# MODIFICATION OF INSULIN RESISTANCE*

By

**EDWARD MARLEY, M.A., M.D.(Camb.), M.R.C.P.E., D.P.M.**

*Registrar*
*The Bethlem Royal and Maudsley Hospitals*
*Formerly at Severalls Hospital, Colchester*

SAKEL (1938a) drew attention to the difficulty of establishing satisfactory comas in a minority of patients attending for Deep Insulin therapy. This phenomenon has since been confirmed by other workers including Tillim (1938) whose patient received 500 units of insulin without the production of deep coma, by Hall (1940) who reported an instance in which 1,000 units of insulin was equally unsuccessful, by Reznikoff and Scott (1942) who described how neither 120 nor 1,000 units of insulin when injected intravenously produced any significant difference in hypoglycaemia in insulin resistant patients, and more recently by Fogarty (1953) whose case required 5,000 units of insulin for the production even of sopor. Other recorded examples of resistance to massive doses of insulin include those of Banting *et al.* (1938) and Tennent (1944).

Various explanations of this perverse response to insulin have been formulated, including that of Jones (1939) who proposed that resistance to insulin was both a problem of true insulin insensitivity and also of an anomalous response of the central nervous system to hypoglycaemia. Meduna *et al.* (1942) preferred to ascribe it to anti-insulin factors in the blood, but a more interesting interpretation derived from Freudenberg (1952) who suggested that if the effects of high insulin dosage employed in insulin coma treatment were regarded as a special instance of a stress response, then the fluctuations and differences in response could be equated in terms of the General Adaptation Syndrome of Selye. High doses were thus an index of an effective "alarm stage" characterized by a discharge from plentiful adrenocortical reserves.

A number of techniques have been subsequently evolved to surmount coma resistance and include that of Sakel (1938b) who found that coma could be produced on subsequent treatment days by the production of epileptic seizures with metrazol about the third hour of hypoglycaemia. He reaffirmed this (1950), further emphasizing his preference for metrazol rather than electrically induced convulsions. Stell (1945) expressed similar satisfaction with an identical regime. Other modified hypoglycaemic procedures are those of Kant, who introduced the divided dose schedule, and of von Braunmühl, who devised the "zig-zag" method. Kalinowsky and Hoch (1946) report very favourably on this latter procedure, remarking that they rarely find it necessary to employ more than 200 units of insulin to produce coma: unhappily this is not a universal experience. Other workers have given sedatives on the evenings prior to treatment, stilboestrol to male patients in the mornings before therapy, or enteric coated tablets of ammonium chloride throughout the day, all in the hope of reducing resistance to insulin. Goldberg and Jefferies (1946) suggested that nicotinyl taurine may provide a relatively non-toxic synergist to reinforce the insulin effect in insulin resistant cases, but their experiments were confined to rabbits.

In view, therefore, of either the inefficacy or time consuming nature of the

* Abstracted partly from a thesis accepted for the degree of M.D.(Cantab.), 1953.



https://doi.org/10.1192/bjp.102.428.576 Published online by Cambridge University Press

accepted methods for surmounting insulin resistance, it was decided to see if a more satisfactory solution of this problem could be attained by attempting to modify the activity of the prime insulin antagonists. These are the anterior pituitary and adrenal cortical hormones (Bouckaert and de Duve, 1947) which are also alleged to increase resistance to a variety of non-specific stressors (Selye, 1950a).

Of course, increase in sensitivity to insulin follows sympathectomy or adrenalectomy (Lewis, 1923; Sundberg, 1923; Hallion and Gayet, 1925; Cannon *et al.*, 1924; Britton *et al.*, 1928; Dworkin, 1931; Brooks, 1934; Zucker and Berg, 1937; McDonough, 1939; Crandall and Cherry, 1939) or as the result of the administration of blocking agents such as ergotamine (Burn, 1923; Schlossberg *et al.*, 1933) or hexamethonium bromide (Schachter, 1951; Laurence and Stacey, 1951).

However, Swann and Fitzgerald (1938) showed that the adrenal cortex was of considerably more importance in the reaction to insulin than was the adrenal medulla, and as Vogt (1947) demonstrated that the reaction of the adrenal cortex is independent of the integrity of the adrenal nerves, whereas that of the medulla is dependent, the administration of a drug such as hexamethonium bromide could not at first sight be expected to lead to any modification of adrenal cortical activity.

But Selye postulated a unified response to stress and emphasized its triphasic nature (1950b). The complex embracing these three stages he termed the General Adaptation Syndrome (1946) the first part of which is the alarm reaction in which adaptation has not yet been acquired. An agent producing such an alarm reaction was termed a stressor (Selye, 1950c) and might exert both specific and non-specific effects (Selye, 1951). Insulin acts both as a non-specific stressor, and also specifically by increasing the peripheral assimilation of sugar and the deposition of glucose in the liver (Soskin, 1941; Bouckaert and de Duve, 1947).

As it is recognized that the systemic stress effect of various alarming stimuli can be summated (Selye, 1938; 1950d) and that an increase in the alarming effect of two simultaneously applied agents has been confirmed for other combinations of stressors (Frank, 1940; Laugier and Leblond, 1943; Friesen and Wangensteen, 1946) it was decided to combine insulin with a stressor, the rationale being, that as both involve corticosteroid utilization, the alliance of the two might induce a relative deficiency of corticoids with reduced antagonism to insulin.

It has also been shown that syncope produced by administering hexamethonium to an erect patient is associated with the changes typical of an alarm or stress reaction (Marley, 1953). Consequently, insulin and syncope induced with hexamethonium was taken as one combination of stressors. Other recognized stressors include histamine (Sayers and Sayers, 1947) and electroplexy (Cleghorn *et al.*, 1948) so a few modifications of hypoglycaemia were attempted by combining these separately with insulin. In addition, "priscol" was occasionally administered with hexamethonium, on the supposition that the summation of their adrenergic and ganglion-blocking properties might modify the reaction to hypoglycaemia.

Now it was previously proposed that the combination of stressors might lead to an inflated corticosteroid utilization. In particular, as the 11-oxysteroids are not only insulin antagonists but are also implicated in resistance to stress procedures (Talbot *et al.*, 1947) and in protecting adrenalectomized animals against circulatory failure (Swingle *et al.*, 1942) it would seem reasonable to



https://doi.org/10.1192/bjp.102.428.576 Published online by Cambridge University Press

surmise that the introduction of an artificial and additional stress during hypoglycaemia vastly implements the body's requirements for such hormones. In fact, Wiggers (1950) suggested that various stresses might lead to an excessive demand for corticosteroids which was not met by an augmented liberation of these substances, and Selye (1946) went so far as to say that the shock phase of the alarm reaction was one of relative adrenal insufficiency. Sayers and Sayers (1947; 1948) also claimed that stress inevitably results in a greater utilization of adrenal cortical hormones. Certainly recent work by Bliss *et al.* (1954) has demonstrated that both insulin coma and electroplexy are accompanied by significant alterations in the level of the blood steroids.

Evidence is also available that shock or shock-inducing stimuli strongly disturb carbohydrate metabolism (Green and Bullough, 1950; Green and Ghadially, 1951) and that an increased demand for carbohydrate is the first effect of stress in general (Engel, 1949). Russel *et al.* (1944) suggested that during shock, the carbohydrate metabolism of the peripheral tissues is probably anaerobic yielding less energy, and obviously this spate of carbohydrate metabolism decreases the amount obtainable by the brain (Engel, 1945). A reduction of the hepatic glycogen also occurs during shock and has been observed in both man and animals (Lambret and Driessens, 1937; Jourdan *et al.*, 1943; Haist and Hamilton, 1944; Nastuk, 1947). Therefore, stress with its ensuing disappearance of hepatic glycogen, extreme protein catabolic impulse and augmented peripheral assimilation of glucose, must further hamper the endocrine adjustment of the insulin antagonists to hypoglycaemia, particularly as it is known that the anterior pituitary and adrenal cortical hormones act mainly by inhibiting the peripheral oxidation of glucose and by stimulating hepatic gluconeogenesis (Engel, 1945).

Himwich (1951a) describes three mechanisms functioning to prevent the complete cessation of brain metabolism during hypoglycaemia. These are: (1) the formation of glucose from cerebral glycogen; (2) the release of hepatic glucose to the blood stream, and (3) a change in utilization from glucose to fat by non-nervous tissues, thus saving the blood carbohydrate for the brain. A comparison of the three mechanisms revealed the second to be of the greatest value to the organism, for it not only acts over a longer period than the first, but is quantitatively the more important. He qualifies this statement by commenting that the efficiency of the second mechanism depends chiefly upon the amount of glycogen in the liver. If the above reasoning be true, then the introduction of additional stress must so expedite the second mechanism, that by the time the large quantities of insulin have been absorbed from the injection site, it will be less effective and the functions of the relatively unimportant first and third mechanisms thereby facilitated in an effort to maintain adequate cerebral metabolism.

## Methods

Hexamethonium bromide was administered either parenterally or intravenously to recumbent insulin resistant patients being treated with Deep Insulin, or given intramuscularly to similar patients stood erect in an attempt to produce syncope, sensitivity to the drug having been determined beforehand. It would be injected with the insulin at 7.30 a.m., the average dose of hexamethonium being 100 mg. administered either subcutaneously or intramuscularly, the maximum dose employed being 200 mg. Intravenous injections of hexamethonium were only utilized in the earlier attempts at modifying hypoglycaemia, with a maximum dose of 50 mg. injected approximately 90 minutes after the insulin had been acting.

https://doi.org/10.1192/bjp.102.428.576 Published online by Cambridge University Press

The technique of inducing syncope involved making the patient stand erect and quite still immediately after the injection of the hexamethonium and supported by two attendants. In this series, syncope was usually induced within 15 minutes of the injection of the hexamethonium; should it not occur, then the patient would be returned to bed, and in certain instances a subsequent attempt at syncope was made, usually within the following 30 minutes. After collapse, it was the routine policy for the patient to remain propped up in bed, so that the maximum effect of gravity was exerted upon the circulation. Frequent assessments of the blood pressure and the pulse rate were recorded, and an emergency tray containing methedrine and coramine was available if required. By these tactics, therefore, a temporary phase of circulatory embarrassment could be produced at will, but it seemed more discrete to induce this state early in hypoglycaemia, rather than have it coincide with the altered cardiovascular dynamics that attend the later stages of hypoglycaemia. In order to record these changes more accurately, Grant and Reeve's classification of Circulatory Patterns was adopted (Grant and Reeve, 1951). The only patterns observed in this series were the Vaso-vagal and that of Warm Hypotension, so these only will be elucidated: the Vaso-vagal pattern includes a low blood pressure, slow pulse rate, cold extremities and a pale face, the patient frequently experiencing nausea; that of Warm Hypotension presents with a blood pressure and fast pulse rate, but is accompanied by warm extremities and a face that might be flushed, well-coloured or pale. Such patterns were only deemed to be present if they persisted for at least 15 minutes after the production of syncope. On the other hand, the brief Vaso-vagal patterns that presented in the majority of cases immediately after syncope were not recorded.

Histamine was another drug employed in an attempt to modify insulin resistance, and this was administered intravenously to recumbent patients having Deep Insulin at 7.30 a.m. the individual's sensitivity to the drug having been previously ascertained and a history of former allergic phenomena excluded. Doses of up to 2 mg. were used. In some of the earlier modifications of hypoglycaemia, "Priscol", orally or intravenously, was combined with hexamethonium and insulin. On one occasion, modification of hypoglycaemia was attempted with electroplexy.

Control hypoglycaemic reactions were recorded on the majority of occasions, either before or soon after the initial modified hypoglycaemic technique for comparison with it. In order to confirm an impression that a certain drug was capable of significantly modifying hypoglycaemia, patients were rested for some days from Deep Insulin therapy previous to both the control investigation and the modified hypoglycaemic procedure. Later in the series when hexamethonium had proved its value, these rest days were omitted. Blood-sugar levels were checked during some of the modified hypoglycaemic reactions, but as it is widely recognized that there is little correlation between the symptoms of hypoglycaemia and the amount of glucose in the blood (Himwich, 1951b) no great importance was attached to the results that were obtained. The blood sugars were determined by the method of Herbert and Bourne (1930) which is an estimation of the true blood sugar. Attention was also directed to the fluctuations and clinical transitions of hypoglycaemic levels, to pulse rate recordings, blood-pressure readings and occasionally to alterations in the eosinophil counts. Blood for the latter was withdrawn at 9 a.m. and 1 p.m. as it has been demonstrated that hypoglycaemia is accompanied by an eosinopenia (Perlmutter *et al.*, 1951) which is most prominent four hours after stress. The first count was performed at 9 a.m. as it is known

https://doi.org/10.1192/bjp.102.428.576 Published online by Cambridge University Press

that following the eosinopenia during the early hours of the morning, the count tends to become stabilized about 9 a.m. (Rud, 1947). Capillary blood was used in eosinophil counting, and both the technique and the phloxine-urea diluent proposed by Manners (1951) were adopted.

The classification of hypoglycaemic levels as suggested by Frostig (1940) was used in a slightly modified form, in order that the transitions from one hypoglycaemic level to another could be described with more precision than would have been possible if the standard descriptive terms of sopor and coma had been employed. Thus Stage 1 Hypoglycaemia represents the earliest detectable clinical phenomena following the latent interval after the injection of insulin and is accompanied by perspiration, salivation and some degree of somnolence. Stage 2 Hypoglycaemia presents with speech and perceptual disturbances, clouded consciousness, fine tremor and motor excitement. Stage 3 Hypoglycaemia is equivalent to sopor, that is the loss of consciousness with the appearance of motor restlessness, clonic twitchings, choreiform and hemibalistic movements; Stage 4 Hypoglycaemia represents the release of the midbrain from higher control and is characterized by the depression of pyramidal functions with increased tone, tonic spasms and tetanic postures. Stage 5 Hypoglycaemia is equivalent to coma, with the presence of postural reflexes, pin-point pupils that exhibit no reaction to light and corneal reflexes that are either very much reduced or absent.

The definition of insulin resistance was arbitrary, and it was assumed to be present when a patient exhibited no more than a Stage 3 Hypoglycaemia following the injection of approximately 500 units of insulin. Ten such cases of insulin resistance were encountered, but for the purpose of brevity only five are reported in detail, a synopsis of findings for the rest of the patients being included in Table I.

The case numbers adopted are those allocated originally to the 35 patients treated with Deep Insulin, the results of which are examined more fully in the thesis from which this paper is abstracted. The patients were all males suffering from schizophrenia. Those found to have hypertension, cardiac dysrhythmias or other heart disease were excluded, even had they been fit enough for Insulin therapy.

## Results

*Case 21.* Catatonic Schizophrenia. Age 23.

This patient had evinced no progression beyond a Stage 2 Hypoglycaemia with as much as 440 units of insulin, but the identical dose of insulin combined with 150 mg. of hexamethonium bromide and the induction of syncope early in hypoglycaemia (23.8.52), resulted in a satisfactory coma. He was subsequently rested from Deep Insulin until 1.9.52, when a control investigation was performed; this entailed the injection of a larger dose of insulin (480 units), but led only to the appearance of a Stage 2 Hypoglycaemia. Again he was rested from Deep Insulin until 4.9.52, when 200 mg. of hexamethonium was injected subcutaneously, the patient being recumbent. The insulin dose was 440 units, and besides the production of a Stage 5 Hypoglycaemia, a marked Vaso-vagal circulatory pattern emerged. In both the above modifications of hypoglycaemia, the pupils were widely dilated during coma. The modification of hypoglycaemia with 1 mg. of intravenous histamine (8.9.52), was not followed by coma.

*Case 24.* Simple Schizophrenia. Age 27.

This patient was proving resistant to insulin, for by 18.9.52 the injection of 480 units of insulin was succeeded only by a Stage 2 Hypoglycaemia. He was therefore rested from Deep Insulin therapy until 23.9.52, when the combination of 400 units of insulin with a divided dose of 125 mg. of hexamethonium and the introduction of syncope early in hypoglycaemia resulted in a Stage 4 Hypoglycaemia, a circulatory pattern of Warm Hypotension occurring subsequent to the syncope. Although satisfactory comas were recorded on the treatment days immediately following this procedure, by 29.9.52 the insulin dose had once more increased to 520 units to induce merely a Stage 2–3 Hypoglycaemia. So on 2.10.52, 400 units of insulin were combined with 1 mg. of histamine injected intravenously, followed by a later dose of 0·5 mg. of intravenous histamine, and an adequate coma ensued. Following this, comas occurred regularly

https://doi.org/10.1192/bjp.102.428.576 Published online by Cambridge University Press

until 13.10.52, after which the administration of as much as 560 units of insulin led consistently to no advance beyond a Stage 4 Hypoglycaemia. The combination of 480 units of insulin with a total dose of 1·5 mg. of intravenous histamine on 20.10.52 was this time ineffective, but the same dose of insulin combined with 100 mg. of hexamethonium and an attempt at producing syncope (21.10.52), produced a satisfactory coma, the pupils again being widely dilated. The recovery following termination was without incident until the patient stood up to dress himself, whereupon he suddenly collapsed, and on examination a few minutes later was discovered to have returned to a Stage 3 Hypoglycaemia requiring interruption with an intravenous injection of glucose solution. Regular comas occurred after this modified reaction, although the dosage of insulin requisite for producing adequate comas still remained at 440 units.

*Case 30.* Schizo-affective Illness. Age 26.

It was obvious that this patient would require a high coma dose, as on 3.1.53 the insulin dose was 520 units which did not produce any progression beyond a Stage 2–3 Hypoglycaemia. He was therefore rested from Deep Insulin therapy until 8.1.53, when the identical dose of insulin was combined with 100 mg. of hexamethonium bromide and syncope induced early in hypoglycaemia. A satisfactory coma ensued, accompanied by the emergence of a Vaso-vagal circulatory pattern after the injection of the hexamethonium. However, no comas were recorded in the succeeding treatment days, and as it had been necessary by 14.1.53 to increase the insulin to 680 units with still no development beyond a Stage 3 Hypoglycaemia, the insulin dose was swung from 80 units (16.1.53), up to 720 units (23.1.53), satisfactory comas occurring on 20.1.53 (600 units of insulin), and 22.1.53 (680 units of insulin). As no further comas developed by 27.1.53 with as much as 640 units, the patient was therefore rested from treatment until 29.1.53, when the dose was reduced to 520 units combined with 100 mg. of hexamethonium bromide and a syncope induced early in hypoglycaemia, but no progression beyond a Stage 4–5 Hypoglycaemia resulted, although once again the pupils were observed to be widely dilated. Even though this stratagem was not completely successful, regular comas were recorded with 680 units of insulin after 31.1.53.

*Case 33.* Hebephrenic Schizophrenia. Age 31.

This patient was manifesting extreme insensitivity to insulin, for during a control investigation on 23.6.52, the injection of 560 units of insulin resulted solely in a Stage 1 Hypoglycaemia. However, the combination of 560 units of insulin with 100 mg. of hexamethonium on 19.6.52, the patient having been rested from Insulin therapy since 14.6.52, led to a Stage 5 Hypoglycaemia. This was interrupted with a routine tube-feed of glucose solution, but as the patient showed no evidence of recovery some 30 minutes later a further 100 c.cs. of 33 per cent. glucose solution was injected intravenously after which he slowly recovered consciousness. On the day following the control test (24.6.52), although the insulin dose was reduced to 480 units, this combined with hexamethonium bromide, resulted in an adequate coma. However, on 25.6.52, 560 units of insulin by itself failed to achieve more than a Stage 2 Hypoglycaemia. The combination of insulin with a total dose of 1·5 mg. of histamine injected subcutaneously on 26.6.52 was also unsuccessful, and an increase of the insulin dosage up to 640 units (28.6.52), ended in no progression beyond a Stage 2 Hypoglycaemia. It was then decided to reinstitute Modified Deep Insulin therapy on 30.6.52 with 440 units of insulin and 150 mg. of hexamethonium bromide, the hexamethonium given subcutaneously, followed by a later and additional increment of hexamethonium bromide injected intravenously, but no coma ensued. The insulin dose was therefore swung from 80 units (2.7.52), up to 600 units (5.7.52) and on this last occasion a coma occurred. However, in an effort to reduce the total dose of insulin, 150 mg. of hexamethonium was combined with 480 units of insulin on 8.7.52 and an attempt was made to produce syncope. This was not realized, but the subsequent tally of events was remarkable for the swift onset of a Stage 5 Hypoglycaemia and it was of additional interest that regular comas followed this modified procedure with 400 units of insulin.

*Case 34.* Paranoid Schizophrenia. Age 21.

This patient was resistant to insulin, for by 19.1.53 there had been no development beyond a Stage 2 Hypoglycaemia with as much as 560 units of insulin. The dose was therefore reduced on 20.1.53 to 480 units of insulin combined with 100 mg. of intramuscular hexamethonium and followed by syncope. A Stage 5 Hypoglycaemia ensued, but although the insulin dose was increased on subsequent treatment days, the next coma to be recorded was on 24.1.53 and followed the injection of 680 units of insulin. For this reason, an electrically induced convulsion was given immediately after the injection of 480 units of insulin on 27.1.53, but on this occasion there was not even the development of a Stage 1 Hypoglycaemia. Therefore, on 29.1.53, 480 units of insulin were combined with 100 mg. of hexamethonium and a syncope induced early in hypoglycaemia, but this too was unsuccessful as only a Stage 4–5 Hypoglycaemia resulted. The insulin dose was then further increased, so that on 3.2.53 the dose was 640 units, but this ended only in the appearance of a Stage 4 Hypoglycaemia. It was therefore decided to reinstitute Modified Deep Insulin therapy, and on 4.2.53 the insulin dose was reduced to 560 units and combined with 150 mg. of hexamethonium bromide, a syncope being induced early in hypoglycaemia. Once more there was no progression beyond a Stage 4 Hypoglycaemia, but comas were recorded regularly after this with 640 units of insulin.

https://doi.org/10.1192/bjp.102.428.576 Published online by Cambridge University Press

As mentioned previously, a simplified synopsis of the results for the modification of insulin resistance encountered in the other five patients is presented in Table I.

TABLE I

*A Synopsis of the Data Relating to the Modification of Insulin Resistance in an Additional Five Patients*

| Case No. | Control Hypoglycaemia | Modified Hypoglycaemia |
|---|---|---|
| 7 | The injection of 480 units of I.M. insulin was followed by merely a Stage 1 Hypoglycaemia (2.1.52). | A Stage 5 Hypoglycaemia followed the combination of 360 units of I.M. insulin with 100 mg. of sbct. hexamethonium bromide, the patient being recumbent (14.1.52). |
| 29 | A Stage 3 Hypoglycaemia followed the injection of 520 units of I.M. insulin (5.1.53). | A Stage 5 Hypoglycaemia ensued after the injection of 480 units of I.M. insulin and 100 mg. I.M. hexamethonium, syncope having been induced early in hypoglycaemia (8.1.53). |
| 31 | The injection of 400 units of I.M. insulin was succeeded after four hours by only a Stage 3 Hypoglycaemia (2.2.52). | The combination of the identical dose of insulin with 50 mg. I.V. hexamethonium and 25 mg. I.V. priscol (4.2.52); 100 mg. I.M. hexamethonium and 25 mg. of I.V. priscol (5.2.52); 75 mg. I.M. hexamethonium and 500 mg. oral priscol (6.2.52) led merely to Stage 3 Hypoglycaemias. |
| 32 | The injection of 480 units of I.M. insulin produced only a Stage 2 Hypoglycaemia (22.5.52). | 480 units of I.M. insulin combined with 100 mg. of I.M. hexamethonium resulted in a Stage 5 Hypoglycaemia, the patient being recumbent (19.5.52). |
| 35 | The injection of 640 units of I.M. insulin led to merely a Stage 3 Hypoglycaemia (3.2.53). | The combination of 520 units of I.M. insulin and 150 mg. of hexamethonium with the induction of syncope, led to the appearance of a Stage 5 Hypoglycaemia (4.2.53). |

The eosinopenias accompanying a few of both the conventional and the Modified Hypoglycaemias were recorded and compared, the results being presented in Table II.

TABLE II

*Comparison of Eosinopenias with Conventional and Modified Hypoglycaemias*

| Case No. | Conventional Hypoglycaemia | | | Modified Hypoglycaemia | | | |
|---|---|---|---|---|---|---|---|
| | Eosinophils per c.mm. | | Eosinopenia (per cent.) | Eosinophils per c.mm. | | Eosinopenia (per cent.) | Modifying Drug |
| | 9 a.m. | 1 p.m. | | 9 a.m. | 1 p.m. | | |
| 21 | 160 | 10 | 94 | 95 | 35 | 63 | Hexamethonium bromide |
| | | | | 111 | 22 | 80 | ,, |
| | | | | 117 | 4 | 96 | Histamine |
| 32 | 137 | 17 | 87 | 136 | 6 | 95 | Hexamethonium bromide |
| 33 | 498 | 160 | 68 | 320 | 50 | 84 | ,, |
| 34 | 79 | 3 | 96 | 84 | 12 | 85 | ,, |
| 35 | 101 | 10 | 90 | 108 | 3 | 97 | ,, |

https://doi.org/10.1192/bjp.102.428.576 Published online by Cambridge University Press

From this, it can be seen that the fall of eosinophils in the modified techniques was sometimes in excess, and sometimes less, than the fall of eosinophils accompanying the control insulin hypoglycaemias.

## Discussion

In view of the work earlier this century demonstrating an increase of sensitivity to insulin following sympathectomy, it is not surprising that hexamethonium when administered with insulin to recumbent patients led to deeper levels of hypoglycaemia than did insulin alone. But insulin is a stressor, and as the systemic stress effect of various alarming stimuli can be summated, the combination of syncope and insulin is just such a summation of stressors. However, as sympathectomized animals are known to be hypersensitive to stress, the induction of syncope utilizing hexamethonium bromide which blocks autonomic activity might have been calamitous. Instead, the combination of insulin and syncope proved to be a practical contribution to the insulin repertoire.

Other combinations of stressors were not so successful for this purpose and in fact the electrical production of a convulsion early in hypoglycaemia was followed only by a Stage 1 Hypoglycaemia. Moreover, the application of subconvulsive electrocerebral stimulation later in hypoglycaemia is known to rouse patients (Montagu, 1953). Histamine which is also a stressor did not potentiate the effect of insulin except when its administration was succeeded by the eventual appearance of a Vaso-vagal state. Another interesting feature was that syncope induced with hexamethonium later in hypoglycaemia had the same effect as electroplexy in that it seemed to retard progression to deeper hypoglycaemic levels. It would appear on the whole then, that stress accompanying syncope must be endowed with a separate and particular quality; certainly, the systemic stress associated with electroplexy appears to be more generalized, whereas that associated with syncope primarily involves the cardiovascular system.

The stability of cardiovascular dynamics is influenced most favourably by the 11-oxysteroids, and presumably syncope as a stress involves the increased utilization of glucocorticoids. As it is a stress involving the cardiovascular system, there is probably a particular augmented utilization of 11-oxysteroids. These and the anterior pituitary hormones are the prime insulin antagonists, and presumably the increased utilization of these in consequence of the introduction of stress procedures must decrease their capacity for resisting insulin. In addition, as the first effect of stress is an increased requirement for carbohydrate, this inflated peripheral expenditure of carbohydrate must decrease the amount available for the brain. As the action of the adrenocortical hormones and the antagonistic effect of carbohydrate occurs in the peripheral tissues (Bondy, 1949) this sudden spate of carbohydrate metabolism must further divert available corticoids and so accelerate the release of hepatic glucose that this stored reserve of carbohydrate is not later at the disposal of the body for the implementation of cerebral metabolism.

At first sight the metabolic derangement produced during stress states and that affected by insulin would appear antipodal, for during shock or stress there is increased glycogenolysis but decreased glucogenesis, whereas large doses of insulin act predominantly by augmenting glycogen deposition in the liver. But Haist and Hamilton (1944) observed that in shock conditions, insulin acts paradoxically and instead of lowering the blood sugar by promoting hepatic glycogen storage, it leads to a reduction of blood sugar presumably due to peripheral activity. However, as to whether the stressor effect of syncope

https://doi.org/10.1192/bjp.102.428.576 Published online by Cambridge University Press

potentiates the effect of insulin by increasing the rate of peripheral glucose expenditure, by augmenting the utilization of corticosteroids or by dint of deranged hepatic function consequent to the altered blood flow to that organ (McMichael, 1938) would entail considerable intricate investigation outside the scope of this paper.

The technique of inducing syncope involved making the patient stand erect and quite still immediately after the injection of the hexamethonium. Paton (1951) noted that for a substantial time after the injection of hexamethonium, profound falls of blood pressure might be obtained in some subjects if they stood immobile for a few minutes. He considered that this hypotension was due to the relaxation of venomotor tone.

Syncope induced early in hypoglycaemia was almost invariably followed on the same day by a Stage 5 Hypoglycaemia, particularly if insulin alone had previously failed to produce comas. In those instances when hexamethonium had been formerly successful in overcoming resistance to insulin only for resistance to recur later, the subsequent modification of hypoglycaemia with hexamethonium would probably be followed at most by the development of a Stage 4 Hypoglycaemia although adequate comas were usually recorded on succeeding treatment days with just insulin.

One of the complications of Deep Insulin therapy is cardiovascular collapse, but the introduction of cardiovascular stress early in hypoglycaemia was not attended by any untoward incidents although transient Vaso-vagal patterns often succeeded the induction of syncope, more lasting deviations from the normal circulatory pattern being less common. If the state of the peripheral circulation following syncope gave cause for anxiety, the bed was blocked and this was in every instance followed by improvement of the circulation. Methedrine was always immediately available, as it is known that it accelerates recovery following vaso-vagal collapse (McMichael, 1945). No irregularities of cardiac rhythm were observed in association with the Vaso-vagal patterns, although Fulton (1949) has commented that vagal stimulation may produce all grades of atrioventricular delay and dissociation.

The hypoglycaemias modified with hexamethonium differed from conventional insulin hypoglycaemias in that the customary prominent salivation and perspiration were less evident. It is therefore topical that Paton (1951) reported that in animals the parasympathetic ganglion to the salivary glands was the most sensitive of all ganglia to the action of hexamethonium. He also commented that perspiration was depressed by this drug. A rapid transition from Stage 3 to Stage 5 Hypoglycaemia was also observed more frequently in modified hypoglycaemias, and patients who had been hitherto resistant to insulin, might in such an instance be in coma two hours after the injection of insulin and the hexamethonium. It was noted also that deep coma was accompanied by widely dilated pupils in place of the pin-point pupils that are normally to be predicted at this stage. Termination of hypoglycaemia must be by the intravenous route as the stomach does not appear to absorb fluid following hexamethonium—a fact that has some bearing on the reports that this drug interferes with the motility and secretion of the stomach (Kay and Smith, 1950; Douthwaite and Thorne, 1951). In addition, confusional states occasionally occurred after termination when these two drugs had been combined, although there were no epileptic attacks during modified hypoglycaemias. It was necessary to keep the patient in bed until late afternoon after the injection of maximum doses of hexamethonium bromide, as on one instance following a modified technique, the patient suddenly collapsed on attempting to stand and dress

https://doi.org/10.1192/bjp.102.428.576 Published online by Cambridge University Press

himself and slid back into a Stage 3 Hypoglycaemia. Another patient developed a spontaneous syncope in the afternoon as a sequel to modified treatment.

Speirs and Meyer (1949) demonstrated that by increasing the amount of stress a greater fall of eosinophils ensued, but the eosinopenia following syncope and large amounts of insulin was sometimes in excess and sometimes less than that recorded with conventional insulin procedures, a similar variability of the eosinopenia being also found for the combination of hexamethonium with small doses of insulin.

It was feasible with this method of syncope and insulin to reduce the coma dose of insulin by between 10 and 30 per cent., but although at the time this technique seemed to enjoy considerable advantages over other established methods of modifying insulin resistance, it would now appear that the recent innovation of Straccia and Schefflin (1952) of implementing the action of insulin with hyaluronidase is, as yet, the most logical and practical approach to this problem. This is not to decry the merits of hexamethonium, for insulin resistance can be quite difficult to surmount and as Stell (1945) has emphasized, it is not advisable to wait for the patient to develop an increased and spontaneous sensitivity to insulin. Moreover, unless the patient is sensitive enough to insulin, he may fail to develop adequate comas, thereby being deprived of the maximum benefit of deep hypoglycaemias. As the phenomenon of insulin resistance has been correlated with a poor prognosis (Halpern, 1940; Freudenberg, 1952) it becomes even more imperative to ensure the development of satisfactory comas.

One of the limiting factors to the use of hexamethonium bromide is, that whilst hyaluronidase is safe and easy to administer, the combination of hexamethonium with insulin necessitates the presence of a doctor continuously in the ward from the moment the two are given, not only to deal with any untoward effects following syncope, but also to interrupt the occasional rapidly developing deep comas that occur subsequent to their use. No further side-effects of hexamethonium were observed (as have been tabulated by Harington and Rosenheim, 1954) other than those mentioned above.

Finally, although hexamethonium bromide was a useful adjuvant for modifying insulin resistance, there are other aspects to its combination with insulin. Thus the work of Funkenstein *et al.* (1952) was directed towards an assessment of autonomic readjustment resulting from shock treatments. Alexander (1953) also stressed this function of hypoglycaemia, remarking on the balanced stimulation of both the cholinergic and adrenergic divisions of the autonomic apparatus. But hexamethonium acts upon the autonomic system and if one were to accept the above hypotheses then by virtue of the administration of a blocking agent one could presumably diminish some of the benefit derived from insulin. Soskin (1941) related the therapeutic effect of excessive doses of insulin to the hypoglycaemia that accrued rather than to any stimulation of the central nervous system and as hypoglycaemia is usually more profound after hexamethonium, this might atone for any reduction of autonomic activity. Kay and Thorley (1951) suggest that it is the adynamogenesis produced by insulin which underlies its therapeutic effect. They further state that it is the aglycaemia following insulin administration which is responsible for the adynamogenesis. As indicated elsewhere, the combination of insulin with a syncope should lead to a very rapid depletion of carbohydrate, this being in other terminology tantamount to both an exaggerated aglycaemia and a more intense adynamogenesis with therefore an augmented therapeutic effect.

Sherwood (1952) injected pentamethonium iodide (a lower member than

https://doi.org/10.1192/bjp.102.428.576 Published online by Cambridge University Press

hexamethonium of the series of polymethylene bistrimethylammonium salts) into the cerebral ventricles of patients in catatonic stupor. His rationale for doing this, was that schizophrenia might be a disease of the autonomic and vegetative centres and hence pentamethonium with its capacity for alteration of autonomic activity could be of therapeutic value. However, as it has been demonstrated that surgical techniques are associated with a systemic reaction, including a significant eosinopenia (Roche *et al.*, 1950) it would be unwise to exclude the factor of non-specific stress as contributory to the clinical improvement that occurred in these patients.

Wagner and Woods (1950) reproduced the motor component of catatonia with bulbocapnine, and discovered they could induce temporary remissions from this cataleptic state with environmental stress. Those patients in this series who were suffering from catatonic schizophrenia and who were treated with the combined stressors syncope and insulin, did manifest a greater degree of rapport immediately after the termination of hypoglycaemia than with insulin alone, but the improvement was invariably of brief duration. Thus, although increase of stress is followed by partial and even total eclipse of insulin resistance, it has no significant effect on the schizophrenic process.


## Summary

Drugs such as hexamethonium bromide, histamine and "Priscol" were used in an attempt to modify resistance to massive doses of insulin.

Hexamethonium bromide when administered to recumbent insulin resistant patients receiving Deep Insulin therapy, led to more profound levels of clinical hypoglycaemia than followed the injection of identical doses of insulin alone. However, the technique of inducing syncope with hexamethonium early in hypoglycaemia was even more successful in surmounting insulin resistance, being almost invariably followed on the same day by coma.

The hypoglycaemias modified with hexamethonium differed from conventional hypoglycaemias in that the customary prominent salivation and perspiration were much reduced. Comas tend to develop more rapidly after the combination of insulin with hexamethonium and it was noted that the deepest phase of hypoglycaemia was accompanied by widely dilated pupils in place of the pin-point pupils normally to be predicted. Termination of the modified hypoglycaemias must always be by the intravenous route as the stomach does not appear to absorb substances following large doses of hexamethonium. Although confusional states occasionally occurred after termination of coma when the two drugs had been combined, these were brief. It was feasible with this method of combined "insulin and syncope" to reduce the coma dose of insulin by between 10 and 30 per cent.

The fall of eosinophils after insulin and syncope was sometimes in excess and sometimes less than the eosinopenias recorded with control hypoglycaemias.

Histamine was of much less value in modifying insulin resistance, being only successful when its administration was succeeded by the eventual appearance of a Vaso-vagal circulatory pattern.

"Priscol" was of no value for modifying resistance to massive doses of insulin.



## Acknowledgments

I should like to take this opportunity of thanking Dr. A. G. Duncan, the Medical Superintendent, Severalls Hospital, Colchester, for his kind permission to publish these findings.

In addition, I should also like to thank Nurses H. Gayler and G. Gordon for their unstinted co-operation in this work.


## References


Alexander, L., *Treatment of Mental Disorders*, 1953. 1st ed., p. 244. Philadelphia.

Banting, F. G., Franks, W. R., and Gairns, S., *Amer. J. Psychiat.*, 1938, **95**, 562.

Bliss, E. L., Migeon, C. J., Nelson, D. H., Samuels, L. T., and Hardin Branch, C. H., *Arch. Neurol. Psychiat., Chicago*, 1954, **72**, 352.

Bondy, P. K., *Endocrinology*, 1949, **45**, 605.

Bouckaert, J. P., and de Duve, C., *Physiol. Rev.*, 1947, **27**, 39.

Britton, S. W., Geiling, E. M. K., and Calvery, H. O., *Amer. J. Physiol.*, 1928, **84**, 141.

Brooks, C. M., *ibid.*, 1934, **107**, 577.

Burn, J. H., *J. Physiol.*, 1923, **57**, 318.


https://doi.org/10.1192/bjp.102.428.576 Published online by Cambridge University Press

CANNON, W. B., MCIVER, M. A., and BLISS, S. W., *Amer. J. Physiol.*, 1924, **69,** 46.
CLEGHORN, R. A., GOODMAN, A. J., GRAHAM, B. F., JONES, M. H., and RUBLEE, N. K., *J. clin. Endocrinol.*, 1948, **8,** 608.
CRANDALL, L. A., and CHERRY, I. S., *Amer. J. Physiol.*, 1939, **125,** 658.
DOUTHWAITE, A. H., and THORNE, M. G., *Brit. med. J.*, 1951, *i*, 111.
DWORKIN, S., *Amer. J. Physiol.*, 1931, **98,** 467.
ENGEL, F. L., *J. Mt. Sinai Hosp.*, 1945, **12,** 152.
*Idem*, *Endocrinology*, 1949, **45,** 170.
FOGARTY, J. P., *J. Irish med. Ass.*, 1953, **33,** 77.
FRANK, J. D., *Endocrinology*, 1940, **27,** 447.
FREUDENBERG, R. K., *J. Ment. Sci.*, 1952, **98,** 441.
FRIESEN, S. R., and WANGENSTEEN, J. R., *Proc. Soc. exp. Biol. N.Y.*, 1946, **63,** 245.
FROSTIG, J. P., *Amer. J. Psychiat.*, 1940, **96,** 1167.
FULTON, J. F., *Textbook of Physiology*, 1949. 16th ed., p. 665. Philadelphia.
FUNKENSTEIN, D. H., GREENBLATT, M., and SOLOMON, H. C., *Psychosom. Med.*, 1952, **14,** 347.
GOLDBERG, A. A., and JEFFERIES, H. S., *Quart. J. Pharm.*, 1946, **19,** 48.
GRANT, R. T., and REEVE, E. B., *Observations on the General Effects of Injury in Man*, 1951, 1st ed., p. 224. London: H.M.S.O.
GREEN, H. N., and BULLOUGH, W. S., *Brit. J. exp. Path.*, 1950, **31,** 175.
GREEN, H. N., and GHADIALLY, F. N., *Brit. med. J.*, 1951, *i*, 496.
HAIST, R. E., and HAMILTON, J. I., *J. Physiol.*, 1944, **102,** 471.
HALL, G. E., *Amer. J. Psychiat.*, 1940, **95,** 553.
HALLION, L., and GAYET, R., *C.R. Soc. Biol., Paris*, 1925, **92,** 945.
HALPERN, F. G., *Amer. J. Psychiat.*, 1940, **96,** 1153.
HARINGTON, M., and ROSENHEIM, M. L., *Lancet*, 1954, *i*, 7.
HERBERT, F. K., and BOURNE, M. C., *Biochem. J.*, 1930, **24,** 299.
HIMWICH, H. E., *Brain Metabolism and Cerebral Disorders*, 1951a. 1st ed., p. 61. Baltimore.
*Idem*, *ibid.*, 1951b, p. 277.
JONES, M. S., *Proc. Roy. Soc. Med.*, 1939, **32,** 958.
JOURDAN, F., LAFLAQUIERE, J., and MAITRE, P., *C.R. Soc. Biol., Paris*, 1943, **137,** 124.
KALINOWSKY, L. B., and HOCH, P. H., *Shock Treatments*, 1946. 1st ed., p. 24. London.
KAY, A. W., and SMITH, A. N., *Brit. med. J.*, 1950, *i*, 460.
KAY, W. W., and THORLEY, A. S., *Proc. Roy. Soc. Med.*, 1951, **44,** 973.
LAMBRET, O., and DRIESSENS, J., *J. int. Chir.*, 1937, **2,** 223.
LAUGIER, H., and LEBLOND, C. P., *Rev. canad. Biol.*, 1943, **2,** 474.
LAURENCE, D. R., and STACEY, R. S., *Lancet*, 1951, *ii*, 1145.
LEWIS, J. T., *C.R. Soc. Biol., Paris*, 1923, **89,** 1118.
MANNERS, T., *Brit. med. J.*, 1951, *i*, 1429.
MARLEY, E., M.D. Thesis, 1953, p. 55. Cambridge.
MCDONOUGH, F. N., *Amer. J. Physiol.*, 1939, **125,** 530.
MCMICHAEL, J., *Quart. J. exp. Physiol.*, 1938, **27,** 73.
*Idem*, *Brit. med. Bull.*, 1945, **3,** 105.
MEDUNA, L. J., GERTY, F. J., and URSE, V. G., *Arch. Neurol. Psychiat., Chicago*, 1942, **47,** 38.
MONTAGU, J. D., *J. Ment. Sci.*, 1953, **99,** 112.
NASTUK, W. L., *Amer. J. Physiol.*, 1947, **149,** 369.
PATON, W. D. M., *Brit. med. J.*, 1951, *i*, 773.
PERLMUTTER, M., and MUFSON, M., *J. clin. Endocrinol.*, 1951, **11,** 277.
REZNIKOFF, L., and SCOTT, J. J., *Psychiat. Quart.*, 1942, **16,** 399.
ROCHE, M., HILLS, A. G., and THORN, G. W., *Proceedings of the First Clinical ACTH Conference*, 1950, p. 55. London.
RUD, F., "The Eosinophil Count in Health and in Mental Disease", *Acta Psychiat. Kbh.*, Supplement XL, 1947, p. 184.
RUSSEL, J. A., LONG, C. N. H., and ENGEL, F. L., *J. exp. Med.*, 1944, **79,** 1.
SAKEL, M., *The Pharmacological Shock Treatment of Schizophrenia*, 1938a, 1st ed., p. 87. New York.
*Idem*, *ibid.*, 1938b, p. 11.
*Idem*, *Congres International de Psychiatrie*, 1950, vol. IV, p. 163. Paris.
SAYERS, G., and SAYERS, M. A., *Endocrinology*, 1947, **40,** 265.
*Idem*, *Recent Progress in Hormone Research*, 1948, **2,** 81. New York.
SCHACHTER, M., *J. Physiol.*, 1951, **115,** 206.
SCHLOSSBERG, T., SAWYER, M. E. M., and BIXBY, E. M., *Amer. J. Physiol.*, 1933, **104,** 190.
SELYE, H., *Arch. int. Pharmacodyn.*, 1938, **60,** 259.
*Idem*, *J. clin. Endocrinol.*, 1946, **6,** 117.
*Idem*, *Stress*, 1950a, 1st ed., p. 105. Montreal.
*Idem*, *ibid.*, 1950b, p. 53.
*Idem*, *ibid.*, 1950c, p. 27.
*Idem*, *ibid.*, 1950d, p. 51.
*Idem*, *Ann. Rev. Med.*, 1951, **2,** 327.
SHERWOOD, S. L., *Brain*, 1952, **75,** 68.
SOSKIN, S., *Physiol. Rev.*, 1941, **21,** 140.
SPEIRS, R. S., and MEYER, R. K., *Endocrinology*, 1949, **45,** 403.

https://doi.org/10.1192/bjp.102.428.576 Published online by Cambridge University Press

STELL, B. S., *Psychiat. Quart.*, 1945, **19,** 438.
STRACCIA, F. A., and SCHEFFLIN, A. E., *Amer. J. Psychiat.*, 1952, **108,** 702.
SUNDBERG, C. G., *C.R. Soc. Biol., Paris*, 1923, **89,** 807.
SWANN, H. G., and FITZGERALD, J. W., *Endocrinology*, 1938, **22,** 687.
SWINGLE, W. W., REMINGTON, J. W., DRILL, V. A., and KLEINBERG, W., *Amer. J. Physiol.*, 1942, **136,** 567.
TALBOT, N. B., ALBRIGHT, F., SALTZMAN, A. H., ZYGMUNTOWICZ, A., and WIXOM, R., *J. clin. Endocrinol.*, 1947, **7,** 331.
TENNENT, T., *Recent Progress in Psychiatry*, 1944, p. 467. London.
TILLIM, S. J., *Med. Rec., N.Y.*, 1938, **147,** 112.
VOGT, M., *J. Physiol.*, 1947, **106,** 394.
WAGNER, H. N., and WOODS, J. W., *Arch. Neurol. Psychiat., Chicago*, 1950, **64,** 720.
WIGGERS, C. J., *Physiology of Shock*, 1950, 1st ed., p. 406. New York.
ZUCKER, T. F., and BERG, B. N., *Amer. J. Physiol.*, 1937, **119,** 539.

https://doi.org/10.1192/bjp.102.428.576 Published online by Cambridge University Press