NON-SPECIFIC EFFECTS OF INSULIN AND ELECTROPLEXY

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The recognition of the non-specific action of chemical or other agents used therapeutically owes much to the theories and experimental work of Selye (1950a). He traced out a pattern of reaction which longitudinally was termed the general adaptation syndrome (Selye, 1946) and in cross-section appears to be essentially triphasic (Selye, 1950b). Selye suggested that the first part of this be known as the alarm reaction, the implication being that adaptation had not as yet been acquired; this was followed by the stage of resistance during which adaptation was optimal, and if the stimulus or stress should persist, then the stage of exhaustion supervened. An agent producing an alarm reaction was termed a stressor (Selye, 1950c) and might exert both specific and non-specific effects (Selye, 1951). Insulin, for instance, acts both non-specifically (Paschkis, Cantarow, Walkling, and Boyle, 1950) and specifically by increasing the peripheral assimilation of sugar and the deposition of glycogen in the liver (Soskin, 1941; Bouckaert and de Duve, 1947).

The value of both insulin and electroplexy (E.C.T.) in the treatment of the schizophrenias has been thought of by some to owe much to their non-specific effects. Thus Roth and Rosie (1953) liken the action of E.C.T. to that of other non-specific therapies such as A.C.T.H. and cortisone, emphasizing that it is unlikely to act directly upon the causes of psychiatric disorders but rather upon the regulatory and defensive mechanisms of the organism. Sackler, Sackler, Sackler, La Burt, van Ophuijsen, and Co Tui (1951), while admitting a number of physiological denominators common to E.C.T., insulin coma therapy, histamine and combined sex hormone therapies, nevertheless considered that to explain away all their effects as being non-specific might amount to the dismissal of other important factors in their action.

It is the purpose of this paper to suggest that various biochemical and tissue deviations that have been hitherto assigned either diagnostic or prog-

nostic status, and which occur concurrently with, and in apparent direct relation to, treatment could as reasonably be integrated with patterns of non-specific homeostasis.

Such criteria include that of Meduna (1950), who postulated a clinical distinction between endogenous schizophrenia and a syndrome he designated "oneirophrenia", one of the differences being that the latter patients exhibited resistance to insulin in the intravenous insulin tolerance test. This resistance was a reversible phenomenon, the reaction reverting to a normal hypoglycaemic response *pari passu* as the patient improved with the administration of E.C.T., the reversion being an additional hall-mark of the benignity of the condition in contrast to the more sinister outlook for the true schizophrenias.

Other work on prognostic criteria includes that of Rud (1947a) who demonstrated that the administration of "cardiazol", E.C.T., and deep insulin therapy was succeeded by an immediate eosinopenia, but that in addition three weeks after beginning insulin there was a distinct increase in the eosinophil cells. He deemed that this rising eosinophil count was of therapeutic importance and that it indicated a patient who might benefit from one of the shock treatments. Sackler and others (1951) also observed an apparent correlation between an improvement in the patient's clinical status and the degree of eosinophilia. Altschule, Siegel, Restaino, and Parkhurst (1952) remarked upon this eosinophilia in patients who showed improvements after shock treatments, and affirmed that in their study patients with decreases in the cell count persisting after the end of treatment were not improved. Similarly, Alexander and Neander (1953) comment that in their series those patients who showed no rise in the resting eosinophil count during therapy evinced no alteration in their eventual mental state. Shands and Menzer (1953) dissent from these opinions, suggesting that the evidence of prognostic significance for the occurrence, or non-occurrence, of eosinophilia in relation to treatment was not convincing.

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Therefore, in an attempt to elucidate the matter further, a series of sequential investigations, including repeated insulin tolerance tests, eosinophil counts, and plasma chloride values, was recorded on patients treated with E.C.T. and with both deep or modified insulin.

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 kg. 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. Blood was first removed for the initial eosinophil count, as it is known that following the eosinopenia during the early hours of the morning the count tends to become stabilized about 9 a.m. with a minimum between 9 a.m. and 11 a.m. (Rud, 1947b). Capillary blood was then withdrawn for 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. The blood sugars were estimated by the method devised by Herbert and Bourne (1930), which is a determination of the true blood glucose. As it has been demonstrated that hypoglycaemia is accompanied by an eosinopenia (Perlmutter and Mufson, 1951) and that this is most prominent four hours after stress, the eosinophils in addition to being counted at 9 a.m. were also checked at 1 p.m. The difference between the 9 a.m. and 1 p.m. counts for the group was calculated and termed the "mean eosinopenia."

As the results of insulin tolerance tests repeated at short intervals were being compared, it was essential to show that repeated tests under normal circumstances manifested no significant statistical dissimilarity. This was done and it was seen that the results of insulin tolerance tests repeated at short intervals were strictly comparable (Marley, 1953). Patients were therefore tested before treatment, during the fifth to twelfth days of treatment, between the thirteenth day and the end of treatment, and within 10 days of the termination 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 observed but also to exclude any immediately preceding effect of recent therapy. The criterion of a fall of less than 50% of the fasting blood sugar, or a fall not occurring for 45 minutes or more, was adopted as being indicative of insulin resistance (Fraser and others, 1941). In addition, the mean fall of blood sugar 30 minutes after the beginning of the test was calculated for the group as a whole and compared before, during, and after cessation of treatment.

Capillary blood was used in eosinophil counting, and both the technique and the phloxine-urea pro-

posed by Manners (1951) were adopted. The eosinophil counts performed during treatment, but not associated with insulin tolerance tests, were also done at approximately 9 a.m., and those reported here derive from the mean of two counts estimated twice weekly.

For each count, two white-cell pipettes were filled to the 1 mark with blood and to the 11 mark with the phloxine-urea diluent. The pipettes were immediately shaken for two to three minutes and then the four counting chambers (two double-sided Fuchs-Rosenthal chambers) were filled by capillation. The counting chambers were set aside in a moist environment prepared by placing a few sheets of filter paper soaked with water in the bottom of a large Petri dish. Within 15 minutes nearly all the leucocytes other than the eosinophils were lysed. The count was then performed under the 16 mm. microscope objective with a $\times 10$ eyepiece. All the ruled area of the chamber was counted, and as the total volume of the four chambers was 12.8 c.mm. and the dilution 1 in 10, the number of eosinophils per c.mm. was ascertained by dividing the total number counted by 1.28.

Plasma chloride values were estimated by first precipitating silver chloride with the addition of a known amount of silver nitrate and then destroying the proteins by heating with nitric acid. The remaining silver nitrate was titrated with thiocyanate and the amount precipitated calculated, and hence the amount of chloride determined (May and Marrack, 1951).

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 malnutrition (Selye, 1950d). For the same reason patients treated in the previous two months with either E.C.T. or deep or modified insulin were rejected (Gellhorn and Safford, 1948; Henneman, Altschule, and Siegel, 1951).

The results of investigations performed on 22 psychotic patients treated with deep insulin (Nos. 1 to 22), five psychotics treated with E.C.T. (Nos. 23 to 27), and seven patients suffering from neurotic illnesses treated with modified insulin (Nos. 28 to 34) were analysed and compared statistically.

All the values included below derive from tests on the entire groups of patients except for the eosinophilias associated with deep insulin treatment which were calculated from repeated counts on 16 of the 22 psychotics, and the plasma chloride readings which were obtained from repeated estimations on seven of the 22 psychotics of that same group.

The patients were all males, those suffering from psychoses being diagnosed as having schizophrenia. In no instance was an alternative diagnosis of oneirophrenia tenable.

Results

The mean values and their standard deviations derived from the results of tests are presented in Tables I, II, and III. The mean fall of blood sugar, the mean eosinopenia, the mean fasting blood sugar levels, and the mean plasma chloride values were

TABLE I
MEAN AND STANDARD DEVIATION VALUES DERIVED FROM TESTS ON PATIENTS TREATED WITH DEEP INSULIN

Indices	Before Therapy	5th to 12th Day of Therapy	13th Day to End of Therapy	After Therapy
Fall of blood sugar (mg.)	40.8 ± 7.41	47.0 ± 9.63	45.3 ± 11.11	46.4 ± 8.12
Fall of blood sugar (%)	53.6 ± 6.44	57.9 ± 10.10	55.4 ± 12.21	57.3 ± 8.75
Fasting blood sugar (mg./100 ml.)	75.5 ± 8.67	81.4 ± 8.82	81.1 ± 9.87	81.2 ± 7.00
Eosinopenia (%)	79.6 ± 14.16	43.9 ± 20.32	25.4 ± 24.42	20.5 ± 30.20
Eosinophils (per c.mm.)	142.7 ± 67.17	208.7 ± 83.92	250.4 ± 129.27	134.4 ± 62.00
Plasma chlorides (mEq.)	92.0 ± 2.76	103.2 ± 10.10	93.5 ± 2.95	95.3 ± 7.39

TABLE II
MEAN AND STANDARD DEVIATION VALUES DERIVED FROM TESTS ON PATIENTS TREATED WITH E.C.T.

Indices	Before Therapy	5th to 12th Day of Therapy	13th Day to End of Therapy	After Therapy
Fall of blood sugar (mg.)	42.8 ± 7.05	49.2 ± 6.22	48.6 ± 5.18	42.0 ± 11.56
Fall of blood sugar (%)	58.4 ± 5.31	62.4 ± 7.54	59.6 ± 6.39	56.8 ± 9.09
Fasting blood sugar (mg./100 ml.)	72.8 ± 5.97	79.2 ± 4.32	81.6 ± 4.39	77.2 ± 4.21
Eosinopenia (%)	82.2 ± 11.44	45.2 ± 13.87	15.4 ± 12.29	13.0 ± 12.62
Eosinophils (per c.mm.)	21.4 ± 11.15	40.6 ± 30.95	125.2 ± 57.09	68.4 ± 39.02

TABLE III
MEAN AND STANDARD DEVIATION VALUES DERIVED FROM TESTS ON PATIENTS TREATED WITH MODIFIED INSULIN

Indices	Before Therapy	5th to 12th Day of Therapy	13th Day to End of Therapy	After Therapy
Fall of blood sugar (mg.)	40.7 ± 5.47	45.0 ± 5.49	46.2 ± 11.84	45.4 ± 19.67
Fall of blood sugar (%)	54.3 ± 4.77	57.1 ± 4.73	56.2 ± 10.27	54.8 ± 18.69
Fasting blood sugar (mg./100 ml.)	74.6 ± 5.25	78.6 ± 4.57	83.2 ± 4.53	80.5 ± 9.99
Eosinopenia (%)	70.4 ± 13.34	49.1 ± 26.73	28.0 ± 27.51	5.3 ± 82.75
Eosinophils (per c.mm.)	187.1 ± 118.16	205.0 ± 154.50	189.4 ± 110.79	96.8 ± 43.84

obtained at the same time as the insulin tolerance tests. The mean level of the eosinophils, as explained previously, was calculated from the mean of twice weekly counts performed before, during, and after therapy, although those included here are the means of the maximum eosinophilias recorded in that period. The mean fall of blood sugar represents the mean of the differences between the fasting blood sugars and the values 30 minutes after the beginning of the insulin tolerance test.

From these Tables it can be seen that the mean fall of blood sugar is increased during and immediately after the cessation of therapy, most particularly between the fifth and twelfth days of treatment. Similarly, the mean of the fasting blood sugars is increased during and immediately after therapy, most noticeably during the later phases of treatment. The mean eosinopenia declines rapidly during and immediately after therapy. The mean value for the plasma chlorides increased during

treatment with deep insulin, most markedly between the fifth and twelfth days of therapy. The mean level of eosinophils increased during treatment, the greatest increase taking place during the earlier stages of the course of modified insulin but during the later phases of treatment with deep insulin or E.C.T. However, this mean increase had disappeared soon after the termination of therapy.

The significance of the differences between these mean values has been assessed statistically and presented in Tables IV, V, and VI. The means compared were those obtained before treatment and those found between the fifth and twelfth days of therapy (Series 1 and 2), the means before treatment and those occurring between the thirteenth day and the cessation of therapy (Series 1 and 3), and those obtained before and after treatment (Series 1 and 4).

From these Tables it can be seen that the hypoglycaemic effect of small doses of insulin is significantly increased during the early phases of deep

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TABLE IV

SIGNIFICANCE OF THE DIFFERENCE BETWEEN MEANS DERIVED FROM TESTS ON PATIENTS TREATED WITH DEEP INSULIN

Indices	Statistical Criteria	Series 1 and 2	Series 1 and 3	Series 1 and 4
Fall of blood sugar (mg.)	t P significance	2.40 <0.01 +	1.53 >0.05 —	2.22 <0.025 +
Fall of blood sugar (%)	t P significance	1.79 <0.05 +	0.54 >0.25 —	1.51 >0.05 —
Fasting blood sugar (mg./100 ml.)	t P significance	2.24 <0.025 +	1.90 <0.05 +	2.57 <0.01 +
Eosinopenia (%)	t P significance	6.75 <0.005 +	8.69 <0.005 +	7.57 <0.005 +
Eosinophils (per c.mm.)	t P significance	2.02 <0.05 +	2.67 <0.01 +	2.65 <0.05 +
Plasma chlorides (mEq.)	t P significance	2.68 <0.025 +	0.91 >0.15 —	1.03 >0.15 —

TABLE V

SIGNIFICANCE OF THE DIFFERENCE BETWEEN MEANS DERIVED FROM TESTS ON PATIENTS TREATED WITH E.C.T.

Indices	Statistical Criteria	Series 1 and 2	Series 1 and 3	Series 1 and 4
Fall of blood sugar (mg.)	t P significance	1.52 >0.05 —	1.50 >0.05 —	0.01 >0.45 —
Fall of blood sugar (%)	t P significance	0.97 >0.15 —	0.37 >0.35 —	0.34 >0.35 —
Fasting blood sugar (mg./100 ml.)	t P significance	1.94 <0.05 +	2.67 <0.025 +	1.35 >0.05 —
Eosinopenia (%)	t P significance	4.65 <0.005 +	4.57 <0.005 +	9.05 <0.005 +
Eosinophils (per c.mm.)	t P significance	4.21 <0.01 +	2.60 <0.05 +	1.33 >0.20 —

TABLE VI

SIGNIFICANCE OF THE DIFFERENCE BETWEEN MEANS DERIVED FROM TESTS ON PATIENTS TREATED WITH MODIFIED INSULIN

Indices	Statistical Criteria	Series 1 and 2	Series 1 and 3	Series 1 and 4
Fall of blood sugar (mg.)	t P significance	1.36 >0.05 —	1.10 >0.10 —	0.61 >0.25 —
Fall of blood sugar (%)	t P significance	1.02 >0.10 —	0.41 >0.30 —	0.07 >0.45 —
Fasting blood sugar (mg./100 ml.)	t P significance	1.52 >0.05 —	3.17 <0.005 +	1.31 >0.10 —
Eosinopenia (%)	t P significance	1.75 >0.05 —	3.38 <0.005 +	2.11 <0.05 +
Eosinophils (per c.mm.)	t P significance	0.23 >0.40 —	0.03 >0.45 —	1.63 >0.05 —

TABLE VII

RESISTANCE TO SMALL DOSES OF INSULIN IN RELATION TO THERAPY

Case No.	Illness	Before Therapy	5th to 12th Day of Therapy	13th Day to End of Therapy	After Therapy	Degree of Improvement
1	P	—	—	+	+	G.I.
4	P	+	—	—	—	G.I.
9	P	—	—	+	+	G.I.
12	P	+	+	+	+	G.I.
13	P	+	—	+	+	U.
14	P	—	—	—	+	U.
27	P	—	—	—	+	S.I.
28	N	—	—	—	—	N.A.
34	N	—	—	+	+	N.A.

P=psychotic illness. N=neurotic illness. +=positive incidence of insulin resistance. —=negative incidence of insulin resistance. G.I.=greatly improved, S.I.=slightly improved, U=unimproved. N.A.=not assessed.

insulin therapy. The mean fall of blood sugar in the groups treated with E.C.T. or modified insulin is similarly augmented, although in these the fall is not significant. Hence, increase in sensitivity to small doses of insulin is the rule rather than the exception with these treatments, and presumably, therefore, bears no relation to prognostic factors. However, there were individual exceptions to these overall results for the group, and these are presented in Table VII.

It can be inferred from the latter that increase of sensitivity during or immediately after treatment, following the previous demonstration of resistance to small doses of insulin, may still not be associated with improvement (Case 13), and that no increase

of sensitivity during or immediately after treatment in a patient originally resistant to small doses of insulin in no way impedes improvement (Case 12). Moreover, the emergence of resistance to small doses of insulin in patients who were previously sensitive to the drug may or may not be associated with improvement (Cases 1, 9, 14, and 27).

The mean level of the fasting blood sugars showed a significant increase during and immediately after therapy with deep insulin and during the later stages of treatment with modified insulin and E.C.T., although the means of the fasting levels were raised even in those instances in which this increase was not statistically significant. There were no individual exceptions to these findings for the group.

The decrease of the mean eosinophilia accompanying insulin tolerance tests was statistically significant for all patients during and immediately after the cessation of therapy with deep insulin and E.C.T.,

but only during the later phases and immediately after the termination of treatment with modified insulin.

Similarly, a significant mean eosinophilia occurred during and immediately after the cessation of therapy with deep insulin, during but not immediately after the completion of a course of E.C.T., and not at all either during or immediately after treatment with modified insulin. The significance of individual mean eosinophilias was assessed by the strict criterion of Berkson, Magath, and Hurn (1940) which requires that any variation from the mean of a cell count should be at least twice the standard deviation of that mean to be significant. The presence or absence of a significant individual eosinophilia was correlated with the clinical status of the patient immediately after the completion of a course of therapy, and the findings are tabulated in Table VIII.

TABLE VIII

CORRELATION OF THE DEGREE OF EOSINOPHILIA WITH THE IMMEDIATE RESULTS OF THERAPY

Therapy	Eosino- philia	Degree of Improvement			Total
		Great	Slight	Unim- proved	
Deep insulin	+	5	4	3	16
	—	0	2	2	
E.C.T.	+	1	3	1	5
	—	0	0	0	

+ = significant individual eosinophilia. — = insignificant individual eosinophilia.

Thus, of those patients treated with deep insulin, and of those manifesting individual significant eosinophilias, five were greatly improved, four slightly improved, and three unimproved, whereas, of those patients exhibiting no significant eosinophilia, two were slightly improved and two unimproved. The eosinophilia was significant for all patients treated with E.C.T., and of these one was greatly improved, three slightly improved, and one unimproved. Thus, in the groups treated with deep insulin or E.C.T. the patients exhibited either no eosinophilia or a significant moderate eosinophilia with a maximum mean of 250.4 eosinophils per c.mm. for those treated with deep insulin and a maximum mean of 125.2 eosinophils per c.mm. for those treated with E.C.T. No instances were observed of the very high counts of 1,000 eosinophils per c.mm. or more recorded by Shands and Menzer (1953) or Freeman, Jones, and Palmer (1954).

The relation of the eosinophilias to prognosis in the group receiving modified insulin was not eluci-

dated, as not all these patients were having treatment exclusively for their mental symptomatology. However, there was an increase in the resting level of eosinophils during the early phase of therapy, although this mean increase was not statistically significant.

Of those patients treated with deep insulin and on whom the plasma chlorides were estimated, all showed an increase of these values except Case 17. In this patient they remained stationary during and immediately after therapy, and the patient remained unimproved as the result of treatment. Of the rest, one was greatly improved, two slightly improved, and three unimproved immediately after the termination of therapy. The mean increase of the plasma chloride values was statistically significant only during the fifth to twelfth days of therapy.

Discussion

From the results presented above it can be concluded that resistance to small doses of insulin occurs in schizophrenics in whom the diagnosis of oneirophrenia would be untenable. In addition, a decrease in resistance to small doses of insulin with concomitant clinical recovery may occur in schizophrenics during the course of therapy, and who, again, do not warrant a diagnosis of oneirophrenia. Furthermore, a decrease of insulin resistance may be unaccompanied by clinical improvement, whereas an increase of insulin resistance may be associated with recovery. More important still, if the groups as a whole were considered, an increase in the hypoglycaemic effect of small doses of insulin occurred during or after treatment, no matter whether therapy was with insulin or E.C.T., and hence these changes bear no particular relation to diagnosis or prognosis.

In addition, there was resistance to small doses of insulin in one patient suffering from a neurotic disorder before treatment, and in another during and after the completion of a course of modified insulin. Thus, resistance to insulin can occur both in neurotics and schizophrenics and in fact has been reported in other conditions, for instance, in patients suffering from the malignant phase of hypertension (Olsen and Nuetzel, 1950). This confirms the opinion of Mayer-Gross (1952) who could discover no positive correlation between the incidence of resistance to small doses of insulin and a diagnosis of oneirophrenia, a conclusion similarly endorsed by Lingjaerde (1952).

An increase of resting eosinophil cells accompanied treatment with insulin or E.C.T. and bore no clear-cut association to clinical improvement. These findings are in accord with those of Shattock

and Micklem (1952), who reported that an increase in the number of eosinophils occurred both in patients who recovered and in those whose clinical progress was disappointing. More recently, Shands and Menzer (1953) and Freeman and others (1954) have arrived at an identical conclusion.

The mean eosinopenia accompanying serial insulin tolerance tests decreased in magnitude during and after the termination of the various therapies, and it is relevant that Altschule, Parkhurst, and Tillotson (1949) reported that in man the response of the eosinophils to electrically induced convulsions decreased with frequently repeated "shocks", but that the response may return to its former level after a rest period of at least nine days. They further remark that their findings are reminiscent of the work of Hills, Forsham, and Finch (1948) who noted a diminished eosinopenia after daily injections of adrenocorticotrophic hormone. Similarly, Sprague, Mason, and Power (1951) observed that a reduced eosinopenic response accompanied continued administration of cortisone.

Other results that mimic closely the findings presented in this paper have been reported by Masson (1941) who found, after exposing animals to various stressors, that the hypoglycaemic effect of insulin was considerably augmented during the stage of resistance of the general adaptation syndrome. He surmised, therefore, that the hypoglycaemic action of this hormone increases during adaptation to non-specific agents. An equivalent phenomenon has been recorded after lumbo-dorsal sympathectomy and interpreted as a manifestation of the general adaptation syndrome (Simeone and Vavoudes, 1948; Simeone, 1949). A transient eosinophilia was observed by White (1951) during the experimental production of the general adaptation syndrome in sheep, and Laragh and Almy (1948) and Johnson, Conn, Iob, and Collier (1950) have suggested that the eosinophilia following upon the stress of traumatic injury may be in some way linked with the adaptation syndrome. Last, Jordan, Pitesky, and Siegel (1950) noted that a diminished eosinopenic response accompanied adaptation to stress induced by adrenalin. Likewise, Jordan, Pitesky, Bond, Johnson, and Last (1950) observed a decreased eosinophil response in association with adaptation to stress. Hence the increased hypoglycaemic effect of small doses of insulin, the diminished eosinopenias, and the elevation of the level of eosinophils, have been observed during adaptation to stress or accompanying the continued administration of adrenocorticotrophic hormone.

As for the other results reported in this paper, the increased values for fasting blood sugars recorded

during treatment with deep insulin have been noted previously by Looney and Cameron (1937). In addition, Gellhorn and Safford (1948) found that the fasting blood sugar of rats was markedly augmented after 10 electro-shocks, but that after a further 14 electro-shocks the fasting blood sugar had declined again to normal values. However, insulin and E.C.T. are so-called stressors, and Selye (1950e) has noted that stress is accompanied by an initial hyperglycaemia succeeded later by hypoglycaemia, although eventually during the counter-shock phase, the blood sugar returns to normal and remains at, or slightly above, this level; that is, throughout the entire stage of resistance of the general adaptation syndrome. But the anterior pituitary and adrenocortical hormones are the major factors in maintaining a fasting blood sugar level (Long, 1952) so the raised fasting blood sugar values presumably reflect some altered activity of these endocrines. It is of interest, therefore, that Forsham, Thorn, Prunty, and Hills (1948) commented on an increase of the fasting blood sugar levels and a marked sodium and chloride retention following the administration of adrenocorticotrophic hormone. Finally, Selye (1938) in experiments on over 700 hooded rats recorded that in the course of adaptation to stressors (cold, formaldehyde, and histamine) there was an initial decrease in the chloride content of the blood, with a subsequent return to normal or even to an increase above the normal values.

Thus, the increase in the hypoglycaemic effect of small doses of insulin, of fasting blood sugar levels and eosinophil cells, and the diminished eosinopenias and increased plasma chloride values that accompany the administration of a course of insulin or E.C.T. are seen also in association with the continued injections of adrenocorticotrophic hormone or the development of the stage of resistance of the general adaptation syndrome. Hence these changes are best considered as being non-specific.

Summary

The presence of resistance to small doses of insulin in schizophrenics, or the disappearance of this resistance during treatment, has no diagnostic or prognostic worth. The same may be said for the increase, or absence of increase, of the values for the resting eosinophil cell counts before, during, or after therapy.

The increased hypoglycaemic effect of small doses of insulin, of fasting blood sugar levels and resting plasma chloride values, of increased eosinophil cell counts, and diminished eosinopenic response associated with the progress of treatment appear to be

non-specific and to represent tissue and biochemical adaptation to the repeated administration of insulin or E.C.T.

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