AN INVESTIGATION OF THE ADRENOCORTICAL RESPONSE OF MENTAL PATIENTS TO E.C.T. AND INSULIN HYPOGLYCAEMIA.

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SOMATIC disturbances in schizophrenia include metabolic, circulatory and endocrine changes frequently associated with disorders of the pituitary gland and adrenal cortex. Depression of the metabolic rate is often severe (Hoskins, 1932), the systolic blood-pressure is sometimes as low as 80 mm. Hg (Hoskins, 1934; Rheingold, 1939; Shattock, 1950[1]), and the pulse pressure only a few millimetres. Peripheral vascular deficiency and atrophy of the tissues (Bleuler, 1920; Mapother, 1924; Minski, 1937; Shattock, 1950[1,2]), asthenia and various cutaneous changes are common; amenorrhoea is almost the rule.

It is remarkable that these disturbances are reversible, and that they are relieved or greatly alleviated during mental remission. Physical health is restored during a spontaneous remission, and a gradual improvement can be observed during a course of insulin comas. Sometimes a dramatic recovery follows electroconvulsion when this initiates a mental remission; somatic improvement is then rapid and the vascular deficiency may be relieved within a few hours (Shattock, 1950[1,2]). Unfortunately these remissions are often brief, and as relapses become more frequent after repeated treatment, physical and mental deterioration may be noticeable a few days after the initial improvement. The point of interest is a concordance of physical and mental changes, and not the therapeutic value of E.C.T. used as an adjunct to insulin treatment or as a means of moderating extreme restlessness in chronic patients.

Physical improvement following E.C.T. is often too rapid to be ascribed to favourable changes in a patient's general condition. Moreover, the same vascular recovery may occur in emaciated or well-nourished patients, in previously immobile or restless schizophrenics. A rise in the blood pressure—with improved peripheral circulation—is not related, in these patients, to intake of fluids or solid nourishment and physical exercise, or convulsions which are not followed by mental remission, do not promote this somatic recovery. Asthenia is relieved more gradually, and menstruation may be resumed in the early days of a remission or delayed indefinitely.

The somatic disturbances of schizophrenic patients, and their rapid reversal during a remission, suggest a functional pituitary and adrenocortical deficiency. This suggestion receives support from the observation (Shattock, 1950[1,2]) that an additional intake of sodium chloride or the administration of D.O.C.A. to chronic catatonic patients is sometimes followed by gratifying physical and mental improvement. The present investigation has been designed to ascertain whether E.C.T. and insulin hypoglycaemia owe part of their curative action to stimulation of the pituitary-adrenocortical system.

TESTS OF ADRENOCORTICAL FUNCTION.

Extracts from blood and urine.—Many tests of adrenocortical function have been devised, none of them entirely satisfactory. Bornstein and Trewhella (1950) have described the assay of extracts from human plasma by Sayers' ascorbic acid depletion test; patients suffering from Cushing's syndrome showed greater activity, and cases of Simmonds' disease showed reduced activity. The rapid disappearance

of adrenocorticotrophic hormone from plasma and the difficulty of timing a rise in concentration of this hormone after E.C.T., added to other technical difficulties inherent in Bornstein's method, have not encouraged its use in this clinical investigation. Cope (1951) has elaborated another technique for detection of cortisone and 17-hydroxycorticosterone in urine and body fluids. This has yielded valuable comparative data, but only rough quantitative information (1951[2]), and has failed to demonstrate the presence of these substances in arterial and venous blood. Ashby (1949) investigated the excretion of cortical steroids in psychotic patients submitted to E.C.T. He found, in the majority of cases, a brisk outpouring of sugar-active and reducing cortins during the first days of treatment. In a later study of a case of periodic catatonia Ashby (1952) confirms the raised excretion of " sugar-active " cortins following E.C.T.

There is no general agreement on the accuracy of methods employed in the extraction of steroids from 24-hourly specimens of urine. These estimations can give only an indication of the effect of particular events or treatment on the total excretion of steroids. Seemingly trivial stimuli, such as venipuncture, which provoke cortical activity may obscure the importance of the stimulus under investigation. In psychotic patients there is the added difficulty of collecting 24-hourly specimens of urine.

Changes in the number of circulating lymphocytes.—Most observers agree that changes in the number of these cells are not a reliable index in man, whereas in some species of animal they are considered to give reliable information on cortical stimulation.

Changes in the number of circulating eosinophils.—Hills *et al.* (1948) have noted that the number of circulating eosinophils is dependent on the activity of the pituitary-adrenocortical system, and they have recorded a fall in the eosinophil count of normal subjects following injection of 25 mg. of ACTH. This observation has introduced a simple test, described by G. Sayers (1950) in a recent review of the subject, as probably the most useful index of adrenocortical function in man. We owe to Sayers (1948) the assay of ACTH in common use (the depletion of adrenal ascorbic acid), and his views on the eosinopenic test applied to man deserve our serious attention. The fall in the number of circulating eosinophils, four hours after administration of ACTH, is less variable and more considerable than the diminution in lymphocyte cells. A greater than 50 per cent. reduction after 25 mgm. ACTH is regarded by Thorn *et al.* (1948) as a " significant " eosinopenic response, although no statistical significance is implied. In Addisonian patients this response is absent, according to Thorn, but Sayers (1950) is more cautious. Although Sayers considers a satisfactory eosinopenic response to be " the first practical test of the functional capacity of the adrenal cortex in shock-like states," he emphasizes the importance of estimating the quantitative relationship between a stimulus and the response of the partially disabled glands of Addisonian patients.

A decrease in the number of circulating eosinophils is believed to be related to an increase in steroids oxygenated at C_{11} and C_{17}. Speirs and Meyer (1949) have found that in adrenalectomized mice the eosinophil count is very sensitive to 11-oxysteroids and less sensitive to 11-desoxycorticosterone. Whereas ACTH causes an increase in all three cortical hormones, Thorn states that the increase in glucocorticoids only is detected by a reduction in the number of eosinophil cells.

Eosinopenia following ACTH, adrenaline, insulin, E.C.T., and various other stresses, has been recorded by numerous observers (Altschule *et al.*, 1949; Recant *et al.*, 1950; Kersley *et al.*, 1950; etc.), who regarded this response as an indication of adrenocortical stimulation in experimental and clinical work. Objections to this test have been raised, however, including the following:

(i) An eosinopenic response is observed when large doses of adrenaline are given to patients who suffer from Addison's disease. Recant *et al.* (1950) record these " unexpected responses," but attribute them to a survival of remnants of functional adrenal tissue. Positive responses do not occur in adrenalectomized dogs, and are absent in Addisonian patients after small doses of adrenaline or ACTH. A variable response to ACTH, particularly in Addison's disease, has been reported by Davidson (1951).

(ii) The eosinopenic response is unsatisfactory when heparin is given in adequate dosage. Eosinophilia persists in spite of administration

of ACTH (Godlowski, 1951), but this persistence may indicate only a positive balance between mobilization and withdrawal, or elimination, of eosinophil cells.

(iii) The most serious objection to the eosinopenic reaction is its dependence on a chain of physiological events. Its comparative simplicity may be misleading, but in the opinion of experienced workers it offers the best indication of adrenocortical responsiveness in man.

Clinicians have regarded changes in the " resting eosinophil level " as a measure of the therapeutic response to ACTH and cortisone treatment. A fall of this level, in patients who suffer from rheumatoid arthritis, is considered a favourable sign. If this reduction is not observed, when clinical improvement is evident, the eosinopenic test is condemned as an unreliable index of adrenocortical stimulation. But the test—as used by us—is confined to the comparison of counts made immediately before and four hours after adrenocortical stimulation, and when applied in this manner the value of the test has not seriously been questioned.

Experimental Procedure.

Collection of samples and counting of eosinophil cells.—Samples of capillary blood were collected at the same time each day, the time being related to the patient's routine and the administration of E.C.T. or insulin treatment. Any change in daily routine was considered in relation to its possible effect on the eosinophil count. Practical details of the technique adopted were based on a preliminary investigation of technical and inherent distribution errors, so that cell counts which did not conform to the expected level of reliability could be discarded.

Blood was collected from the patient's thumb, in two standard pipettes, and eight serial counts by Randolph's technique (1949) were made in a B.S.S. counting chamber, type "A" ruling (Neubauer). From this the mean number of eosinophils per c.mm. of blood was calculated. Although Randolph's stain has proved satisfactory, we have found (as others have done) that its crystallization can be delayed by using a slightly higher dilution than was originally advocated.

The work of earlier observers is difficult to interpret. They did not always relate timing of the counts to the administration of physical treatment. Randolph (1950) has also pointed out that, when modifications of Dunger's eosin acetone diluent are used, it is necessary to fill the counting chamber within three minutes of the collection of each sample, in order to avoid a serious error in the count. This precaution can rarely be observed when samples are collected in the ward and examined in the laboratory. In the absence of these precautions the eosinophil count is not a reliable index of adrenocortical stimulation.

Clinical Investigation.

Investigations were carried out on 72 mental patients (34 males and 38 females), of whom 40 were schizophrenics, 17 were suffering from an affective illness (15 depressives and 2 hypomanics), and 15 neurotic (anxiety, hysterical and obsessive) patients. Four hundred and sixty-four eosinophil counts were made on 68 patients.

Preliminary investigation.—This comprised twenty-one 2-hourly eosinophil counts, between the hours of 8 a.m. and 8 p.m., on 17 patients. Twelve counts, on days on which no physical treatment was given, showed great variability and only minor changes. Rud (1947), whose experience of eosinophil counts is probably unequalled, has noted the same lack of conformity in counts of different subjects. Nine 2-hourly counts, made on patients given E.C.T. at 10 a.m., showed a maximal fall at 2 p.m.—four hours after this treatment.

It was concluded that a comparison of two counts made at 10 a.m., immediately before E.C.T. was administered, and at 2 p.m., would give reliable information on a patient's eosinopenic reaction to a particular treatment.

Eosinophil counts on control days.—The counts of 40 patients on 50 days on which no physical treatment was given showed a tendency to a slight rise in the afternoon count. In 12 cases a more pronounced rise, and in 2 (a schizophrenic and a depressive) a fall greater than 50 per cent. The reason for this unexpected depression of the count is not known. It may be of interest to recall that three patients, not included in the present series, showed a similar fall after inhalation

of a minimal quantity of ether, and in one case after an emotional disturbance. These stresses are easily recognized, others may escape detection.

Effect of E.C.T. on the eosinophil count.—The 2 p.m. count of 37 patients, on 49 days on which E.C.T. was administered, showed in 31 cases (15 schizophrenics, 6 depressives and 10 neurotics) a fall greater than 50 per cent., and an occasional complete disappearance of eosinophil cells. In 12 cases (4 schizophrenics, 6 depressives and 2 neurotics) the afternoon count showed only an inconsiderable fall, in 6 others (1 schizophrenic, 2 depressives, 1 manic and 2 neurotics) an actual rise. An adequate eosinopenic response to E.C.T. was therefore lacking in approximately one-third of the total number of cases. Patients who failed to respond included 6 chronic schizophrenics who were sedated by E.C.T. but not otherwise benefited. Seven other chronic schizophrenics who also derived no benefit from this treatment showed, however, a depression greater than 50 per cent. in their afternoon count. Altschule (1949) has stated that the eosinopenic response is always adequate after a first electroconvulsive treatment, and that it may fail when repeated treatment is given at short intervals. Our results do not support his contention; responses were sometimes inadequate after first, second, third or later convulsions.

Effect of insulin hypoglycaemia on the eosinophil count.—A preliminary investigation was undertaken to determine the effect of insulin hypoglycaemia on the eosinophil count of schizophrenic patients. Fifteen observations were made on 8 patients who received coma doses of soluble insulin at 7 a.m. A sample of capillary blood was collected at the same time for a first eosinophil count. The second count, at 10 a.m. in 11 cases and at 11 a.m. in 4 cases, showed only minor and inconstant changes in all but one case, in which a rise of 45 per cent. was noted. The 2 p.m. count showed, however, in every case a considerable reduction in the number of eosinophil cells, a fall of 62–94 per cent. (mean fall, 74 per cent.) compared with the 10 a.m. count. It was concluded that comparison of 10 a.m. and 2 p.m. counts would give the required information on the patient's eosinopenic response to that treatment.

Twenty-seven of our patients, submitted to daily insulin hypoglycaemia, were investigated on 68 separate occasions. In every case where coma developed a significant fall in the eosinophil count was recorded at 2 p.m., 7 hours after injection of insulin and approximately 4 hours after the onset of coma. Seven patients (5 schizophrenics and 2 neurotics) who received only 10 to 50 units of insulin (mean value 20 units) developed no sopor or coma and only insignificant changes in the afternoon eosinophil count. A rise was present in five cases and an insignificant fall in two others.

Kersley *et al.* (1950) have found a maximal depression of the eosinophil count approximately 7 hours after insulin injection, in patients suffering from rheumatoid arthritis. This observation is in agreement with our findings after injection of greater doses of insulin. Kay and Thorley (1951) observed inconstant changes in eosinophil counts performed on a portion of resting and half-hourly blood samples taken from male schizophrenic patients undergoing insulin treatment. Three-and-a-half hours after injection of 4–24 units they noted a fall greater than 50 per cent. in 8 out of 10 cases, and after injection of 120–280 units a fall greater than 50 per cent. in 5 out of 9 cases. The technique adopted by Kay and Thorley differs in some important respects from that used in the present investigation. It seems probable that these differences would account for the early inconstant changes in the eosinophil count, noted by them 3½ hours after insulin injection. Withdrawal of venous blood at half-hourly intervals must provide additional emotional and physical adrenocortical stimuli which are absent in our cases. We have found, on the other hand, that observation over 6 or 7 hours is necessary to detect the characteristic late depression of the count, following insulin administration.

Hypoglycaemia is marked half-an-hour after injection of insulin. It is unlikely that it provides the direct stimulus for an eosinopenic reaction which is maximal 7 hours later, that is, 4 hours after cerebral changes attended by diminished awareness, sopor or coma. These changes may furnish the stimulus that liberates ACTH, induces an adrenocortical response and the consequent fall in the number of circulating eosinophils. Proof for this supposition is lacking, and it rests insecurely on the time-relation of these reactions. To ascertain whether glucose solution, given at 10.45 a.m. to interrupt coma, was responsible for the late reduction in the eosinophil count, the same quantity of glucose was given at the usual time to 6 patients from whom insulin was withheld. No fall in their 2 p.m. count was

observed, and it was concluded that this quantity of glucose is not the adrenocortical stimulus responsible for delayed eosinopenia.

The "resting-level eosinophil count" shows a gradual rise in many patients treated with insulin. This rise, reported by several observers (Rud, 1947; Sackler *et al.* 1951), has been confirmed by comparison of successive morning counts of a number of our patients. The rise was often considerable, the number of eosinophils being sometimes doubled and trebled during the second and succeeding weeks of treatment. It is not possible to say from our observations whether this rise is related to an eventual clinical improvement, as believed by Rud (1947) and also by Sackler *et al.* (1951).

The following investigations were undertaken to ascertain by indirect evidence whether eosinophil cells, which disappear from the peripheral circulation after E.C.T. or hypoglycaemic coma, are destroyed, or whether they are only temporarily withdrawn and stored in the tissues. A few interesting facts have emerged, but the question has only partly been answered.

(*a*) *Total leucocyte counts* on days when no physical treatment was given showed only minor variations throughout the day, but after E.C.T. a rise in the afternoon count was noted in many cases.

(*b*) *Differential leucocyte counts* showed, in some cases, a relative neutrophilia 4 hours after insulin coma, as compared with the pre-treatment count.

(*c*) *Cooke's neutrophil count* showed a marked shift to the left in the majority of cases examined, the number of immature granulocytes exceeding the accepted "upper normal limit."

(*d*) *Sternal marrow biopsies* were carried out on 6 patients who had previously received 20–60 coma doses of insulin. In 3 cases a slight rise in the number of eosinophil cells above the accepted "upper normal limit" was observed, and in the remaining 3 cases a relative increase in the number of immature eosinophil cells.

It was concluded on the above evidence that some at least of the eosinophil cells, which disappear from the peripheral circulation after adrenocortical stimulation, are destroyed or permanently withdrawn, and that the bone marrow is stimulated to increased activity by insulin hypoglycaemia.

Discussion.

The therapeutic value of E.C.T. and insulin hypoglycaemia in the treatment of mental disease is generally recognized, but the mode of action of these physical remedies is still unknown, and we do not know why E.C.T. is more useful in the treatment of one mental illness and hypoglycaemia in that of another. Physical changes are common in schizophrenia, particularly in catatonia, but they are only striking during active phases of the illness. Relief of a disorder which suggests pituitary-adrenocortical dysfunction directs our attention to the effect of E.C.T. and repeated hypoglycaemia on the activity of the adrenal cortex.

The mental withdrawal of schizophrenic patients is facilitated by a diminution of physical responsiveness, depression of the metabolic rate and a fall in blood-pressure. Pincus *et al.* (1949), Parsons *et al.* (1949) and their associates have noted the inadequate adrenocortical response of schizophrenic patients to psychogenic and various environmental stresses, although their response to stronger stimuli, such as E.C.T., is usually adequate. Early *et al.* (1951) have noted that E.C.T. mobilizes large amounts of ACTH, and that the effect of one E.C.T. may be equivalent to a greater than 50 mgm. dose of ACTH.

The usefulness and limitations of the eosinopenic test, applied to patients undergoing treatment by E.C.T. and insulin, have been discussed, and a series of investigations are reported which prove insulin hypoglycaemia to be a reliable adrenocortical stimulus, and E.C.T. not so constant in its effect. The eosinopenic response is elicited by the liberation of oxycorticosteroids (Thorn *et al.*, 1948), which follows indirect stimulation of the adrenal cortex by E.C.T. and insulin hypoglycaemia. There is, however, no convincing evidence that these steroids, and particularly cortisone, possess therapeutic properties, and many disturbances of mental function have been reported after their administration to patients who suffer from rheumatoid arthritis. In two cases of "recurrent schizophrenia," studied by Rowntree and Kay (1952), a rise in sugar-active cortins was observed

during remissions and an increase in the electrolyte controlling factor at the onset of an attack. The physical signs of these patients were unusual, and in some important respects the converse of those generally encountered, and those observed in our cases. One of Rowntree and Kay's patients showed a rise in pulse rate, blood-pressure and pulse-pressure, flushing, sweating and a rise in temperature at the beginning of an attack (after the first signs of mental change), and a slower pulse and lower blood-pressure during remissions. The other patient showed less consistent clinical and biochemical abnormalities. The interest of a comparison with our cases lies in the demonstration of raised electrolyte controlling activity at the time the blood-pressure is higher, that is to say at the onset of an attack in their two patients, but at the time of a remission in ours.

If " sugar-active " cortins are not the only or main cortical steroids to be concerned in the improvement of the average case of schizophrenia, following adrenocortical stimulation, a positive eosinopenic reaction may only serve as an indication of more general cortical stimulation. Most workers are, however, agreed that retention of sodium and chlorine ions, similar to that induced by desoxycortone, follows the administration of ACTH (Morris, 1951). Bornstein and Gray (1951) also remind us that the so-called, " glycogenic hormones " affect sodium metabolism. A rigid subdivision into glyco- and mineralocorticoids is therefore undesirable, and the effect of ACTH liberation on mineral metabolism will depend on the relative proportion of steroids set free from the adrenal cortex and on their relative " electrolyte regulating " and " sugar-active " properties. The present study has supplied additional evidence of adrenocortical stimulation by two physical methods of treatment. Activation of the adrenal cortex, as revealed by the eosinopenic reaction, may explain the relief of physical disturbances which suggest an adrenocortical deficiency, although other possible and probable effects of these treatments are not excluded.

Summary.

1. Clinical evidence in favour of adrenocortical dysfunction in schizophrenia and tests of adrenocortical activity are briefly reviewed.

2. The value of the eosinopenic test in man is discussed and the reasons for its adoption are stated. The technique adopted is described.

3. Four hundred and sixty-four eosinophil counts were made on 68 schizophrenic, affective and neurotic patients. A greater than 50 per cent. reduction in the total eosinophil count (by Randolph's method), 3–4 hrs. after stimulation, has been accepted as evidence of a satisfactory adrenocortical response.

4. Twenty-one 2-hourly counts, made on no-treatment days on 17 patients, showed only minor inconstant changes; comparison of the 10 a.m. and 2 p.m. counts of 40 patients, on 50 no-treatment days, showed no significant change.

5. A fall greater than 50 per cent. in the eosinophil count of 37 patients was noted, 4 hrs. after E.C.T., on 31 of 49 occasions on which this treatment was administered; no significant change was observed on 12, and a rise on 6 occasions. Depressive and neurotic patients failed to show a satisfactory response in one-half, and schizophrenics in one-third of the cases.

6. A fall greater than 50 per cent. in the eosinophil count of 27 patients was noted 7 hrs. after insulin injection on every one of 61 occasions when coma developed, but not on 7 occasions when only 10–50 units of insulin were given and the patient experienced neither sopor nor coma.

7. A rise in the resting-level eosinophil count after repeated insulin hypoglycaemia treatment, a left shift in the neutrophil count and evidence of bone-marrow activation suggest replacement of eosinophil cells, rather than temporary storage after adrenocortical stimulation.

8. The bearing of these observations on the treatment of schizophrenic patients is discussed.

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