ALTERED RESPONSE TO SMALL DOSES OF INSULIN ASSOCIATED WITH ELECTROPLEXY AND HYPOGLYCAEMIC THERAPIES *

BY

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From Severalls Hospital, Colchester

The measurement of response to insulin utilizes a number of qualitative and quantitative variables. For example, in the treatment of diabetes there are varying criteria as to what constitutes satisfactory control of the disorder, whereas with deep insulin treatment for schizophrenia in which the end-point is the production of coma, the variables include the definition of coma, the degree of resistance to the drug, and the possibility that the nervous system of each individual treated shows its own selective susceptibility to insulin as it does to many other drugs (Kalinowsky and Hoch, 1952).

Fortunately, the response to small doses of insulin can be determined more precisely by the use of the insulin tolerance test, and the results reported in this paper derive from sequential insulin tolerance tests on psychotic and neurotic patients receiving either deep or modified insulin, or electroplexy (E.C.T.). However, not even this assessment of response to insulin is devoid of controversy, for, although the conventional procedure requires the calculation of the test dose in terms of the body weight, doubt as to the validity of the strict adjustment of dosage to body weight has been expressed by Somogyi (1949). Tests were performed before, during, and after treatment, and the results that accrued were validated statistically.

This technique of using the patient as his own control in the comparison of sequential tests has much to recommend it, variations due to differences in responsiveness between patients being eliminated (Reid, 1954), but the inconstancy of physiological equilibrium in schizophrenic disorders has been emphasized by Hemphill and Reiss (1948), who cautioned that if biochemical investigations such as the insulin tolerance and the sugar tolerance tests were repeated frequently in these patients, much day-to-day variation in results became evident. This is not the only factor that may introduce an error into the results, for Hubble (1954) demonstrated phasic insulin resistance in a young diabetic girl. He found that the insulin-resistant phases were usually pre-menstrual and the insulin-sensitive phases post-menstrual. Other workers had previously shown that oestrogens are diabetogenic, whereas androgens have a contrary effect (Houssay, 1951). It is for reasons such as these that the only patients included in this series are males.

Although there have been many investigations into the possibility of a relation between the results of insulin tolerance tests and the dose of insulin required to produce coma (Kaplan and Low, 1939; Harris, 1942; Borenz, Schuster, and Downey, 1949), the only reported results that I have been able to discover comparing the results of insulin tolerance tests before deep insulin therapy with those obtained either during or immediately after the termination of treatment derive from Borenz and others (1949) who comment on the lack of any constant change in the test results after therapy apart from some slight increased tolerance to small doses of insulin. There is a similar paucity of literature concerning any variation in the response to small doses of insulin following the administration of E.C.T., but Delay and Soulairac (1944) have observed that the hyperglycaemia produced by electro-shock is singularly resistant to insulin, a finding that has been confirmed by others (Marley, 1952).

Methods

The technique adopted for the insulin tolerance test was that proposed by Fraser, Albright, and Smith (1941) who recommend the intravenous administration of 0.1 unit of insulin per kilogram of ideal body weight. As the previous diet influences the response to insulin (Himsworth, 1935), the patients were given at least 300 g. carbohydrate daily for three days before the test. All patients came to the ward at 7.30 a.m. and remained at rest in bed until the test began at approximately 9 a.m. when they had then been fasting for 12 hours. Capillary blood was first withdrawn for the estimation of the fasting blood sugar, after which the insulin was injected. At 20, 30, 45, 60, 90, and 120 minutes afterwards further samples of blood were taken.

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The response of the blood sugar to insulin can be differentiated into two phases: the initial decrease of blood sugar which is indicative of insulin sensitivity, and the secondary rise which is representative of the responsiveness to hypoglycaemia. The difference between the fasting and the 30-minute blood sugar value was adopted as an index of the first function, the mean values for these differences being calculated for the group. As suggested by Fraser and Smith (1941), a measure of the responsiveness to hypoglycaemia was obtained from the product of the percentage blood sugar values at 45, 60, 90, and 120 minutes after the beginning of the test and the time interval of these from the previous sample, a quarter of an hour being taken as unity. These products were then added together and termed the hypoglycaemia responsive index (H.R.I.). Fraser and Smith (1941) claim that this integer is a close approximation of the area enclosed between the insulin tolerance curve and the zero blood sugar line, and is therefore an inverse measure of the degree and persistence of hypoglycaemia after the 30 minutes' sample. The mean H.R.I. obtained from these results was calculated for the group. The limits of the H.R.I. as quoted by these authors varied in the normal from 474 units to 621 units, with a mean of 530 units.

As the results of insulin tolerance tests repeated at short intervals were being compared, it was essential to show that repeated tests under standard circumstances manifested no significant statistical dissimilarity. This was done, and it was seen that even in schizophrenics the results of insulin tolerance tests repeated at short intervals were strictly comparable (Marley, 1953a). Patients were therefore tested within 10 days of beginning treatment, between the fifth and twelfth days of treatment, between the thirteenth day and the end of treatment, and again within 10 days after the completion of therapy. In the case of those tests performed during the course of treatment, patients were rested from the latter for three days before testing not only to ensure that the strictures as regards diet were obeyed but also to exclude any immediately preceding effect of recent therapy.

The blood sugars were estimated by the method devised by Herbert and Bourne (1930), which is a determination of the true blood glucose.

No patient was accepted for testing if he was markedly underweight, as it has been demonstrated that changes attributable to the general adaptation syndrome are constantly present in association with severe malnourishment (Selye, 1950a). For the same reason, patients treated in the two months before the investigation with either E.C.T. or deep or modified insulin were rejected (Gellhorn and Safford, 1948; Henneman, Altschule, and Siegel, 1951).

**Results**

The results of insulin tolerance tests on 22 psychotic patients treated with deep insulin, five psychotics treated with E.C.T., and seven patients suffering from neurotic illnesses treated with modified insulin were analysed and compared statistically. There were, of course, individual exceptions to the mean results reported later in the paper, but these have not been abstracted from the context as it was considered that the analysis of group changes was more informative.

The patients were all males, those suffering from psychoses being diagnosed as having schizophrenia.

The mean values, and their standard deviations derived from the results of insulin tolerance tests, are presented in Table I. It can be seen that the mean fall of blood sugar following the administration of small doses of insulin was increased during and immediately after the cessation of treatment with either deep or modified insulin, but only during and not after E.C.T. The maximum fall of blood sugar occurred on testing between the fifth and the twelfth days of therapy with deep insulin or E.C.T., and between the thirteenth day and the end of treatment for those patients having modified insulin. The mean H.R.I. for the different groups showed a progressive decline during and after all therapies.

The significance of the differences between these mean values has been assessed statistically and presented in Table II. The means compared were those obtained before treatment and those found between the fifth and twelfth days of therapy

### Table I

**MEAN AND S.D. VALUES DERIVED FROM INSULIN TOLERANCE TESTS ON PATIENTS TREATED WITH DEEP AND MODIFIED INSULIN AND E.C.T.**

<table>
<thead>
<tr>
<th>Indices</th>
<th>Before Therapy</th>
<th>5th-12th Day of Therapy</th>
<th>13th Day to End of Therapy</th>
<th>After Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients treated with deep insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall of blood sugar (mg.)</td>
<td>40.8 ± 7.41</td>
<td>47.0 ± 9.63</td>
<td>45.3 ± 11.11</td>
<td>46.4 ± 8.13</td>
</tr>
<tr>
<td>Fall of blood sugar (%)</td>
<td>53.6 ± 6.44</td>
<td>57.9 ± 10.10</td>
<td>55.4 ± 12.21</td>
<td>57.3 ± 8.75</td>
</tr>
<tr>
<td>H.R.I.</td>
<td>498.6 ± 59.36</td>
<td>452.0 ± 42.15</td>
<td>462.1 ± 44.40</td>
<td>417.6 ± 43.46</td>
</tr>
<tr>
<td><strong>Patients treated with modified insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall of blood sugar (mg.)</td>
<td>40.7 ± 5.47</td>
<td>45.0 ± 5.49</td>
<td>46.2 ± 11.84</td>
<td>45.4 ± 19.67</td>
</tr>
<tr>
<td>Fall of blood sugar (%)</td>
<td>54.3 ± 4.77</td>
<td>57.1 ± 4.73</td>
<td>56.2 ± 10.27</td>
<td>54.8 ± 18.69</td>
</tr>
<tr>
<td>H.R.I.</td>
<td>550.7 ± 63.07</td>
<td>491.4 ± 53.44</td>
<td>464.2 ± 48.32</td>
<td>453.7 ± 80.73</td>
</tr>
<tr>
<td><strong>Patients treated with E.C.T.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall of blood sugar (mg.)</td>
<td>42.8 ± 7.05</td>
<td>49.2 ± 6.22</td>
<td>48.6 ± 5.18</td>
<td>42.0 ± 11.56</td>
</tr>
<tr>
<td>Fall of blood sugar (%)</td>
<td>58.4 ± 5.31</td>
<td>62.4 ± 7.54</td>
<td>59.6 ± 6.39</td>
<td>56.8 ± 9.09</td>
</tr>
<tr>
<td>H.R.I.</td>
<td>464.6 ± 8.29</td>
<td>437.0 ± 13.22</td>
<td>418.4 ± 16.34</td>
<td>413.2 ± 21.95</td>
</tr>
</tbody>
</table>
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(Series 1 and 2), the means before treatment and those between the thirteenth day and the cessation of therapy (Series 1 and 3), and those obtained before and after treatment (Series 1 and 4).

Table II
SIGNIFICANCE OF DIFFERENCE BETWEEN MEANS DERIVED FROM TESTS ON PATIENTS TREATED WITH DEEP AND MODIFIED INSULIN AND E.C.T.

<table>
<thead>
<tr>
<th>Indices</th>
<th>Statistical Criteria</th>
<th>Series 1 and 2</th>
<th>Series 1 and 3</th>
<th>Series 1 and 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated with deep insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall of blood sugar (mg.)</td>
<td>P &gt;0.05 &lt;0.01 &lt;0.025</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>significance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall of blood sugar (%)</td>
<td>t &gt;1.79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H.R.I.</td>
<td>P &gt;0.05 &gt;0.05</td>
<td>1.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>significance</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patients treated with modified insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall of blood sugar (mg.)</td>
<td>t &gt;1.36 &lt;1.10 &gt;0.61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>significance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall of blood sugar (%)</td>
<td>t &lt;0.01 &lt;0.01 &lt;0.025</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>significance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H.R.I.</td>
<td>t &gt;2.27 &lt;0.005</td>
<td>3.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>significance</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

From Table II it can be seen that the mean hypoglycaemic effect of small doses of insulin is significantly increased during the early phases of deep insulin therapy. The mean fall of blood sugar in the groups treated with modified insulin or E.C.T. is similarly augmented, although in these the fall is not significant. Similarly there is a significant decline in the mean values for the H.R.I. obtained on testing with small doses of insulin during and after all therapies, the one exception being the insignificant decline of the mean H.R.I. associated with testing between the fifth and twelfth days of treatment with modified insulin. It is worthy of note that the mean values for the H.R.I. derived from these tests were frequently lower than the minimum of the range of normal values for the H.R.I. reported by Fraser and Smith (1941).

Another interesting feature is that whilst the hypoglycaemic effect of small doses of insulin was most increased between the fifth and twelfth days of deep insulin therapy and the value for the H.R.I. least decreased, the mean dose of insulin required at this time to produce or attempt to produce coma was 317.7 units. Although this augmented hypoglycaemic effect of small doses of insulin was not so evident on testing towards the completion of a course of deep insulin and the mean value for the H.R.I. had further decreased, the mean dose of insulin given at this time to produce or attempt to produce coma was still as high as 276-6 units.

Discussion

The results presented above show that for the groups as a whole there was an increase in the hypoglycaemic effect of small doses of insulin during or after treatment, no matter whether therapy was with insulin or E.C.T. As resistance to the hypoglycaemic effect of insulin depends on the activity of the anterior pituitary and adrenal cortical hormones (Bouckaert and de Duve, 1947), presumably this augmented hypoglycaemic response represents some alteration in the requirements or activity of these hormones.

A similar phenomenon was reported by Masson (1941). He found that rats continuously treated by exposure to cold, forced muscular exercise, or with injections of formaldehyde, after 24 hours, that is, during what he considered to be the “alarm stage” of Selye’s general adaptation syndrome, manifested a small and perhaps insignificant decrease in the hypoglycaemic action of insulin. However, during the “stage of resistance” of this syndrome, that is, after nine days of such treatment, the hypoglycaemic action was considerably increased. Thus, both on the sixth and ninth days of exposure to these three noxious agents, the identical dose of insulin consistently produced a particularly severe drop in the blood sugar. He surmised, therefore, that the hypoglycaemic action of this hormone increases as the animal adapts itself to the non-specific damaging agents. In addition, the increased insulin tolerance seen in patients during the immediate post-operative period after lumbo-dorsal sympathectomy is followed by a secondary stage of increased sensitivity to the drug. This alteration in insulin resistance has been interpreted as a manifestation of the general adaptation syndrome (Simeone and Vavoudes, 1948 ; Simeone, 1949). The non-specific effect of E.C.T. has been commented on by Roth and Rosie (1953) and in the same manner insulin has a non-specific action besides its effect on the blood sugar (Paschikis, Cantarow, Walking, and Boyle, 1950). Presumably, then, this altered hypoglycaemic response to small doses of insulin reflects an adaptation on the part of the body to the repeated administration of large doses of insulin or the repeated application of E.C.T. It is this phase of optimal adaptation that Selye has termed the “stage of resistance” of the general adaptation syndrome (Selye, 1946).
The mean values for the H.R.I. were significantly reduced both during and after treatment, and as responsiveness to hypoglycaemia depends on the action of adrenal cortical hormones and efficient gluconeogenesis, the unresponsiveness can be equated once more in terms of altered activity of the adrenal cortex. Furthermore, as the mean fall of blood sugar was in all instances greater than 50% of the mean values for the fasting blood sugars, the unresponsiveness could not be attributed to an inadequate stimulation of the blood sugar raising mechanisms.

The results of these tests would therefore seem on first impressions to imply an inadequate response of the anterior pituitary and adrenal cortex during and immediately after the completion of treatment, but any actual deficiency of these particular endocrines is readily excluded by the fact that those patients receiving hypoglycaemic therapy still required large doses of insulin for the production of satisfactory comas. An explanation of this paradox becomes feasible when it is recognized that the blood steroid levels are significantly elevated during treatment with deep insulin or E.C.T. (Bliss, Migeon, Nelson, Samuels, and Hardin Branch, 1954), and that the steroids include the group of 11-oxycorticosteroids, one of which is cortisone. Sayers and Sayers (1947) have suggested that its release inhibits the production of A.C.T.H. by the pituitary, and further considered that its inhibition was self-regulatory inasmuch as the pituitary secretes A.C.T.H. at a rate which is adjusted to the requirements of the peripheral tissues. But the action of small doses of insulin is mainly peripheral (Bouckaert and de Duve, 1947) as is also the antagonistic effect of adrenal cortical hormones on carbohydrate metabolism (Bondy, 1949). Thus, the results of insulin tolerance tests measure preponderantly the peripheral anti-insulin activity, whereas the larger doses of this hormone, such as are employed during deep insulin therapy, act mainly on the liver (Bouckaert and de Duve, 1947). Presumably then adaptation to the continued injection of large doses of insulin alters the peripheral requirements for corticoids and so modifies the response to small doses of the substance. A similar rationale must apply to the diminished response with sequential insulin tolerance tests accompanying the repeated application of E.C.T.

These findings are reminiscent of the work of Last, Jordan, Pitesky, and Siegel (1950) who excluded exhaustion of either the anterior pituitary or the adrenal cortex during an investigation of adaptation to epinephrine stress. They therefore suggested that adaptation to stress implied a decreased utilization of corticoids and consequently a decreased stimulus for the production of A.C.T.H. Finally, it seems relevant to include the view sponsored by Selye (1950b), who maintained that during the stage of resistance of the general adaptation syndrome carbohydrate metabolism readjusts itself so that the adrenal hormones become less important in the maintenance of the blood sugar level. In the terms of this interpretation, the repeated administration of large doses of insulin or E.C.T. results in a readjustment of carbohydrate metabolism revealed in serial tests with small doses of insulin.

Other tissue and biochemical deviations that accompany these therapies and seem also to represent non-specific adaptation have been formulated elsewhere (Marley, 1953b).

Summary

The mean hypoglycaemic effect of small doses of insulin is significantly increased during the early phases of deep insulin therapy. The mean fall of blood sugar after small doses of insulin is similarly but insignificantly augmented in the groups treated with modified insulin or E.C.T. This increased hypoglycaemic effect persisted for a short time after the termination of deep or modified insulin but not after E.C.T.

There is a significant decline in the mean values for the hypoglycaemia responsive index during and after all therapies.

These changes seem to imply a decreased peripheral requirement for corticoids and to represent an adaptation on the part of the body to the repeated administration of large doses of insulin or the repeated application of E.C.T.

Exhaustion of either the anterior pituitary or the adrenal cortex was excluded in the case of those patients being treated with deep insulin.

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

In addition, I should also like to thank Nurse H. Gayler and Nurse G. Gordon for their unstinted assistance and cooperation which facilitated the progress of this investigation.

References

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THE NOVEMBER (1955) ISSUE

The November (1955) issue contains the following papers:


The Pathological Effects Produced by Sera of Animals Immunized with Foreign Nervous or Splenic Tissue. Part II: Intra-arterial Injection of Serum. E. Weston Hurst.


Non-specific Effects of Insulin and Electroplexy. E. Marley.

A Preliminary Report on a Perceptual Maze Test Sensitive to Brain Damage. Alick Elithorn.

Head Injury as a Cause of Internal Carotid Thrombosis. C. B. Sedzimir.


An Electrode Holder for Direct Encephalography with Its Own Sterilizing Cabinet. G. Pampiglione and R. Cooper.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1. price 12s. 6d.
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