which it has also been shown is pituitary-dependent. A further point of some practical significance emerges in that if insulin is still being secreted in the early stages of acute diabetes, what active steps should be taken to conserve actively functioning islet tissue before irreversible damage takes place. To answer this question satisfactorily there is clearly an urgent need for extensive studies on this type of patient.

Summary

A case of severe diabetes in a young adult is described, presenting with ketosis, in whom apparent clinical remission took place.

Serum insulin studies have suggested that in the initial ketotic phase insulin was present, though its effect was masked by the presence of an antagonist. With remission of the diabetes the insulin antagonism disappeared.

The possible bearing of these findings on some aspects of the aetiology of human diabetes is discussed briefly.

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ADDENDUM.—While this paper was in preparation, observations became available on circulating insulin in the serum of an insulin-resistant patient who also showed remission (Joslin, Root, White, and Marble, 1959). In this patient, who was maintained on a very small dose of injected insulin, whole serum, taken in remission, exhibited considerable insulin-like activity, as measured by effects on $^{14}CO_2$ production in the rat epididymal fat pad. These observations are in keeping with results presented in this paper.

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HYPOTHERMIC COMA IN MYXOEDEMA

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Though coma in myxoedema has been described with increasing frequency during the past six years, the condition has received only grudging recognition in the standard textbooks. The 1959 edition of Cecil and Loeb's *Textbook of Medicine* makes no reference to it, while the 1956 edition of Price's *Textbook of the Practice of Medicine* mentions it only in passing. This paper describes three further cases. Two of the patients died during their first episode of coma; the third recovered from quite a deep coma on two separate occasions.

Case 1

A housewife aged 56 was admitted to hospital on January 16, 1959, complaining of progressive swelling of the feet for the previous six weeks. On further questioning, she admitted to some shortness of breath and to abdominal discomfort and distension. She had not suffered from angina of effort and had been able to carry out her normal household duties. For a year before her admission she had noticed that her voice was becoming gruff and that her hair was falling out.

On examination she was jovial and co-operative, though slow. Her eyebrows were absent, the scalp hair was coarse, and axillary and pubic hair was scanty. Her eyes were puffy; the skin was dry and coarse in texture, and cold. Her heart was fibrillating at 60 a minute; the heart sounds