BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 27 1959

ACTION OF PREDNISONE IN INSULIN-RESISTANT DIABETES

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The term "insulin resistant" has generally been applied to those diabetics whose daily insulin requirement exceeds 200 units. Such diabetics are relatively rare; Kleeberg, Diengott, and Gottfried (1956) found only some 50 instances in the literature. The purpose of this paper is to report the results of immunological and other studies on an additional 13 cases, 6 of them treated with prednisone.

The factors responsible for insulin resistance are not known with certainty, but include certain hormones and other substances in the serum, some of which have the properties of antibody and others which are of a different nature. The ability of serum from insulin-resistant diabetic patients to protect animals from the hypoglycaemic action of insulin was demonstrated in rabbits by Glen and Eaton (1938) and in mice by Lowell (1942), who developed the mouse-convulsion test. Marsh and Haugaard (1952), using the rat-diaphragm technique described by Stadie *et al.* (1949), reported insulin inhibition by sera from normal patients, from mild diabetics, and, to a much greater degree, from three severely insulin-resistant diabetics. Using a similar diaphragm technique, Field and Stetten (1956) were able to demonstrate the presence of an insulin antagonist in the alpha-globulin fraction of diabetics with severe ketosis, and Vallance-Owen, Dennes, and Campbell (1958) in the albumin fraction of plasma from uncontrolled insulin-requiring diabetics and also from normal subjects.

For various reasons insulin has been regarded as poorly antigenic, but successful immunization in rabbits has been reported by Wasserman, Broh-Kahn, and Mirsky (1940), and also by Moloney and Coval (1955), who produced immune serum in guinea-pigs, using cattle and pig insulin as antigens. Berson *et al.* (1956) have shown that, in almost all human subjects receiving exogenous insulin, antibodies capable of binding insulin *in vivo* and *in vitro* soon appear. It would seem, therefore, that the difference between insulin resistance and non-resistance in insulin-treated patients may be essentially a quantitative one. In this connexion the work of Berson and Yalow (1957) suggests that the total insulin-binding capacity of sera from non-resistant treated subjects is of the order of 10 units per litre of plasma, whereas binding capacities of as much as 500 units per litre of plasma were found in sera from insulin-resistant patients.

In 1938 Glen and Eaton reported the case of a severely insulin-resistant girl whose insulin requirement fell after the administration of oestrogen, but, apart from this isolated instance, until recently no effective method of treatment has been described. Fortunately, perseverance with large doses of insulin has in most cases been followed by a spontaneous fall in insulin requirement to a much lower but still usually fairly high figure.

Collens and Banowitch (1955) reported the case of a severely insulin-resistant diabetic whose daily insulin requirement subsequently fell from 1,000 to 200 units when given cortisone in large doses. Colwell and Weiger (1956), using corticotrophin, obtained an even more spectacular reduction of insulin requirement from 11,400 to 100 units in a case of haemochromatosis. Similar responses to corticotrophin have been reported by Kleeberg, Diengott, and Gottfried (1956) and by Gitelson and Wislicki (1956).

Methods

In the present study anti-insulin factors were demonstrated by one or more of the following three methods—the mouse-convulsion test, the glucose uptake of the rat hemi-diaphragm, and passive cutaneous anaphylaxis in the guinea-pig. The first two tests have been described by Lowell (1942) and Field and Rigby (1959) respectively; they have been used to demonstrate the presence of anti-insulin substances without distinction between insulin antagonists and insulin antibodies; while the third test, hitherto never used in this connexion, has been adapted by one of us (A.C.C.) to detect insulin antibodies.

Mouse-convulsion Test

In this test samples of plasma from an insulin-resistant diabetic, an insulin-sensitive diabetic, and a normal control are examined. Dilutions of insulin are made in each plasma and injected into fasted mice housed at 34° C. The same concentration of insulin in acid saline is injected into control groups of mice, and hypoglycaemic convulsions are recorded over a period of one and a quarter hours.

Glucose Uptake of Rat Hemi-diaphragm (R.D. Test)

This test depends on the fact that a rat hemi-diaphragm exposed to insulin and serum will utilize about 40% more glucose than a control hemi-diaphragm exposed only to serum. A significant decrease in this insulin effect in the presence of the test serum is

interpreted as evidence for the presence in the serum of an anti-insulin factor. A quantitative estimation of the amount of such factor or factors has been made by testing tenfold dilutions of the test serum, an example of which is shown in Table I; the titre has been expressed as the highest dilution causing a significant decrease in the insulin effect.

TABLE I.—*Rat Diaphragm Titrations on Plasma from a Resistant Diabetic and from Normal Patients*

Dilution of Plasma	Insulin Effect (Micromols Glucose Equivalent per g. Tissue (Mean ±S.E.)		
	Plasma from Case 4		Normal Plasma
	Before Treatment	After Treatment	
1:1	−0·23±0·33 (3)	—	2·74±0·17 (51)
1:10	0·58±0·49 (3)	1·34±0·57 (6)	2·41±0·10 (89)
1:100	−0·02±0·26 (3)	2·35±0·51 (3)	2·07±0·23 (15)
1:1,000	2·32±0·16 (3)	—	2·16±0·27 (3)

Figures in parentheses indicate number of experiments.

Passive Cutaneous Anaphylaxis in the Guinea-pig (P.C.A. Test)

This test depends upon three facts. (1) The guinea-pig is highly susceptible to anaphylaxis and can be readily sensitized to shock by passive transfer of antibody. (2) Whereas a relatively large systemic dose of the appropriate antigen is required to induce fatal anaphylactic shock, the intracutaneous injection of a very much smaller amount results in an immediate and essentially reversible skin reaction, known as cutaneous anaphylaxis, which is characterized by a transient increase in capillary permeability. Since wealing does not occur in guinea-pig skin and erythema is difficult to observe, this increased permeability is best detected when the animal has previously been injected with a suitable dye, and its extent can then be measured by the staining of the skin which results from the escape of dye from the circulation (Ramsdell, 1928). (3) A strictly localized area of sensitization can be produced by the injection of small doses of antibody into the skin. Ovary (1952) and Ovary and Bier (1953) showed that the extent of this local sensitization could be used as a very delicate measure of precipitating antibody in rabbit serum. The procedure they found most sensitive is that known as reversed P.C.A.; in this, the antiserum is injected intracutaneously, and the challenge dose of the appropriate antigen is given intravenously together with "pontamine" or Evans blue; an interval of 4 to 24 hours for skin sensitization is left between the injection of the serum and the challenge with antigen.

Brocklehurst, Humphrey, and Perry (1955), who titrated a pneumococcus polysaccharide-antipneumococcus serum system by reversed P.C.A. in the rat, noted that the diameter of the area of increased permeability, shown by dye escape, was proportional to the logarithm of the dose of antibody, and pointed out the greater precision of titration that can result from this knowledge. The same dose–lesion relationship was found by Cunliffe (1959) while titrating several different antigen–antibody systems by P.C.A. in the guinea-pig.

The reversed P.C.A. technique was used for the detection of antibody to insulin after preliminary experiments had shown that intravenous insulin resulted in well-marked anaphylactic reactions in guinea-pigs previously injected with serum from an insulin-resistant diabetic; control sera gave no reaction. That this was a specific reaction to insulin and not to other tissue antigens of the animal from which the insulin was obtained is proved by the fact that sera gave almost identical P.C.A. reactions to pig and to ox insulins; no increased permeability reactions were produced when ox or pig serum was used as antigen in place of insulin. A quantitative result was obtained by injecting a series of dilutions of the serum under test and comparing the size of the resulting P.C.A. lesions with those given by a standard serum injected into the same animals. This use of a reference serum was necessary because of the considerable variation in the reactivity of individual guinea-pigs.

Details of Technique of P.C.A. Test for Insulin Antibodies

The procedure is that of reversed P.C.A. The animals used were albino guinea-pigs weighing 350–500 g., all of which were bred from the same stock. Depilation was obtained by a short application of a barium sulphide paste to the previously clipped hair of the back and flanks (Miles and Miles, 1952). Pontamine sky blue 6 BX (G. T. Gurr) was made up in sterile saline to a 5% solution. The dose given to the animals was 6 mg./kg. body weight. Insulin (Boots), strength 320 units per ml., was used at a dosage of 160 units/kg. as the challenge antigen. The sera were stored without preservative at −20° C.; these were thawed and dilutions made in physiological saline immediately before testing.

The serum from Case 1 was kept as the reference serum and assigned the arbitrary titre of 1 in 27. Threefold dilutions of both test and reference sera were made and 0.1 ml. was injected intracutaneously at 16 random sites on the back and flanks of three or more depilated guinea-pigs. Four to 24 hours later pontamine blue was given into the femoral vein and followed immediately by insulin in a dose of 160 units/kg., also intravenously. (When human sera of relatively low titre were titrated, the 24-hour period of sensitization was found more satisfactory than shorter intervals because of non-specific permeability effects.) The animals were examined 30 minutes after the injection of insulin for evidence of increased capillary permeability at the sites where serum was injected. The diameter of the blue-stained lesions was measured and the titre recorded after comparing the lesion size of various dilutions of the unknown with the reference serum.

Results of P.C.A. Tests

The P.C.A. test has been carried out on 30 non-diabetic controls and on 72 diabetics, of whom 20 were untreated, 13 were on diet only, 26 were treated with insulin over long periods, and 13 had severe insulin resistance; the results are summarized in Table II. The

TABLE II.—*Passive Cutaneous Anaphylaxis Tests for Antibody to Insulin*

Source of Serum	No. of Sera with Titre				Total
	<1/3	1/3	1/9	1/27	
Non-diabetics (controls) ..	30				30
Diabetics:					
Untreated	20				20
Diet only	13				13
Insulin (15 years) ..	24		2		26
,, resistant ..	2	1	4	6	13

two long-standing insulin-treated diabetics who gave positive P.C.A. tests were males receiving 100 and 74 units of insulin daily respectively.

Six of the 13 insulin-resistant cases were treated with prednisone and are described below. The results obtained in the remaining seven are shown in Table III, from which it will be seen that, although in five there had been a spontaneous fall in insulin requirement, all gave a positive P.C.A. test.

TABLE III.—*Details of Seven Untreated Cases of Insulin Resistance*

Case No.	Sex and Age	Insulin Onset to Insulin-resistance	Insulin Requirement (Units/Day)		Serum Titres	
			Maximum	When Serum Tested	P.C.A	R.D.
7	M 78	6 months	1,920	112	1:27	>1:1
8	M 74	1½ ,,	780	76	1:9	1:10
9	M 64	12 years	780	200	1:1	1:1
10	F 75	12 months	570	500	1:27	1:10
11	M 66	5 ,,	272	180	1:3	1:1
12	F* 37	Not known	212	212	1:3	>1:1
13	M 68	8 months	1,008	56	1:9	N.T.

* Pregnant N.T.—Not tested

In view of the encouraging reports of the use of corticotrophin and cortisone in the treatment of severely insulin-resistant diabetics referred to above, it was decided to treat with prednisone any such cases that attended the diabetic clinic at King's College Hospital, and we were fortunate in finding five such patients within the course of a comparatively few months; to this number Dr. J. D. N. Nabarro has kindly allowed us to add a sixth (Case 4), similarly treated by him at the Middlesex Hospital.

Clinical Details of Patients Before Treatment

Case 1.—A man of 64 gave a nine-months history of diabetes with subacute onset, and had lost 4 stone (25.4 kg.) in the six months before treatment. The diabetes had been initially controlled by a diet containing 200 g. of carbohydrate and 36 units of insulin zinc suspension. He began to develop insulin resistance after he had been on insulin for about three months, and when first seen by us was taking over 1,000 units daily; he had been on as much as 2,500 units. There was no family history of diabetes. On examination the only abnormal physical findings were slight enlargement of the liver, some brown pigmentation of the skin of both forearms, and well-marked signs of diabetic neuropathy. Special investigations, which included the electrophoretic pattern of plasma proteins, urinary steroid excretion, serum iron concentration, and Co_2 combining power, were all normal. The sedimentation rate, usually raised in cases of insulin resistance, was only 9 mm. After seven weeks in hospital the diabetes was finally controlled by two daily doses of soluble insulin together amounting to 816 units (Fig. 1).

Case 2.—A man of 54 developed diabetes with subacute onset in 1950 at the age of 46. There was no family history of diabetes. The disease was controlled by a diet containing 220 g. of carbohydrate and a mixed dose of 16 units of soluble insulin with 8 units of protamine-zinc insulin. After nine months the insulin requirement began to rise, and in 1954 was 284 units. He was first admitted to the diabetic department at King's College Hospital in 1956, the positive findings then being an enlarged liver, pigmentation over shoulders and back, testicular atrophy, and marked signs of diabetic neuropathy. Liver-function tests were at or just above the upper limit of normal, and steroid excretions, serum iron, and iron-combining power were all normal. E.S.R. was 52. Insulin requirement at that time was 448 units, and was unaffected by carbutamide. In 1957 he was readmitted for treatment with prednisone. The physical signs and investigations were much as before, but liver-function tests showed improvement. There was a slight increase in gamma-globulin by electrophoresis, and the E.S.R. was 71. Tomograms of the pituitary fossa were normal. The diabetes was stabilized on 720 units (Fig. 2).

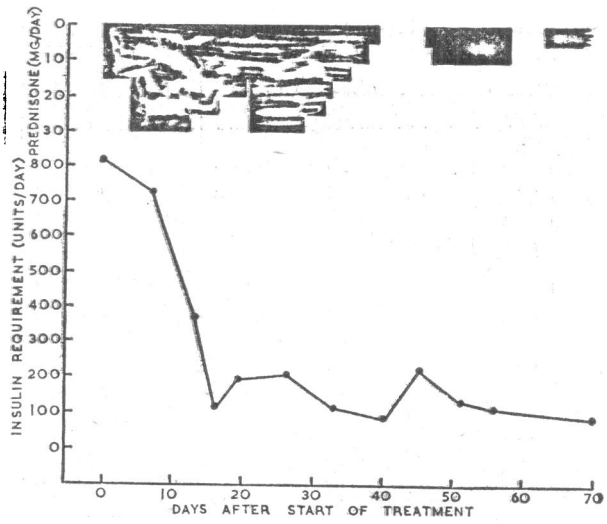

FIG. 1.—Case 1 Response to prednisone after four months of severe insulin resistance.

Case 3.—A man of 73 had had diabetes since 1938. After a brief initial period of insulin therapy, his diabetes was controlled by diet alone until March, 1958, when insulin had again to be given; good control was maintained until June. In July the insulin dosage began to mount, and when he was admitted to King's in pre-coma on July 31 it had risen to 200 units daily, his blood sugar then being 540 mg./100 ml. On examination he was anaemic, Hb 60%, and there was enlargement of the liver, spleen, and lymph nodes. Thymol turbidity was 7, but other liver-function tests were within normal limits. Total serum proteins were 5.9 g./100 ml., and electrophoresis showed a slight increase in the $alpha_2$-fraction. Other investigations were normal, but biopsy of a lymph node showed the histological picture of lymphosarcoma. The insulin was rapidly increased until stabilization was achieved on a daily dose of 1,264 units of soluble insulin (Fig. 3).

Case 4.—A man aged 73 was found to have diabetes in 1954, and responded well to diet and insulin. He was able to discontinue insulin in 1955, at which time he developed rheumatoid arthritis. In October, 1957, he was put on prednisone for a short while, but as this aggravated his diabetes and necessitated a return to insulin it was discontinued. By December, 1957, he was taking 1,400 units

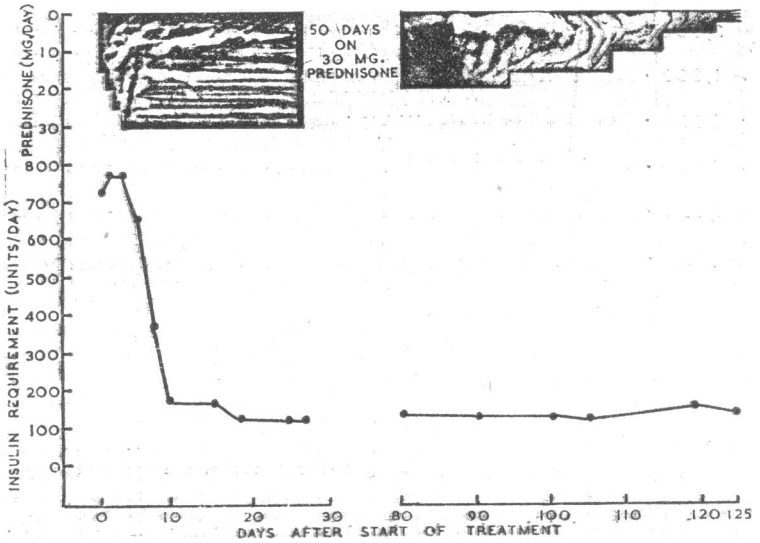

FIG. 2.—Case 2. Response to prednisone after 18 months of severe insulin resistance.

of insulin daily, in spite of which he had marked hyperglycaemia and ketonuria. He was admitted to the Middlesex Hospital under Dr. Nabarro, and after reaching a maximum insulin requirement of 2,240 units was stabilized on a diet containing 100 g. of carbohydrate and 1,440 units of insulin (Fig. 4).

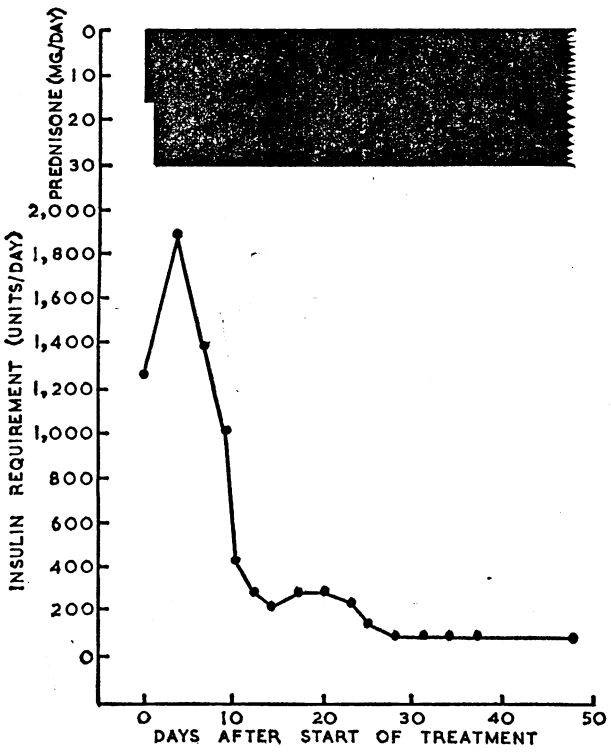

FIG. 3.—Case 3. Response to prednisone after six weeks of severe insulin resistance.

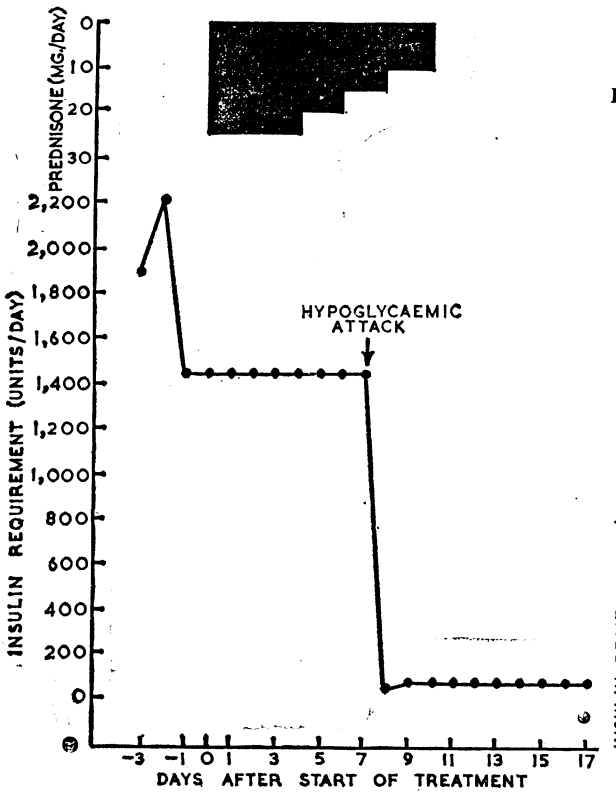

FIG. 4.—Case 4. Response to prednisone after two months of severe insulin resistance.

Case 5.—A girl of 13 developed signs of obstructive jaundice in May, 1957. She was admitted to the Mayday Hospital in June with jaundice, enlarged liver and spleen, and evidence of severe liver damage. Plasma bilirubin was 7.3 mg./100 ml., zinc sulphate floculation 39 units, and plasma proteins 9.4 g./100 ml., with great excess of gamma-globulin. In September she developed diabetes with ketosis and a blood sugar of 398 mg./100 ml. There was no family history of diabetes. Liver biopsy showed diffuse hepatic fibrosis, more pronounced within the portal tracts. On admission to the diabetic department at King's she was slightly jaundiced; her liver was three fingerbreadths below the costal margin and the spleen just palpable. Plasma proteins were 9.0 g./100 ml., with marked increase in gamma-globulin fraction. Liver-function tests were all abnormal, and her E.S.R. was 67 mm. Urinary steroids were low, but plasma cortisol was within normal limits, as also was the serum iron concentration. The diabetes was first satisfactorily controlled on 200 g. of carbohydrate and 236 units of soluble insulin (Fig. 5).

Case 6.—A West Indian man aged 32 was first seen three weeks after the acute onset of diabetes. There was a

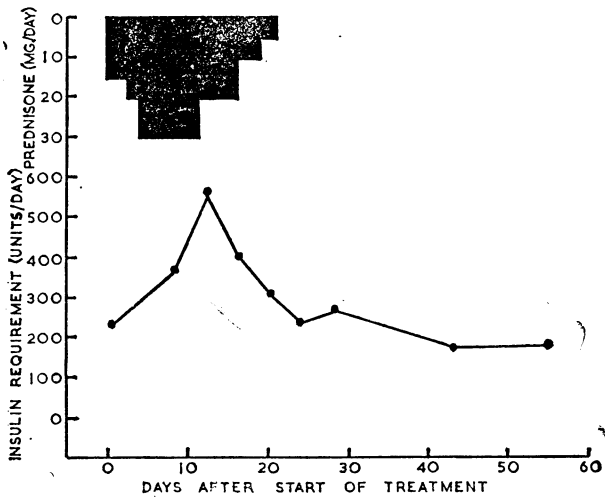

FIG. 5.—Case 5 Response to prednisone after five months of moderately severe insulin resistance.

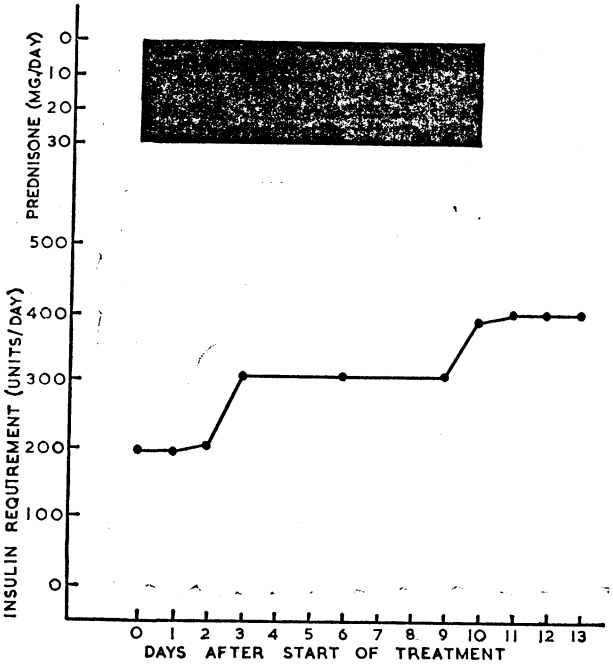

FIG. 6.—Case 6. Response to prednisone four weeks after diagnosis of diabetes.

doubtful history of mild diabetes in his father but no other family history of the disease In addition to the classical symptoms there was a history of generalized pruritus and boils for four to five months. Physical examination was negative, and the E.S.R. 9 mm Liver-function tests, total serum proteins, and electrophoresis were all normal, as also were 17-ketosteroid and ketogenic steroid levels. The diabetes was controlled on a diet containing 250 g of carbohydrate and 312 units of insulin (Fig 6); this was later reduced to 200 units

Results of Treatment with Prednisone

The results of treatment with prednisone in respect both of insulin requirement and of P.C.A. and rat-diaphragm tests are summarized in Table IV, individual responses to prednisone being shown in Figs. 1 to 6. In Cases 1 to 4, inclusive, the P.C.A. test was positive and there was a prompt and sustained fall in insulin requirement, beginning four to seven days after the onset of treatment with prednisone The first case was treated before it was possible to carry out any biological tests for insulin resistance, and the serological tests were made three months after the drug had been stopped. The mouse convulsion test was performed before and after treatment in Case 2 only; before prednisone the plasma from this case protected mice against the hypoglycaemic convulsive action of injected insulin, while after prednisone the action of the plasma in this respect was similar to that of plasma from an insulin-sensitive diabetic and afforded no such protection

Prednisone treatment in Cases 2, 3, and 4 was followed by a more marked reduction in the titre of both P.C.A. and R.D. tests than was observed in Case 1, but these sera were taken either while the patients were still on prednisone or very soon after its withdrawal.

In Case 5 the administration of prednisone was followed by a steep rise in insulin requirement (400 units), and the P.C.A test was negative both before and after treatment; the R.D. test was weakly positive at both times (Fig. 5). Case 6 was the only patient resistant to insulin from the start of treatment. In this case the P.C.A. test was negative on three occasions, but it was not possible to carry out R.D. tests. The insulin requirement rose steadily while prednisone was being given, and since its withdrawal has so far shown no sign of falling (Fig. 6).

Late Results.—Case 1 had no prednisone for eight months and his daily insulin requirement remained at about 100 units; this rose during the next three months to 176 units, and he was put back on 5 mg. of prednisone, on which he now requires 108 units. Case 2 felt unwell and developed anorexia when prednisone was withdrawn; 17 months later he was having 2 mg. of prednisone and 136 units insulin. Case 3 has been maintained on 15 mg. of cortisone because of lymphosarcoma, and his insulin requirement has remained unchanged at 80 units. Case 4, when last seen in March, 1958, needed 320 units of insulin, and was having 10 mg of prednisone to control his arthritis. Case 5 has been maintained on 10 mg. of cortisone, as this seems to be having some beneficial effect on her liver condition; her insulin requirement is now 156 units. In Case 6 the insulin requirement six weeks after the onset of treatment was 400 units

Discussion

The demonstration of the presence in the sera of insulin-resistant diabetics of substances capable of neutralizing the action of insulin has led to many attempts to discover their nature and aetiological significance. Evidence that some of these sera contained insulin antibodies was obtained by haemagglutination (Arquilla and Stavitsky, 1956) and less directly by the insulin-binding property of the globulin fraction (Berson *et al.*, 1956)

The results reported in this paper favour the view that insulin resistance may be produced by an excess of insulin antibodies inasmuch as prednisone has been shown to cause a rapid and dramatic fall in the insulin requirement of those cases in which it has been possible, by means of the P.C.A. test, to demonstrate the presence of antibodies; the failure of prednisone to exert this action in the two cases in which the P.C.A. test was negative is in keeping with this view, but requires confirmation. The multiplicity of action of prednisone makes it unwise to presume its site of action, but it is not possible at present in any other way to explain this action of prednisone, which normally increases insulin requirement.

From evidence already quoted it would appear that the production of insulin antibody is common in insulin-treated diabetics, but the haemagglutination studies of Moinat (1958) showed no relation between the titre and either the dose of insulin or the duration of its administration. We were unable by means of the P.C.A test to demonstrate antibody in the sera of insulin-sensitive diabetics except in two cases receiving respectively 100 and 74 units of insulin; both gave low titres, and in one the history suggested the possibility of previous episodes of resistance. It is reasonable, therefore, to conclude that either the P.C.A. test is less sensitive than the techniques of haemagglutination and insulin-binding or that it is detecting a different type of insulin antibody.

In our cases the time interval between the onset of insulin administration and that of insulin resistance is relatively short, being 12 months or less in 12 out of 13 cases and six months or less in seven cases. Owing to the inevitable difficulty in assessing the time of onset of resistance, these figures suggest the possibility of an even closer time relationship. It may also be significant that in two cases there was a history of insulin having

TABLE IV.—*Details of Five Cases of Insulin Resistance Treated with Prednisone*

Case No.	Sex and Age	Pre-prednisone				Post-prednisone		
		Insulin Onset to Insulin-resistance in Months	Insulin Requirement Units Day	P.C.A. Titre	R.D. Titre	Insulin Requirements	P.C.A. Titre	R.D. Titre
1	M 64	3	816	N.T.	N.T.	80	1:27	1:10
2	M 54	9	720	1:27	1:100	120	<1:3	1:1
3	M 73	4	1,264	1:27	1:10	84	<1:3	1:10
4	M 73	3*	1,440	1:27	1:100	80	<1:3	1:1
5	F 13	Nil	236	<1:3	1:1	240	<1:3	1:1
6	M 32	,,	200	<1:3	N.T.	400	<1:3	N.T.

* Insulin for short while 3 years previously. N.T.=Not tested.

been given for a short time and then restarted after a long interval of treatment by diet alone. In this connexion it is not very uncommon for manifestations of insulin allergy to be associated with a return to insulin therapy. None of our cases showed such manifestations, but the association between allergy and resistance has been noted on a number of occasions (Berne and Wallerstein, 1950). The reason why greater amounts of antibody are not formed in response to insulin treatment may possibly be related to the method of its administration; in no course of prophylactic immunization is antigen given once or more daily over long periods. The restarting of insulin might well be expected to act as a booster dose, and, on general principles, be more likely to lead to greater antibody production.

The results of the P.C.A. and R.D. tests obtained in our cases support the widely held view that there are a number of different causes of insulin resistance. It can be assumed that a serum giving a positive P.C.A. test contains insulin antibodies, whereas the R.D. test is capable of detecting several different types of antagonist. In Case 5 the P.C.A. test was negative and the R.D. test positive, but it is significant that P.C.A. antibodies have not been found when the serum contained no demonstrable antagonist. At present prednisone appears to benefit a group of insulin-resistant diabetics whose daily insulin requirement is nearer 1,000 than 200 units and in whom can be found no apparent cause for the resistance. The time interval between the start of insulin treatment and the development of resistance is usually less than a year, and often between three and six months; in our experience all such cases have had demonstrable insulin antibodies.

Summary

Thirteen cases of insulin-resistant diabetes are presented, six of which have been treated with prednisone. The anti-insulin factors have been studied, and the mouse convulsion test and glucose uptake of the rat diaphragm (R.D.) have been used to demonstrate the presence of insulin antagonists; insulin antibodies have been detected by a reversed passive cutaneous anaphylaxis (P.C.A.) technique. This P.C.A. test is described, with results obtained in normal controls and in insulin-sensitive and insulin-resistant diabetics.

Prednisone produced a dramatic fall in insulin requirement in the four cases in which the P.C.A. test was positive, but had the opposite and more usual effect in the two cases in which this test was negative. The suggestion is made that those diabetics in whom insulin resistance is associated with demonstrable insulin antibodies possess certain common clinical features.

We thank Dr. G. A. Stewart, of the Wellcome Biological Control Laboratories, for carrying out the mouse convulsion tests, Dr. Herbert Levy for allowing us access to Cases 10 and 12, and Dr. J. D. N. Nabarro for permission to publish the details of Case 4. This work was supported by a grant from the Joint Research Committee of King's College Hospital and Medical School.

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CHEMOTHERAPY OF NON-TUBERCULOUS PULMONARY INFECTIONS*

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The acute and chronic non-tuberculous infections of the lung constitute an excellent subject for debate concerning the principles and practice of chemotherapy. The respiratory tract is probably subject to attack by a greater number of species of bacteria and of viruses than any other. The effects of these organisms range from trifling illnesses to disorders which are rapidly fatal. Chemotherapy can claim some of its most brilliant successes in this field, but must also admit to disastrous defeat. If the subject of chemotherapy is really so delightfully logical as our bacteriological colleagues assure us, it should be easy to lay down the principles of treatment for the patient with a pulmonary infection. Unfortunately, clinicians know that there are no simple rules for success and that diagnostic acumen and vigilant observation are demanded by each and every case.

Background for Pulmonary Infections

It is a truism that chemotherapy has transformed the prognosis for the case of ordinary pneumonia and that the mortality from pneumonia has declined dramatically. Yet it is often forgotten that the decline in mortality antedated the introduction in 1938 of the sulphonamides active against the pneumococcus. Since then the mortality from pneumonia has declined further and all age groups have shared in the benefit. Much less change has occurred in the death rate from bronchitis, which, in any case, shows some fluctuation from year to year. The actual numbers of cases of pneumonia are, of course, greatly influenced by influenza epidemics, and it is probably unwise to attribute alterations in prevalence to the effects of therapy. But a great change has undoubtedly occurred in the past twenty years in the clinical presentation of pneumonia. Lobar pneumonia is no longer seen with any frequency in hospital practice. And the situation in general practice has become complex.

Thus the pneumonias of the aged and acute illnesses in those subject to chronic disease such as bronchiectasis

*Read to a Plenary Session at the Annual Meeting of the British Medical Association, Birmingham, 1958.