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The Biochemistry of Affective Disorders

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Introduction

The title of this review would be regarded by some psychiatrists as provocative; they would relegate the biochemical concomitants of depression and mania to a secondary position and deny that biochemical changes have any place in the aetiology of these conditions. However, in my view, the weight of evidence, although it is by no means conclusive, suggests that biochemical changes are most important in the aetiology of affective disorders. A biochemical aetiology implies that there are certain biochemical changes in the brain which need to be restored to normal before the patient's clinical condition will improve. This does not deny that psychological and environmental events may precipitate and maintain the biochemical events which in turn lead to the affective disorder. The study of these biochemical events is clearly at too early a stage for speculations about the interrelationship between environmental and endogenous elements to be fruitful; this study must wait until the biochemical aetiology is clearer than at present.

However, it must be admitted that it is paradoxical that a psychiatric syndrome such as a depressive illness could be considered biochemical in origin. After all, depressive reactions are a part of everyday life, and it has been argued that a depressive illness differs only by its severity from these common experiences. One of the most cogent reasons for believing that there is a biochemical basis for depression or mania is the astonishing success of physical methods of treatment of these conditions. Perhaps one of the most remarkable events in medical treatment is the transformation of a deeply depressed, retarded, deluded, anorexic patient to normality by a small number of electrically induced convulsions. Although so successful, this treatment has thrown little light on the aetiology of depression, because in spite of very many investigations, its mode of action is quite unknown (101). More recently, antidepressive drugs such as the monoamine oxidase inhibitors and imipramine have come into general use, and the study of their mode of action, which is becoming more and more clearly understood, has led to many fruitful investigations into the metabolic changes in depression and in mania. Indeed, it might be added here, their very success has added to the difficulties of investigating the biochemistry of these conditions, as it is becoming increasingly difficult to find patients who have not been already treated with these drugs. This is of considerable importance since it is likely that the antidepressive drugs exert their therapeutic effect by altering the biochemical abnormalities that are responsible for the illness. This practical difficulty now facing investigators of depression and mania (where treatment is usually even more urgent than in depression) must be successfully overcome, for otherwise it will be impossible to differentiate between the biochemical effects of the illness and of the therapy.

Most of the studies that will be reviewed deal with acute changes taking place during the illness. The equally interesting and important question of constitutional susceptibility, stated in biochemical terms, has hardly been investigated, although studies in body-build and body-composition suggest that this may exist in the form of abnormal endocrine development during puberty, particularly lack of androgens (155, 170, 156, 46). The biochemical changes during the illness will also, sooner or later, have to be linked with the known epidemiological data. For example, why is depression predominantly an illness of the middle-aged or elderly, commoner in women than men, with a higher incidence in late spring or early summer (135)?

In this review, the controversy regarding the

classification of affective disorders (e.g. 136, 37, 151) need not concern us, since most investigators of the biochemistry of these conditions have not, with few exceptions (e.g. 6, 31, 177, 26), differentiated between any sub-groups; it can probably be assumed that most patients in a metabolic study are suffering from severe depression which most clinicians would classify as "endogenous" or "psychotic". However, as it is probable that depression and mania are not homogeneous conditions, it would be valuable if investigators gave more clinical information than they usually do.

There is one very important limitation imposed on the investigator of the biochemistry of psychiatric disorders in man. It is virtually impossible to examine the organ that is most directly concerned with the illness—the brain—although the problem is being attacked by studying the brains of subjects who have committed suicide while depressed (169). Most investigators have to rely on examination of body fluids such as the blood or urine. Changes in body metabolism as a whole may be reflected in changes in the blood or urine, but there is no certainty that changes of metabolism in the brain, with its blood-brain barrier, will be reflected in changes detectable in blood or urine. It is possible that abnormalities in the central nervous system would be more readily detectable in the cerebrospinal fluid or by cerebral arterio-venous techniques, but it is difficult to apply these methods of examination to patients suffering from an illness which can usually be readily and promptly treated. In other ways affective disorders lend themselves readily to investigation. It is possible to examine a group of patients suffering from severe depression initially, at the height of their illness, and then again one or two months later when they have recovered. It is therefore possible to use each patient as his own control. A small number of patients relapse rapidly after treatment, and it is possible to use this group as a control group for the effects of being in hospital and of having received treatment.

Although it is perhaps debatable whether most cases of affective disorder are produced biochemically, it should be pointed out that there are certain cases of affective disorder that are almost certainly of biochemical origin. These are cases produced by drugs and by certain illnesses. This aspect will not be reviewed here, except when it has relevance to the more everyday syndromes of depression and mania; but it is quite well established that, just to give two examples, reserpine or high doses of ACTH or cortisol (140) can produce a state very similar to that of "endogenous" depression. Again, there is an extensive literature on the affective disturbances attending very many physical illnesses, such as thyrotoxicosis, Cushing's syndrome, hypocalcaemia and following influenza and infective hepatitis.

This review will not attempt to be exhaustive, and the selection of material is inevitably influenced by the reviewer's own interests and prejudices. The review will be concerned mostly with work reported in the last ten years. There are reviews by Bellak (14) and Sperry (176) dealing with earlier work on the subject.

Monoamines

Physiology, Biosynthesis and Metabolism

A good deal of interest and speculation has been directed to the possible role of brain monoamines in the causation and treatment of affective disorders. This has been largely a result of the introduction of antidepressive drugs which apparently exert their therapeutic effect by their action on the brain monoamines. The amines on which most attention has been focused are the catecholamines, especially dopamine and noradrenaline, and 5-hydroxytryptamine (5HT), also known as serotonin.

The structure and a simplified account of the biosynthesis and metabolism of these monoamines are shown in Figs. 1 and 2. There are numerous reviews and papers dealing with these monoamines, including those by Kety (111); Himwich and Himwich (99), and Crossland (60). These monoamines are not distributed equally throughout the central nervous system but are concentrated in certain areas. For example, the highest concentration of dopamine is found in the corpus striatum, and only low concentrations are found elsewhere. Noradrenaline and 5HT have generally the same distribu-

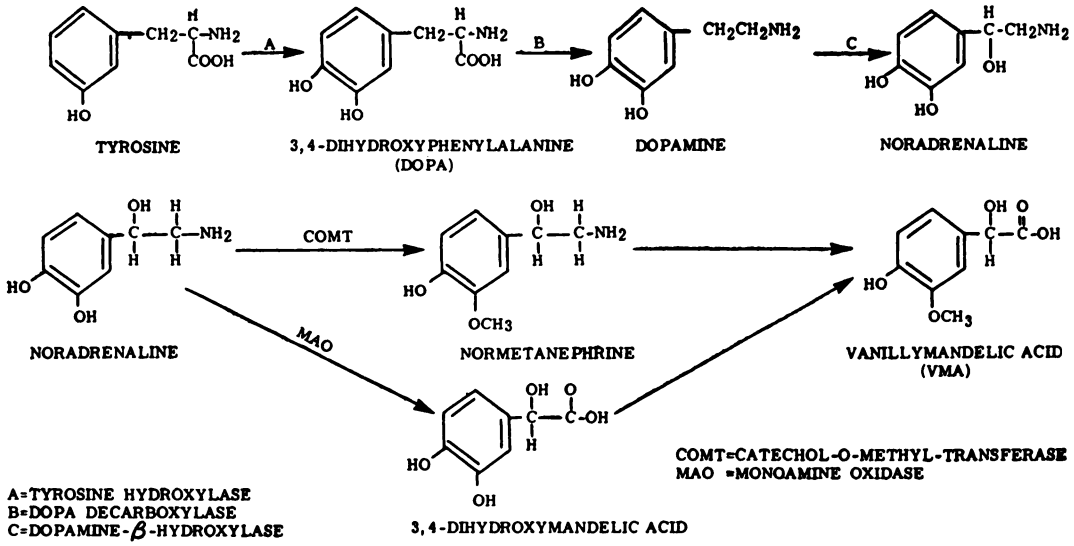

FIG. 1.—Biosynthesis and metabolism of catecholamines.

tion in the brain, and their highest concentrations are found in the hypothalamus. However, the limbic system contains high concentrations of 5HT but little noradrenaline. Adrenaline is found only in low concentrations in the brain and probably has little functional importance.

There is now good evidence that the monoamines are stored in two compartments or pools in nerve cells (121). Although the evidence for this is mainly derived from experiments on the sympathetic nervous system, it is probable that monoamines are stored in a similar way in the central nervous system. Again, though much of this work has been carried out on the catecholamines, it is likely that similar storage mechanisms occur with the other monoamines. These stores are illustrated in Fig. 3. One pool, the deep monoamine pool, is where the newly synthetized monoamine is stored and it is situated near the mitochondria. The mitochondria of numerous tissues of the body contain monoamine oxidase (MAO) which catalyses oxidative deamination of noradrenaline, 5-hydroxytryptamine and other monoamines. The enzyme is inhibited by a class of antidepressive drugs known as monoamine oxidase inhibitors

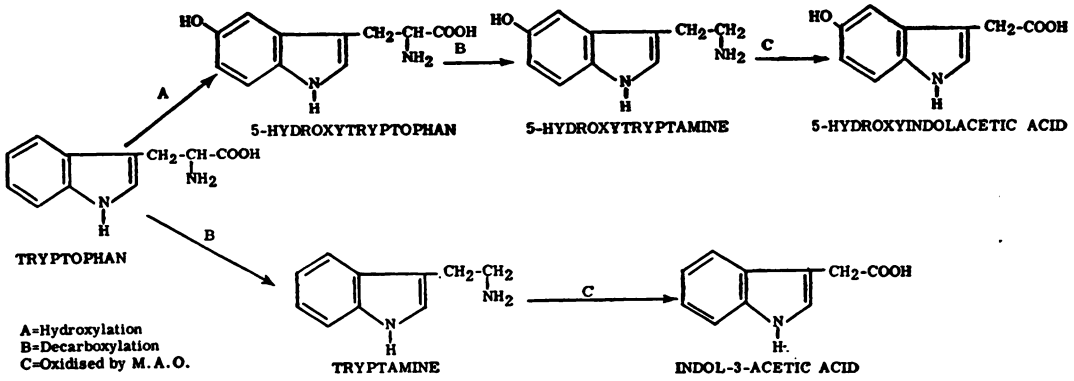

FIG. 2.—Biosynthesis and metabolism of indol amines.

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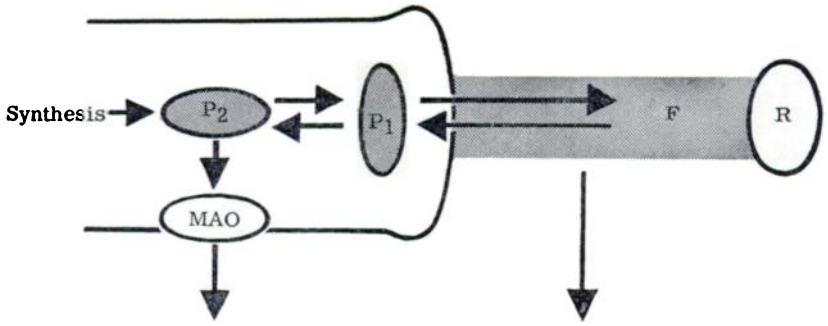

Simplified model of sympathetic nerve-ending, showing the various monoamine pools (modified from Pletscher 1965).

P_1 = readily available pool.
P_2 = deeply bound pool.
F = free monoamines.
R = adrenergic receptor.
M.A.O. = monoamine oxidase.

FIG. 3.—Simplified model of monoamine pools (after Pare, 1965).

(MAOI). Another pool, the superficial monoamine pool, contains monoamines which are released by nervous stimulation and so can exert their physiological effects on the nerve endings. The stored monoamines in their storage organelles are functionally inactive, and only the free monoamine can exert a physiological effect. Free catecholamines are inactivated in three ways: most (over 90 per cent.) of the monoamine released by nervous stimulation is inactivated by being almost immediately rebound in the superficial monoamine pool, and the remainder is metabolized to vanillylmandelic acid via normetanephrine by means of catechol-O-methyl transferase. Monoamines released from the deep pool, either physiologically or by reserpine, are oxidized by monoamine oxidase in the mitochondria via 3, 4-dihydroxymandelic acid which is then methylated to vanillylmandelic acid.

Effect of Antidepressive Drugs on Monoamines

A great stimulus to the study of the role of monoamine metabolism in affective disorders was the discovery of the antidepressive activity of the monoamine oxidase inhibitor (MAOI) iproniazid (129). This and other MAOI increase the levels of brain monoamines by inhibiting their metabolism by MAO. In animals given large doses inhibition occurs in a few hours (149), but in man, where small doses are administered, it takes much longer to act. Pare (146) measured brain 5HT in patients who had been given MAOI for varying periods before they died, and found post mortem that it took 2 to 3 weeks of administration of the drug before the levels of brain 5HT began to rise. This period corresponds to the time taken for MAOI to exert their maximum antidepressive effect.

The increase in brain 5HT and catecholamines that occurs with the administration of a MAOI may be considerably enhanced by feeding the animal large doses of the aminoacid which is the precursor of the monoamine. For example, administering a MAOI together with tryptophan will result in a very considerable increase in the levels of brain 5HT and tryptamine in the rat (97). Presumably the same process occurs in man, but, as we shall see, it is not always possible to extrapolate findings on small laboratory animals to man. MAOI, therefore, as well as providing a very useful means of treating depression, provides a means of manipulating brain monoamines in man, especially when used with 3, 4-dihydroxy-

phenylalanine (DOPA) or tryptophan which are the precursors of the catecholamines and 5-hydroxytryptamine respectively. Indeed, the combination of MAOI and tyramine has been found to have considerable dangers because of the marked pressor action of tyramine. Consequently there have been hypertensive crises and deaths in patients treated with MAOI who have eaten foods rich in tyramine, such as certain cheeses (16). Although the therapeutic efficiency of MAOI can be clearly related to the inhibitory action they have on the destruction of brain monoamines, other classes of drugs, typified by imipramine (122) which is also a very useful antidepressive drug, act in a different manner. Imipramine does not appear to alter the concentration in the brain of 5HT and other monoamines, and at first it presented difficulties for hypothesis of the aetiology of depression based on a supposed deficiency of monoamines. However, imipramine has been shown to potentiate the peripheral and central actions of noradrenaline, and there is evidence that the drug interferes with the cellular binding and permeability of the cell to noradrenaline and thus serves to increase the amount of the free, and presumably physiologically active, amine present (171, 82, 95). As well as these effects on catecholamines, drugs of the same type have been shown to inhibit the uptake by tissues of 5HT (11). Ashcroft, Eccleston, Knight, McDougall and Waddell (8) showed that amitriptyline, another drug of this type, increases the proportion of infused tryptamine that is excreted in man, which suggests that the drug blocks the tissue uptake of the amine. It is of relevance in this connection that imipramine is reported to potentiate the actions of amphetamine, which in turn is believed to act by releasing noradrenaline in the brain (162). It will be seen that, although the mode of action of the MAOI and imipramine groups of drugs is different, they have the property in common of increasing the amount of physiologically active amine. The former by inhibiting its metabolism, the latter by hindering its inactivation by cellular rebinding. Combined it would be supposed these drugs are a formidable combination, and indeed the combination has proved to be very toxic in large doses (102).

A third group of drugs that have stimulated interest in the role of monoamines in depression is exemplified by reserpine, which depletes both brain catecholamines and 5HT (23). It is now well documented that a certain proportion of patients receiving this drug for hypertension will develop a depressive illness not distinguishable from a severe endogenous depression (2, 143, 107, 30, 125). Bunney and Davis (30) reviewed the literature on the relationship between reserpine therapy and depression, which is of great importance because of the light it can throw on the role of monoamines in this condition. Most series report that some 15 per cent. of hypertensive patients treated with reserpine seem to develop a depressive illness. The most convincing series was presented by Lemieux and his co-workers (125) who compared hypertensive patients treated with reserpine with those treated by other means, and found that 30 out of 195 of the former developed depression compared with none in the latter group. Nineteen improved rapidly after being taken off the drug, but 10 were admitted to hospital and five of these had to be treated with electroconvulsive therapy, which proved successful. The risk of depression increases with the dose of reserpine. This work does not prove that monoamines are involved in most cases of depression, but taken in conjunction with the antidepressive actions of MAOI and imipramine it does suggest very strongly that monoamines are of great importance in determining mood in man. A drug with a similar action to reserpine —tetrabenazine—has also been shown to produce depression (127).

A marked sedative action is also shown to occur in animals after the administration of reserpine, but the way in which this effect is brought about is still disputed. Reserpine will deplete both catecholamines and 5HT in the brain (24), and it is possible that sedation is associated with loss of one or all of these amines. The fact that the administration of DOPA (the precursor of dopamine and noradrenaline) reverses the depression induced by reserpine would suggest that the depletion of catecholamines is of primary importance here (36). However, Brodie and his associates have argued against this and would implicate loss of 5HT

in this condition (23, 22). Brodie *et al.* (22) reported that when the brain catecholamines and brain 5HT are reduced to 55 per cent. of normal by reserpine there is marked sedation. However, if catecholamines alone are reduced to as much as 20 per cent. of normal, as long as brain 5HT is maintained there is no sedation. Brodie *et al.* go on to present evidence that the sedative effect is related to rate of 5HT released from its stores and that this rate is markedly affected by reserpine. In man, the position is far from clear; Degkwitz, Frowein, Kulenkampff and Mohs (64) report that the psychological effects are reversed by DOPA, but we have observed recovery from two cases of severe depression, apparently produced by reserpine, following the administration of monoamine oxidase inhibitors and tryptophan. In these sporadic cases, however, it is never possible to be sure either of the aetiology of the depression or the therapy responsible for recovery. It should be mentioned here that one of the effects of electrically induced convulsions in animals has been to increase the blood-brain barrier to noradrenaline (159).

It is clear that these drugs offer means of manipulating brain monoamines and that they can be of considerable use in evaluating the role of the monoamines in maintaining normal mood or causing mania or depression. The prospects are that these studies will be more sharply defined as more specific pharmacological tools become available. For example, alpha-methyl-tyrosine is a specific inhibitor of tyrosine hydroxylase and will deplete brain catecholamines but leave brain 5HT intact. It should therefore be possible to directly test the hypothesis, for example, that reduced brain noradrenaline is responsible for depression. So far the evidence in a small series of 20 patients is that alpha-methyl-tyrosine produces a transient and mild sedation (172). There has been little to suggest a relationship between mania and reserpine, and it could be postulated that in mania the levels of brain monoamines are increased. However, this supposition does not receive any support from the observations of Mosher, Klerman and Greanly (142) that alpha-methyl-dopa, which lowers brain catecholamine concentrations, has no clinical effect in manic patients.

Therapeutic Actions of Monoamines

Initially, therefore, cerebral monoamines were incriminated aetiologically in depressive illness because of the therapeutic success of MAOI and the depressive side-effects of reserpine. The antidepressive actions of imipramine are also compatible with this notion. However, the actions of these drugs may merely represent therapeutic manœuvres which in themselves may be quite unrelated to aetiological factors underlying the majority of cases of depression. Moreover they throw no light on which monoamines are involved.

Some recent reviews put forward the view that the catecholamines rather than 5HT may be of primary importance (112, 30, 163); at the moment evidence for cerebral deficiency of either catecholamines or indoleamines is scanty and circumstantial only, but work in our laboratory is now in progress examining the brain monoamine levels in patients who have committed suicide (169).

One indirect method of trying to isolate the monoamines involved in depression is to test the therapeutic effect of administering MAOI together with a precursor of one of the monoamines—either tryptophan, from which is derived 5-hydroxytryptamine and tryptamine, or DOPA, which forms dopamine and noradrenaline. It is necessary to give these precursors, and not the monoamines, because the latter do not readily enter the central nervous system across the blood-brain barrier. There is a good deal of evidence to suggest that large doses of tryptophan (for example, 25 mg. of L-tryptophan per kilogram of the patient's body weight) given together with a monoamine oxidase inhibitor can elevate mood both in mentally normal subjects (174, 144) and in patients suffering from schizophrenia (150, 124). Encouraged by these results on normal subjects and schizophrenic patients, Coppen, Shaw and Farrell (54) carried out a carefully controlled trial in which they compared the antidepressive action of MAOI together with tryprophan with that of MAOI alone. The results are shown in Fig. 4. Tryptophan was administered for a week (during rating C and D in the Figure) and it will be seen that the ratings change (depression decreases) more in

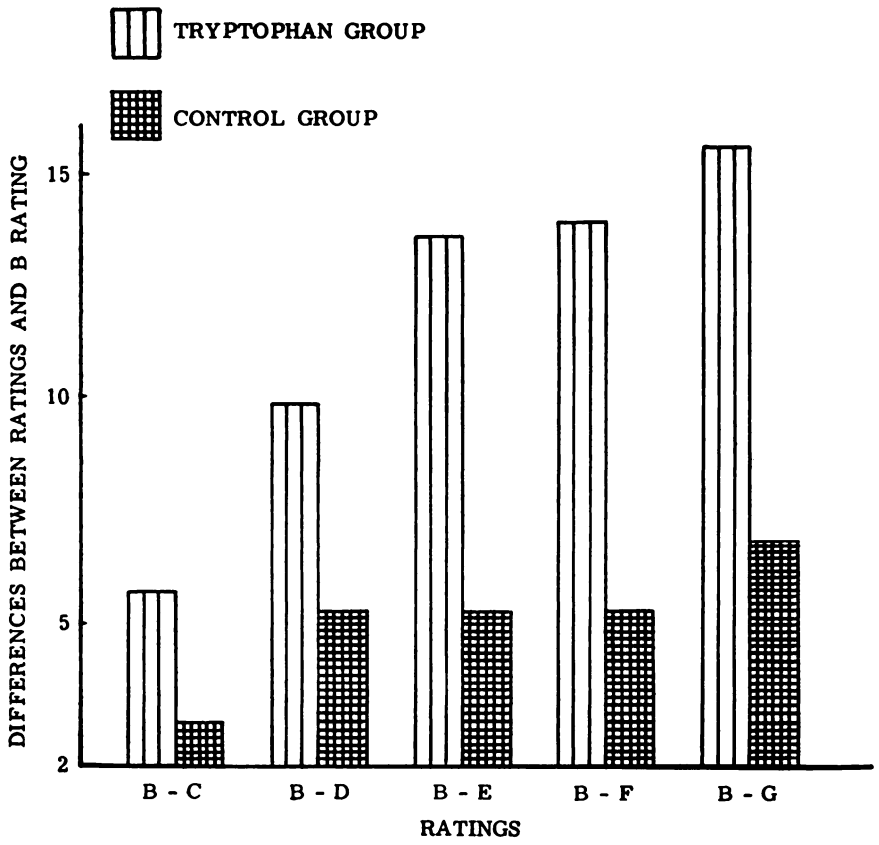

FIG. 4.—Potentiation of the antidepressive effect of a monoamine oxidase inhibitor by tryptophan. Differences between baseline rating B and successive ratings performed twice weekly.

the patients that received the tryptophan together with MAOI than in the group that received MAOI alone. These findings have been confirmed by Pare (146). A similar investigation was carried out combining MAOI and 5-hydroxytryptophan, which crosses the blood-brain barrier and which is the immediate precursor of 5HT. However, in spite of initially very encouraging observations by Kline and Sacks (119), these investigators were not able to confirm their work in a subsequent and more carefully controlled study (120). A further investigation (57) showed that a combination of tryptamine and monoamine oxidase inhibitor—which together act as a most powerful antagonist of reserpine-induced depression in animals (180)—is without any apparent effect in man, even when the tryptamine is administered intravenously in doses of up to 50 mg. This is all the more puzzling because there is evidence that tryptamine is one of the most potent exciting monoamines in small laboratory animals (65). It is a reminder that animal work cannot always be extrapolated directly to human subjects.

These experiments suggest that 5-hydroxytryptamine may be an important monoamine in reducing depression, although it should be emphasized that not all patients fully remit when treated by MAOI and tryptophan and that the treatment is not so effective as E.C.T. What is the role of the catecholamines? A similar investigation has been carried out with DOPA and MAOI, which, as we have seen, have been

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used to reverse reserpine-induced depression in animals (36) and man (64). Klerman, Schildkraut, Hasenbush, Greenblatt and Friend (118) treated a series of depressed patients with DOPA both with and without MAOI and failed to detect any therapeutic effect whatsoever. This seems to argue very much against the importance of catecholamines in the aetiology of depression, although it is possible that insufficient DOPA was administered to increase brain catecholamines significantly. As it has been found that 5-hydroxytryptophan and tryptamine are less active than tryptophan in man, it is possible that in man only aminoacids such as tryptophan and tyrosine are transported in sufficient quantities into the appropriate sites in the brain where they can be used to form amines. Although we have not carried out a systematic investigation on the therapeutic action of tyrosine and MAOI, a small pilot study showed little effect. However, because of the importance of the issue a systematic study is required.

Catecholamines and Depression

Investigations on the metabolism of monoamines in patients suffering from depression are still in an early stage and must perforce be mainly confined to studies of the body outside the brain. However, it is not unlikely that factors which affect the body as a whole may also affect the brain. Investigations on the urinary excretion of noradrenaline and adrenaline are somewhat inconclusive (179, 61), but the most extensive investigation, by Bergsman (15), reported significant increases in the urinary excretion of both adrenaline and noradrenaline in mania, although the urinary excretion of these amines in depression was normal except after insulin stress, when it tended to be lower than normal. Rosenblatt and Chanley (158) reported interesting changes in the metabolism of noradrenaline in depression. They employed a test in which they infused radioactive noradrenaline into the subject and measured the urinary excretion of various metabolites of the amine. These they divided into metabolites retaining the amine group (mainly normetanephrine) and oxidized metabolites (mainly vanillylmandelic acid). At a period 12 to 24 hours after commencing the infusion the ratio between these two groups of urinary metabolites was stable, and Rosenblatt and Chanley argued that at this stage the infused noradrenaline had equilibrated with the various compartments within the body and that the metabolism of the labelled noradrenaline represented the metabolism of endogenously released noradrenaline. They investigated 20 patients and found raised ratios of amine metabolites to oxidized metabolites in 8 depressed patients diagnosed as manic-depressive psychosis; the ratio in reactive depression was the same as in mentally normal subjects. After treatment with E.C.T., Rosenblatt and Chanley found that the ratio returned to normal values in the manic-depressive patients. The numbers of patients investigated remains small and the interpretation of the results is difficult, but the results indicate that there may be important changes in the metabolism of noradrenaline in certain cases of depression.

Indoleamines and Depression

We turn now to the metabolism of the indoleamines in depression. In our laboratory we have examined the urinary excretion of tryptamine and its metabolite indoleacetic acid in 13 patients before and after recovery from a depressive illness. Urinary tryptamine is probably derived from the decarboxylation of tryptophan in the kidney and is not derived to any significant extent from the gut. Feeding patients with tryptamine, or even injecting intravenously large doses of tryptamine in patients treated with a MAOI, only increases its urinary excretion by a fraction of the injected dose (57). Sterilizing the gut with neomycin does not alter the excretion of tryptamine (Coppen and Shaw, unpublished observations). In this sort of investigation it is necessary to standardize and control various important matters such as diet (especially protein), urinary volume and urinary pH, which can all affect the urinary excretion of tryptamine. Urinary pH is especially important as the urinary excretion of compounds like amines decreases greatly as the pH becomes alkaline (13). We also measured the urinary excretion of tryptamine and indole-

acetic acid after loading the patients with a large dose of L-tryptophan (50 mg./kg. body weight). The results were quite striking and highly significant statistically. Before treatment, when the patients were severely depressed, they excreted, on average, 39 μg. per 24 hours; after treatment and recovery the average excretion was 67 μg., which is about the average for normal subjects found with the method used. The corresponding figures for the load test were 54 μg. per 24 hours before recovery and 118 μg. afterwards. Therefore there seems unequivocal evidence of a change in tryptophan metabolism in depression at least as far as the kidney is concerned. The urinary excretion of indoleacetic acid, which, unlike tryptamine, is partly derived from the gut (185) was unchanged.

These results are in keeping with an earlier study by Rodnight (157) who investigated the urinary excretion of tryptamine and 5HT in normal subjects and in schizophrenic and depressed patients. The diet, urinary volume and pH were not controlled, but the results were very similar to ours in that the urinary excretion of tryptamine and 5HT were significantly decreased in patients suffering from depression compared to normal subjects and to schizophrenic patients. We are also studying the urinary excretion of tryptamine in a small series of patients suffering from mania. From the data on the first ten patients it is clear that the results are not so homogeneous as in depression. About half the patients have normal or raised excretion of tryptamine and half have substantially decreased rates, similar to those of the depressed patients.

There is one report dealing with 5-hydroxyindoles within the central nervous system. Ashcroft and Sharman (9) compared the concentrations of 5-hydroxyindoles in the cerebrospinal fluid of 10 patients undergoing brain encephalography for diagnostic purposes with a group of 9 patients suffering from a depressive psychosis. The former group had significantly higher concentrations (mean 32·2 ng./ml.) than the latter group (mean 13·2 ng./ml.). The authors give no details of treatment of the depressive group. A second report by Fotherby, Ashcroft, Affleck and Forrest (80) indicated however, that there was no difference between the concentration of 5-hydroxyindoles in the cerebrospinal fluid of depressed and schizophrenic patients. Unfortunately for the interpretation of these results, both groups were being treated with phenothiazines, and it is not clear what effect these drugs would have on the concentration of 5-hydroxyindoles in cerebrospinal fluid.

Before considering the implication of these findings I should like to present two further investigations. Feldstein, Hoagland, Wong, Oktem and Freeman (74) investigated monoamine oxidase activity in patients suffering from depression by administering radioactive 5HT orally to 22 depressed patients and 22 normal subjects. Feldstein *et al.* found that the recovery of radioactive 5-hydroxyindoleacetic acid (to which 5HT is metabolized), calculated as the proportion of the radioactivity administered, showed no difference between normal and depressed subjects. They concluded from this work that monoamine oxidase is normal in depression.

Another investigation, from our laboratory, throws some light on another link in the production of amines—the process of decarboxylation. We measured this by injecting intravenously a small amount of 5-hydroxytryptophan labelled with radio-active carbon (^{14}C) in the carboxyl group and estimating the rate of expiration of radioactive carbon dioxide. We have performed this test on 10 patients, and although the initial results indicated that the rate of decarboxylation was slowed in depression (55) patients tested subsequently showed no change (53). The test needs to be performed on larger groups, but our view at the moment is that the decarboxylation of 5-hydroxytryptophan is normal in the majority of depressed patients.

Conclusions about Monoamines

What are the implications of this work on the indoleamines? It should be emphasized that our information is at the moment derived from studies on urinary metabolites and that these mainly reflect kidney metabolism. The kidney may or may not be a representative organ, but the substantial changes of tryptamine excretion in depression, taken into consideration with the studies on drugs reviewed earlier, suggests that

there may be parallel changes in the monoamines of the brain. If we accept that there is some disturbance in amine metabolism, where does it lie? The work of Feldstein *et al.* suggests that monoamine oxidase activity is normal, and the work on 5-hydroxytryptophan decarboxylation indicates that the abnormality does not lie there, in the majority of cases at any rate. However, at the moment we have no evidence concerning the decarboxylation of tryptophan or its transport into cells and across the blood-brain barrier. There is no direct evidence on this latter point at all, although studies on the transfer rate of radioactive sodium from blood to cerebrospinal fluid indicate that this is considerably slowed in depression (43).

Granted that there are changes in tryptophan metabolism, what is the underlying cause? Can these changes be linked with other biochemical abnormalities that have been found in affective disorders? Tryptophan metabolism may be considerably altered by hormones. Cortisol, for example, can induce tryptophan pyrrolase (161) and thus divert tryptophan metabolism away from the indole-amine pathways (132). However, the picture is complicated because cortisol can increase and thyroxine decrease hepatic decarboxylation of aromatic amino acids (62). There is some evidence, therefore, that hormonal changes can alter amine metabolism, but it must be confessed that the *in vivo* study of such changes is in a rudimentary state. We have started to study the effects of hormones such as cortisol, triiodothyronine and chorionic gonadotrophin, but these hormones produce no significant alteration in the excretion of tryptamine (Coppen and Shaw, 1966; unpublished observations). Another group of biochemical changes that I shall describe in this review are changes in electrolytes, and, as we shall see, these indicate an increase in intracellular sodium and decrease in intracellular potassium. These changes could have a considerable effect on intracellular metabolism. Intracellular potassium is known to be essential for many enzymatic processes within the cell (see in review by Kernan (109)), and it is possible that low intracellular potassium may, for example, reduce the rate of formation of protein (105). A direct effect of potassium deficiency on protein synthesis has been demonstrated by Lubin and Ennis (130) in mutant strains of E. coli. Conn (41) has reported evidence that low intracellular potassium may reduce the production of insulin and be associated with an impaired glucose tolerance curve. Changes in electrolyte distribution also could have important metabolic consequences for the transport of amino acids into cells (38). Of particular interest is the work of Christensen, Inui, Wheeler and Eavenson (39) and Vidaver (183) which indicates that the sodium gradient between cells and their surrounding medium is one of the important determinants of the rate of transport of certain amino acids in some cells. As we have seen, one explanation of the amine abnormalities in depression could be an abnormality in the transport of tryptophan. Whether there is any slowing in tryptophan transport remains to be seen, but these speculations show how the electrolyte and hormonal changes in depression could also alter amino acid metabolism and the production of these important monoamines. Our study of this question is still at an early stage; only a small number of biochemical pathways have been studied and it is probable that changes in metabolism are not confined to just one area; however, the results so far are encouraging enough to warrant much greater efforts to study amine metabolism in affective disorders and also physiological variables that can alter it in man.

Studies on Electrolytes

Physiological Importance of Electrolytes

The study of water and electrolytes in affective disorders goes back at least half a century (3). Only a small proportion of depressed patients are obviously dehydrated, and it is not clear why in the first place so much attention was paid to the study of electrolytes in those disorders. Clinical research is the art of the practical, and there is no doubt that many investigations have been stimulated by the development of simple and accurate methods of estimating sodium and potassium and other electrolytes by flame photometry, and by the increasing availability of radioactive isotopes of these ions. The development of isotope dilution

techniques now enables studies to be made on the distribution of electrolytes between cells and their surrounding fluid in patients. By distribution I mean an estimation of the relative masses and concentrations of the electrolytes in the cells and in the extracellular fluid. The distribution of these electrolytes has profound biological importance: for example, the resting potential of neurones and other excitable cells depends on the ratio of the concentration of potassium inside and outside the cell. The action potential is dependent on the ratio of the concentrations of intracellular to extracellular sodium. The cell membrane is freely permeable to potassium and chloride, but is less permeable to sodium, and there is active transport of sodium which keeps the concentration of sodium within the cell at about 1/10th of the concentration of sodium in the extracellular space. Because of this uneven distribution of sodium and the presence within the cell of non-permeating anions, potassium and chloride are also unevenly divided between the cell and its surrounding fluid; potassium has a very high intracellular concentration and chloride a low intracellular concentration compared to their concentrations in the extracellular space. Other important ions that have not been studied so intensively as sodium and potassium are calcium and magnesium. Calcium and magnesium have mutually antagonistic effects centrally and peripherally, and calcium has been used to counteract the anaesthesia induced by intravenous magnesium sulphate. These ions also have considerable effects on neuro-muscular transmission. For example, the acetyl-choline released from the neuromuscular junction is decreased when the plasma concentration of magnesium is increased and the concentration of calcium is decreased (104). Calcium and magnesium ions may also stabilize all membranes, perhaps in a manner similar to the antidepressant drug imipramine (1). However, clinical investigations of these ions are sparse. The techniques available for studying them are more complicated than for sodium or potassium, as it is the ionized form that must be studied and presumably it is this form that is physiologically active. Again, although isotopes of calcium and magnesium are available, the dynamics of their distribution is complex, as a considerable proportion of exchangeable magnesium and calcium is in bone.

Early Studies

The first thorough study of water and electrolyte metabolism in mental illness was made by the Norwegian investigator Gjessing (89) in his classic studies on periodic catatonia. His painstaking longitudinal studies on a small number of patients are a model for all investigators on the metabolic aspects of mental illness. The initial reports on affective disorders were on patients with a rapidly fluctuating mental state, in which the patient swings within a few days or weeks from periods of depression to normality or mania. Although these patients are very uncommon and perhaps are not at all characteristic of affective disorders in general, they are very convenient for metabolic balance studies: the subject has been well reviewed by Gibbons (84).

Klein and Nunn (116) reported their findings in a male patient who regularly had five days of depression followed by two days of mania. When depressed he retained water and sodium, which he lost during the two days of mania. The output of potassium, ammonia, calcium, phosphate and nitrogen did not vary with mood. Other changes in water and sodium excretion have been reported by Crammer (59), Klein (114) and Ström-Olsen and Weil-Malherbe (179), in which all observed that fluctuations in clinical state were apparently associated with changes in electrolyte and water balance, but no consistent pattern was associated with particular mental states in different patients. However, these cases, although illuminating, are very uncommon, and it is uncertain what relationship they bear to the more usual type of affective disorder which lasts for weeks or months.

Russell (160) studied water, sodium and potassium balance in 15 depressed patients before and during recovery from depression. The patients, of whom 11 recovered or were considerably improved during the study, were on a constant intake of sodium and potassium, and the urinary losses of these electrolytes were estimated daily for period of up to 5 weeks while they were treated by E.C.T. The results showed

there was no significant alteration in the balance of water, potassium and sodium as a depressed patient recovered from his illness. The only significant finding was a transient retention of sodium and water on the day that electroconvulsive therapy was administered. These transient changes, however, occurred even after patients were subjected only to the procedures preliminary to E.C.T., e.g. when they were given atropine and intravenous barbiturate as an anaesthetic but were not given the shock and convulsion. It is probable, therefore, that the sodium and water retention were related to the emotional reaction to E.C.T. rather than the convulsion itself.

Isotope Dilution Techniques

The balance technique has several limitations in the study of mentally ill patients. To carry out a long-term balance study over weeks in a co-operative mentally normal patient is a matter of considerable difficulty; to do so in mentally ill patients makes very great demands both on the patients and the medical and nursing staff, and inevitably there is bound to be considerable selection in the choice of patients investigated. Another limitation of the balance study is that it can throw no light on the distribution of water and electrolytes between the cells and the extracellular fluid. However, the availability of radioactive isotopes of sodium, potassium and bromine and of tritiated water now enables this to be carried out in man. For a fuller review of this work see Coppen (44).

Body sodium can be measured by means of an isotope dilution technique using the radioactive isotopes of sodium ^{24}Na, which has the relatively short half-life of 15 hours, or ^{22}Na, which has a half-life of 2·6 years. Using this technique (58, 51), it is possible to measure exchangeable sodium, that is the mass of body sodium with which the isotope mixes or "exchanges" in a given time. Usually the stated time is twenty-four hours, and the twenty-four-hour exchangeable sodium contains the bulk of body sodium except for some of the sodium in bone which does not exchange completely in this time.

The first to apply the isotope dilution technique to measure exchangeable sodium and potassium in depression was Gibbons (83). His investigation was prompted by the report by Schottstaedt, Grace and Wolff (164) that periods of depression in normal people were accompanied by a decreased urinary excretion of sodium. Gibbons examined the twenty-four hour exchangeable sodium and potassium in a group of 24 adult patients suffering from severe depression. Estimations were carried out just after admission and again several weeks later when 16 of the patients had recovered. Eight of the patients who had failed to respond to treatment were also retested. Gibbons found that in the patients who recovered the twenty-four hour exchangeable sodium decreased by about ten per cent.; the patients who were not improved showed no significant alteration in exchangeable sodium. Alterations in diet did not appear to produce these results; patients suffering from malnutrition were not included in the series, and ten of the patients, who were kept on a constant intake of sodium and potassium for balance studies, showed the same changes as the rest of the patients. Exchangeable potassium showed no significant alteration with recovery.

These findings are in apparent contradiction to the findings of Russell, whose balance studies revealed no change in sodium balance during recovery from depression. However, it is possible that the difference between the two sets of results could be explained by postulating that there is a change in the distribution of sodium in depression so that sodium which normally is not exchangeable is included in the twenty-four hour exchangeable sodium during the depressed phase.

Distribution of Sodium and Potassium in Depression

We therefore decided to study exchangeable sodium and potassium in depression more fully (58). Initially we studied exchangeable sodium by means of a technique using ^{22}Na. This isotope, when used with a body counter, enables daily estimations of exchangeable sodium to be made over a period of several weeks and combines the advantages of a balance technique with those of exchangeable isotope methods. We tested 12 patients during recovery from depression and found, in contrast to the report of Gibbons, no change in exchangeable sodium during this time.

At this stage we became interested in the more important question of electrolyte distribution between the cells and extracellular fluid, and we therefore decided to investigate this distribution by utilizing the isotope dilution techniques. Total body water was estimated by tritiated water, and extracellular water was measured by ^{82}Br. Total body potassium was measured by estimating the naturally occurring isotope of potassium ^{40}K. Potassium normally contains 0·012 per cent. of this isotope, and radioactivity due to ^{40}K can be determined by means of a sensitive body counter suitably calibrated (51).

I shall describe first the changes found in extracellular and intracellular water in depression. Altschule and Tillotson (4), using the thiocyanate method for measuring extracellular space, found a significant increase in extracellular space on recovery from depression. Dawson, Hullin and Crocket (63) found a reduction compared to their normal state in extracellular space in 4 patients during both depression and mania.

In our study (51), using tritiated water and ^{82}Br, we found that the extracellular water significantly increased by 0·5 litre after recovery and total body water by 1·2 litre. The ratio between intracellular and extracellular water was unchanged during depression and recovery. These findings are in keeping with other studies on changes in extracellular space in depression, using different methods.

The most striking abnormality we found during depression lay in "residual sodium". "Residual sodium" is the sodium outside the extracellular space and consists mainly of intracellular sodium and a small amount of exchangeable bone sodium (182). "Residual sodium" was increased by nearly 50 per cent. during the depressive illness and returned to normal after recovery. Total body potassium and intracellular potassium were low and did not change with clinical recovery. The average intracellular potassium concentration was about 135 mEq. per litre which is considerably lower than the normal value found by this method of 165 mEq. per litre (170). One limitation of this latter investigation was that data for normal subjects were obtained from other laboratories because of the restriction now imposed on the administration of radioactive isotopes to normal subjects. It should be noted that in depression there is no change in either extracellular potassium or sodium concentrations, which are normal both in plasma and in cerebrospinal fluid (43, 71). It has not been demonstrated that these changes in electrolyte distribution involve the central nervous system as well as the rest of the body; if they did there would be considerable alteration in brain excitability. We calculated (170) that the resting potential of cell membranes, which is dependent on the ratio of the intracellular and extracellular concentration of potassium, would be reduced from the normal −97 millivolts to −89 millivolts. The difference, 8 millivolts, is similar in magnitude to those excitatory post-synaptic potentials which are large enough to initiate action potentials. Moreover, the increase in residual sodium, which probably represents an increase in intracellular sodium, would reduce the action potential by some 7 millivolts.

These findings suggest that there may be some deficiency in sodium transport mechanism across the cell membrane so that intracellular sodium concentration and water increases and intracellular potassium concentration decreases. Although the movement of sodium between cells and extracellular water is not easily studied in man, its rate of transfer from the blood to the cerebrospinal fluid can be studied. The rate of transfer of sodium from blood to cerebrospinal fluid was estimated, using ^{24}Na, in a series of 20 depressed patients (43). In these patients the transfer rate was found to be half the normal rate when they were depressed, while after recovery the transfer rate of sodium was normal. In another investigation (80) these findings were confirmed in patients with severe endogenous depression, but they were not found in those patients who were suffering from *chronic* depression and who were being treated with phenothiazines.

Anderson and Dawson (5, 6) described a group of depressed patients who had abnormally high blood concentrations of acetyl-methyl carbinol. The depressed patients who showed this elevation were characterized by certain features of depression, such as retardation in

speech and preoccupation with depressive ideas. They also had a decreased urinary sodium potassium ratio, a tendency to sodium retention, and certain EEG changes. These findings are of particular interest since it is thought that a raised fasting blood concentration of acetyl-methyl carbinol is associated with increased intracellular sodium.

Magnesium and Calcium in Depression

There have been few studies of magnesium and calcium in depression. Flach (77) followed the urinary excretion of calcium in depressed patients maintained on a constant intake of calcium and phosphorus before and during recovery from their illness. He found that patients who recovered showed a significant decrease in the urinary excretion of calcium, but patients suffering from neurosis did not show such a change. In a more recent study, Flach (78), using balance studies and the radio-isotope ^{47}Ca, was able to calculate the body retention of the isotope and also to estimate the bone resorption rate. In a small series of 6 patients, Flach found a decrease in the bone resorption rate and an increased retention of ^{47}Ca on clinical recovery. However, Gour and Chaudrey (91) found plasma calcium normal in depression. Cade (34) reported significantly raised plasma magnesium concentrations in depressed patients, before and after recovery, and also in schizophrenia, but these observations are as yet unconfirmed.

Electrolytes in Mania

There are few investigations of electrolytes in mania. In a series of 22 patients suffering from mania, Coppen, Shaw, Malleson and Costain (56) measured the distribution of sodium and water by a similar technique to that used in the investigation of depression. The mental state of the patient was assessed on each occasion the test was performed. It was found that the "residual sodium" showed an average 200 per cent. increase over normal when the patients were manic; some of the manic patients became depressed, and these patients then showed a 50 per cent. increase in residual sodium, i.e. similar to the levels found in patients suffering from a depressive illness. After recovery the patients' residual sodium returned to normal. Manic patients, therefore, showed a similar but greater deviation from normal than depressive patients. These findings on sodium are illustrated in Fig. 5.

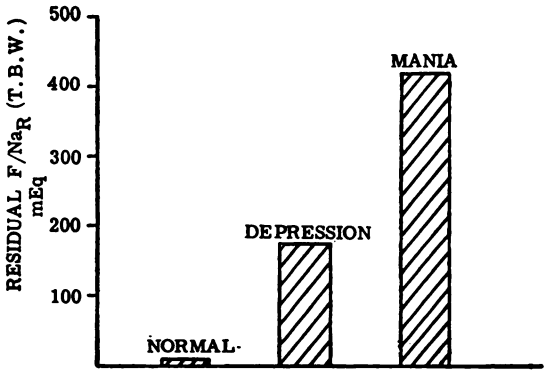

FIG. 5.—Residual F Na_R (T.B.W.) in patients grouped according to their mood at the time of testing. This represents the residual sodium in excess of that expected for the patient based on his total body water.

One other interesting observation emerged from this investigation. The measurement of total body water enables an estimate of lean body mass to be made on the assumption that it is 73·2 per cent. water (145). By subtracting lean body mass from body weight an estimate of total body fat can be obtained. It was found that whereas depressed patients had slightly less total body fat than normal for their age, height and sex, manic patients had on average about 8 kilograms more body fat than would normally be expected. It is not possible to say whether these findings represent a constitutional difference in these subjects or whether the increased body fat is the result of changed dietary habits because of the illness.

Aetiological Significance of Electrolyte Abnormalities

What is the aetiological significance of this change of electrolyte distribution in affective disorders? At this stage it is not possible to evaluate their importance. Very little is known about factors that can alter the distribution of electrolytes; obvious possibilities are steroid hormones such as cortisol, aldosterone or

oestrogens, and also the posterior pituitary hormones. However, as we shall show in the section on endocrinology, the only endocrine functions that have been really extensively examined in this condition are 17-hydroxy-corticosteroids and the thyroid gland. Although there is evidence of some increased adrenal cortical activity, this seems relatively slight, and indeed in manic patients, where there are such profound changes in sodium distribution, plasma corticosteroids are normal. There is also no evidence for abnormalities in thyroid function, so if there is an endocrinological basis for the metabolic changes underlying depression its nature is quite unknown. Are these changes in electrolytes causal or secondary to the changes in mood? As we have seen, the basic physiological abnormalities underlying the changes are unknown, and it has proved very difficult to manipulate body water and electrolytes back to normal by dietary or pharmacological methods such as the administration of a low salt diet diuretics, aldactone, aldosterone or desoxy-corticosterone (52). It will only be possible to ascertain the role of electrolytes in depression when we can manipulate them and restore their normal distribution. There is, however, some work that suggests that changes in water and electrolyte distribution may alter mental state. One may cite the work of Büssow (33), who gave water and vasopressin to patients suffering from mania or depression and found that both the manic and the depressive patients became very much worse. The same procedure repeated on six normal subjects (108) produced the symptoms of a depressive illness.

Lithium Salts and Affective Disorders

One method of therapy which is of particular relevance in this context is the administration of lithium salts, which has been shown to have a very beneficial effect on states of mania (131, 165, 166) and possibly depression (93). It has also a striking prophylactic action in patients prone to attacks of frequently recurring depression or mania or both (12). The action of this salt has a very interesting and unique influence on sodium metabolism and sodium transport across biological membranes. Keynes and Swan (113) have shown that during an action potential, when sodium normally enters the cell, lithium and sodium enter with equal facility, but lithium is removed from the cell at about 1/10th–1/25th the rate of sodium. The actions of lithium on affective disorders are of particular relevance in view of its action on the distribution of electrolytes that is found when the salt is administered in therapeutic doses. Most investigations of the biological effects of lithium salts have dealt with the short-term effects of lithium used in much higher concentrations than are found in patients being treated with lithium salts. We therefore decided to investigate the effect of lithium on the distribution of sodium in a small group of patients. We gave the usual therapeutic dose of lithium carbonate for 7 days and estimated the distribution of sodium before and after its administration (48). The results were surprising. Exchangeable and residual sodium showed a marked drop. The volume of the space in which sodium was detected was reduced and the volume of the bromide space increased. Total body potassium and the urinary excretion of sodium, potassium and chloride were not significantly changed. The most likely explanation for these findings is that lithium had increased the permeability of cells to bromide (and presumably chloride) and decreased its permeability to sodium. This investigation shows that lithium salts, which are known to affect mood in mania, when taken in therapeutic doses, greatly alter the distribution of sodium and chloride, and it may provide a hint of a causal connection between the abnormal electrolyte distribution and the affective disorders.

If these changes in electrolyte distribution occur in the central nervous system then certain functional changes should manifest themselves. Woodbury, Timiras and Vernadakis (187), for example, found that the excitability of the brain (as measured by the electroshock seizure threshold) was correlated with changes in intracellular and extracellular sodium concentrations in the brain. Driver and Eilenberg (69), however, failed to demonstrate any abnormality in brain excitability in depressed patients as measured by the photoconvulsive threshold. Shagass and Schwartz (167, 168) measured the potential evoked at the cortex by peripheral

sensory stimuli and reported abnormal cortical recovery curves in patients suffering from a depressive illness which are consistent with changes in brain excitability.

The Premenstrual Syndrome

Finally, it is perhaps relevant to mention here the premenstrual syndrome. This syndrome consists of various symptoms such as depression, irritability, tension, anxiety and headaches, which occur a few days before the onset of the menstrual period and are usually relieved by the period (92). In a sample of 500 randomly selected women, it was found that about 10 per cent. considered themselves severely affected by one or more of the psychological symptoms of the syndrome (47, 110). The psychological symptoms were significantly correlated with sensations of swelling of the abdomen and breasts. However, although many women complain of increased weight in the premenstrual period, Bruce and Russell (29) failed to find any evidence of sodium or water retention at this time; Klein and Carey (115), in an investigation into day-to-day variation in exchangeable sodium (using ^{22}Na), failed to find any evidence of premenstrual retention. There are no studies yet on the distribution of electrolytes at this time, but this would be of obvious interest since the sensation of swelling may be related to a redistribution of electrolytes and water at this time. Indeed, the whole question of the premenstrual syndrome would repay study, for it represents the commonest form of endogenous depression and as yet it has been hardly studied biochemically. The relationship between the premenstrual syndrome and depressive illness has, however, been examined at clinical level. It was found (45) that the incidence of premenstrual symptoms such as depression, anxiety and tension was no commoner in patients suffering from affective disorders than in normal controls. Before their period only some 10 per cent. of the patients felt much worse, as far as their psychiatric condition was concerned; about 74 per cent. were unchanged or only slightly worse. Indeed some 16 per cent. felt psychiatrically better around the time of the period. It seems, therefore, there is little association between affective disorders and the premenstrual syndrome.

Endocrine Function in Affective Disorders

If affective disorders are determined by reversible biochemical changes, it is tempting to suppose that endocrinological changes are primarily responsible. This notion is supported by the increased incidence of affective disorders during and after the involutional period and by the occurrence of the premenstrual syndrome. However, endocrinological investigations on affective disorders have been very limited in scope, and the only hormones that have been investigated in any detail are the thyroid hormone and cortisol and its metabolites.

This review will not attempt to cover the very considerable literature describing the psychological concomitants which accompany practically every endocrinological disease (17, 140). However, the changes in mood and psychiatric disturbances which are known to accompany Cushing's syndrome, Addison's disease and thyrotoxicosis have prompted many investigators to examine thyroid and adrenocortical activity in depression and, more rarely, in mania, and it is this work that is reviewed here.

Thyroid Gland

Every clinician is familiar with the psychological symptoms of hyperthyroidism, which include many symptoms of a depressive illness such as agitation, anxiety, depression and emotional lability. However, the incidence of severe psychiatric illness is somewhat disputed, though some reports put it as high as 20 per cent. (126, 117, 32). The most common type of psychosis appears to be a schizophrenic-like illness (32, 117) although manic-depressive psychosis is by no means uncommon; and in one series at least was the most common mental illness (70). The symptoms usually remit when the thyrotoxicosis is successfully treated.

In myxoedema there is no doubt that psychological symptoms, again many of an affective nature, are a common occurrence; they include depression, apathy, retardation and poor memory, suspiciousness and hallucinations; mania has also been reported. Substitution therapy often, but not always, produces a marked remission of symptoms (28, 10, 140, 148) and

an improvement in the EEG changes that accompany the illness.

It is clear, therefore, that symptoms of depression and mania, sometimes very similar to manic-depressive illness, can attend both over- and underactivity of the thyroid gland, although such accompaniments are by no means invariable. These psychological symptoms will also remit with successful treatment of the underlying endocrine condition.

Protein-Bound Iodine

Three commonly applied measures of thyroid function are estimates of the serum concentration of protein-bound iodine (PBI), the basal metabolic rate, and measurements of the rate of uptake of radioactive iodine by the thyroid gland. All three approaches have been applied to the study of patients suffering from affective disorders. Reports of PBI in depression have all shown this to be within the normal range. Bowman, Miller, Dailey, Simon and Mayer (20), Gibbons, Gibson, Maxwell and Willcox (87), Brody and Man (25) all found average PBI concentrations to be within the range 5·0-6·0 μg. per 100 ml., which is quite normal. However, both Gibbons *et al.* (87) and Board, Wadeson and Persky (19) found small (on average about 0·5 μg. per 100 ml.) though statistically significant decreases in PBI in patients suffering from depression after clinical recovery. It is quite possible, therefore, that the severe emotional disturbance found in depression causes a slight increase in PBI, but it seems unlikely that such small changes could be of any aetiological importance.

Basal Metabolic Rate

Although it is generally accepted that severe anxiety or tension can increase the basal metabolic rate (B.M.R.) of a subject, Mezey and Coppen (138) found a normal B.M.R. in 18 patients suffering from depression and anxiety. Although these patients' initial B.M.R. was within the normal range and not significantly different from a control group, their B.M.R. declined significantly by about 10 per cent. on recovery. The most marked abnormality in these patients was shown during exercise, when they expended about 16 per cent. more energy than did the control subjects. The administration of amylobarbitone sodium made the patients' performance more normal, although it had little effect on the control subjects (49). Patients re-tested after recovery shifted towards normal. In further experiments, Mezey and Coppen (137) found that these metabolic abnormalities could be mimicked in normal subjects given prednisone. One finding that may be mentioned here, which is of relevance in many experiments, is the finding that a relatively painless venepuncture raised the metabolic rate of normal subjects by an average of 11 per cent. in the following five minutes. Even 25 minutes after the venepuncture the metabolic rate was still raised by 4·4 per cent. (50).

Uptake of Radioactive Iodine

The measurement of the uptake of radioactive iodine by the thyroid gland has not been widely made in affective disorders, although the work of Gibbons *et al.* (87), Dongier, Wittkower, Stephens-Newsham and Hoffman (68), Lingjaerde, Skaug and Lingjaerde (128) suggests it is normal in these conditions.

In spite of the common psychiatric disturbances found in diseases of the thyroid, it seems that we can conclude from these studies that it is unlikely that the thyroid gland plays any role in most cases of depression and mania. It is possible that during the illness there is a very slight increase in thyroid activity, but it seems most unlikely that this has any aetiological significance.

The Adrenal Cortex

Introduction

The well-established relationship between emotional arousal, of almost any kind, and the endocrine system, particularly the hypothalamic-pituitary-adrenal axis, has led to many endocrinological investigations in affective disorders. From what is now well established about the sensitivity to stress of this latter system, both in animals (134) and in normal human subjects (18) it would seem most unlikely that there should be no changes in endocrine function. The problem has been to delimit the changes that occur during depression and mania, and to

see if these changes are specific in any way to these conditions and if there is a causal relationship between the illness and the endocrine changes. If the results to date are somewhat negative, it should be remembered that many earlier investigations had to use crude indices of adrenal cortical activity, such as the urinary excretion of 17-ketosteroids; but this is now being remedied by the use of more specific and meaningful measures, such as estimates of hormones in plasma, the secretory rate of hormones by isotope dilution techniques and by immuno-assay methods. At present there is limited knowledge of the precise effects of steroid hormones on various metabolic processes, especially those that may be concerned with affective disorders, such as amino acid and amine metabolism. It is becoming realized that the central nervous system is an important target organ for adrenocortical and gonadal steroids and thyroid hormone (35, 186), and that specific parts of the brain, such as the hypothalamus and pre-optic area, may be particularly sensitive, for example, to oestrogens which they selectively accumulate (139).

Psychiatric Disturbances in Hyper- and Hypo-adrenalism

One spur to the intensive investigations of cortisol in affective disorders is the prevalence of severe mood changes in Cushing's syndrome and following medication with large doses of glucocorticoids. In Cushing's syndrome there is a very considerable increase of cortisol secretion and a large increase in the unbound fraction of plasma cortisol (67). There is also a marked change in the diurnal rhythm, and evening plasma 17-hydroxycorticosteroid concentrations differentiate between Cushing's syndrome and normal more effectively than do morning samples (72). Most cases of Cushing's syndrome are caused by adrenal hyperplasia, which in turn is often caused by a basophil adenoma of the pituitary. Less common causes are adrenal adenoma or carcinoma. Besides increased secretion of cortisol, there is also a variable increase in other steroids produced by the adrenal, and many women show evidence of androgenic stimulation such as hirsuties and general virilism. General aspects of the syndrome are well reviewed by Cope (42), and Michael and Gibbons (140) review psychiatric aspects of the syndrome.

There are now many series reported of Cushing's syndrome, and it seems well established that psychiatric sequelae occur in about half the patients and severe mental disturbances are found in about one patient in five (181, 90, 103). By far the commonest syndrome is a depressive response, with severe depression, agitation or retardation, delusions and auditory hallucinations. Euphoria and mania are uncommon. The psychiatric syndrome, as would be expected, is dependent to some extent on the previous personality of the patient (81). The mental symptoms almost always remit with successful treatment of the syndrome.

The prolonged administration of ACTH and cortisol for therapeutic purposes also produces mental changes, but much less commonly than in Cushing's syndrome (140, 154). Another difference between steroid administration and Cushing's syndrome is the common occurrence of euphoria in the former and its rarity in the latter. It is also alleged that ACTH and cortisone have different actions on mood, in that ACTH is thought to provoke depressive reactions and cortisone elation (79). However, there is no general agreement on this subject. There has also been little attempt to correlate changes in mood with the precise endocrinological changes taking place in Cushing's syndrome, and as both its aetiology and the pattern of hormones produced varies from case to case this sort of investigation may yield valuable information.

Psychological symptoms are also prominent in the great majority of cases of Addison's disease in which there is adrenal insufficiency. Depression, apathy and irritability are amongst the most common symptoms, and memory deficiency is also common (140, 178). Here again the symptoms remit or improve with adequate therapy, although some observers think that Addisonian patients are unduly susceptible to psychosis induced by cortisone.

Although the exact pathogenesis is by no means established, the high incidence of affective swings in these conditions strongly suggests that the adrenal cortex is intimately concerned with mood, and it is not surprising that so many investigations of adrenal cortical

function have been carried out in affective disorders. The hypothesis that affective disorders are caused by biochemical changes consequent on alterations on adrenal cortical functioning is attractive, but so far the evidence has been rather disappointing.

It is now clearly established that emotional stress, both in animals and in normal subjects and psychiatric patients, is accompanied by increased secretion of adrenocortical steroids (140). The relationship between adrenocortical function and mood, especially the pathological changes found in affective disorders, is not so clearly defined. Different investigators have found varying increases of adrenal cortical activity in a varying proportion of patients suffering from severe depression, and the aetiological importance of these changes is far from clear.

Measurement of Adreno-cortical Activity

One problem in investigating this subject lies in the difficulty of measuring adrenocortical activity. Many steroids are produced by the adrenal cortex; they include cortisol, corticosterone, aldosterone and androgens such as dehydroepiandrosterone. In man, cortisol is the steroid which responds most markedly to emotional stress, and it is the only one that has been extensively investigated in affective disorders. There are several methods of investigating adrenal cortical activity: these include measurement of the urinary excretion of 17-hydroxycorticosteroids, measurement of plasma cortisol, and estimates of the secretion rate of cortisol which can be made by isotope dilution techniques. The various methods each have certain advantages and limitations. Measurement of adrenal cortical activity is also complicated by the diurnal variation that occurs in the secretion of cortisol; plasma levels of cortisol are two to three times higher at 8 a.m. than they are at night (66). Cortisol is normally largely bound to plasma protein. The fraction of unconjugated cortisol not bound to the globulin transcortin is probably the physiologically active fraction capable of entering tissue spaces, including the central nervous system. This fraction becomes increasingly important when the plasma cortisol concentration rises above 20 μg. per 100 ml., the level at which transcortin is normally saturated. It is probable that any symptoms would therefore be more clearly correlated with the unbound cortisol than with the total plasma cortisol concentration. One factor that can influence the binding capacity of plasma is oestrogen secretion; it is the increased production of oestrogens during pregnancy that accounts for the raised plasma levels of cortisol found in pregnant women, where, in fact, the concentration of free cortisol is unchanged. Ideally, therefore, studies on plasma steroids should be accompanied by studies of the plasma concentration of free steroid present, but so far this has not been carried out in studies of affective disorders. The complexities in measuring adrenocortical activity will not be enlarged on here, but the subject is very clearly reviewed by Cope (42).

Emotional Disturbance and the Adrenal Gland

Another complicating factor is the sensitivity of the hypothalamic-pituitary-adrenal system to changes in the environment which has been found both in normal subjects and psychiatric patients. Both Mason (133) and Persky, Gross, Norton and McMurty (147) have found raised plasma 17-hydroxycorticosteroid levels in normal subjects admitted to hospital for experimental purposes, and comparable increases in the urinary excretion of 17-hydroxycorticosteroids have been reported by Sloane, Saffron and Cleghorn (173), Hetzel, Haba and Hinkle (98) and Fishman, Hamburg, Handlon, Mason and Sachar (76). Usually it is found that the urinary steroid excretion falls during the week following admission; an exception was in a group of students who were under stress before they came into hospital. Their stressful situation was alleviated by admission to the research ward. In this group of students the urinary excretion rose during their stay in the unit, presumably in anticipation of their discharge to their outside difficulties. It is therefore important to standardize conditions as much as possible, for, as Anderson and Dawson (7) found, there was a significant difference in plasma 17-hydroxycorticosteroid levels in depressed patients examined on an admission ward and those examined in a metabolic unit, and this they attributed to the different milieu.

Cortisol and Depressive Illness

Turning now to specific investigations on affective disorders, Board *et al.* (19) found that patients suffering from depression had considerably raised plasma cortisol concentrations (19·5 μg. per 100 ml.) compared with normal controls (12·3 μg. per 100 ml.). After recovery they found that plasma cortisol levels generally fell, although some increased after an apparently successful course of E.C.T. Gibbons and McHugh (88) examined a series of 18 depressed patients before and at weekly intervals during recovery from depression. They found that the initial mean plasma cortisol level of 20·8 μg. per 100 ml. (taken about a week after admission) was significantly increased compared to the mean plasma level after recovery of 10·8 μg. per 100 ml. There was a significant correlation between improvement in clinical state and decline in plasma levels. However, five patients did not show any marked change in their levels during recovery. Gibbons (85, 86) confirmed the supposition that the increased plasma levels or raised urinary excretion rates of 17-hydroxycorticosteroids observed in severe depression do in fact represent an increased rate of cortisol secretion. However, not all reports confirm that cortisol production is markedly raised in depression, and many patients show normal or even low-normal corticosteroid output (21). Stenbäck, Jakobson and Rimón (177) found the average excretion of urinary 17-hydroxycorticosteroids to be only very slightly above that of a normal group, and they also found no significant change in the average urinary excretion after clinical improvement. They suggested that examination of the individual cases indicated the existence of a sub-group of patients with initial high excretion, whose excretion declined with clinical recovery. Bunney, Mason and Hamburg (31), although they reported a correlation between urinary 17-hydroxycorticosteroids and variations in mood in patients not treated by physical methods, found that only 5 out of 17 patients had abnormally high steroid excretion. In our laboratory we examined morning and evening plasma 11-hydroxycorticosteroids (11-OHCS) in 29 patients recovering from a depressive illness (26). We found an average plasma steroid concentration just after admission of 22·1 μg. per 100 ml.; this fell to 20·0 μg. per 100 ml. after one week, before treatment had started (when the patients were still severely depressed), and was 17·9 μg. per 100 ml. on discharge when all but two were recovered or substantially improved. It seemed, therefore, that admission to hospital influenced morning plasma 11-OHCS values as much as recovery from a depressive illness. This was further illustrated by the fact that patients first tested within two days of admission had significantly higher plasma 11-OHCS concentrations than those first tested two days or more after admission. The proportion of cortisol to corticosterone was examined in 11 of these patients and was found to be unchanged with clinical recovery. The patients were divided into "endogenous" and "reactive and mixed" groups on the basis of Mendel's (136) method, and it was found that the former group showed a significantly greater change with recovery than did the latter, whose mean morning plasma 11-OHCS concentration was virtually unchanged during their stay in hospital. The normal diurnal variation was not affected, but it was found that evening plasma 11-OHCS concentrations correlated better with clinical state than those found in morning samples. Even so, the changes in 11-OHCS were not great, and indeed the levels found in plasma were surprisingly normal when one considers the mental anguish felt by many of these patients, and even on admission only 5 out of the 29 had levels above the normal range. These results are in contradiction to those obtained by Gibbons and McHugh (88), but are more in keeping with the more modest changes found by Bunney *et al.* (31), Stenbäck *et al.* (177), and in our previous investigation, Coppen *et al.* (46). The correlation between evening plasma 11-OHCS and clinical conditions may point to a change in the secretion of corticotrophin, which is of interest since Wasserman, Belton and Millichap (184) have reported that this hormone produces a significant increase in brain intracellular sodium in rats. The qualitative pattern of corticosteroid secretion has been examined by fractional analysis of urinary corticosteroid metabolites, and some indication of possible abnormal patterns has been seen in two investi-

gations (123, 106), but was not found by Ferguson, Bartram, Fowlie, Cathro, Birchall and Mitchell (75).

Other Steroids Investigated in Depression

There are few observations on steroids other than those derived from cortisol or its metabolites. Ferguson *et al.* (75) reported low levels of 11-deoxy- 17-oxosteroid excretion in five depressed female patients, and found that the excretion rates returned towards normal on clinical recovery. However, in our laboratory (46) we could not confirm this in a series of male patients suffering from depression. We found that the urinary excretion of total 17-ketosteroids, 11-hydroxandrosterone and 11-hydroxyaetiocholanolone was significantly raised. We concluded that during depression there was a moderate increase in adrenal cortical activity affecting both 17-hydroxycorticosteroids and 17-ketosteroids. In the same investigation the urinary excretion of oestrogens was measured, and it was found that the excretion of oestrone and oestradiol was significantly decreased during depression. The significance of these results is not obvious, but it is possible that urinary oestrogen excretion in males is an indirect measure of testicular endocrine function (141). This may be of significance in view of abnormalities in physique of patients suffering from depression which suggest that these patients may have lacked normal stimulation by androgens during their development in adolescence (156). There are as yet no reports of testosterone production in affective disorders, but androstenol, a steroid that may be derived from testosterone, is normal in depression (27).

Cortisol and Mania

Studies on patients suffering from mania are much more sparse than investigations on depression. Earlier studies were of a sporadic kind and gave rather conflicting reports (140). However, we were able to examine eight manic patients before treatment and we found the average concentration and range of plasma 11-OHCS were entirely within the normal range and that there was no significant change with clinical recovery (26). It seems, therefore, that the disturbances in electrolyte distribution in affective disorders are unlikely to be related to changes in 11-OHCS, as the electrolyte changes were most marked in mania and yet in this condition there is no evidence of changes in plasma steroid concentrations.

Other Endocrine Studies

In view of the considerable disturbances in electrolyte distribution found in depression studies on aldosterone secretion would be most valuable, but they are still lacking, although Elmadijan (73) reported a considerably increased urinary excretion of aldosterone in a group of patients suffering from a variety of conditions, including anxiety and depression. However, increased production of aldosterone is unlikely to be a causal factor, as mental disturbances are not common in patients suffering from hyperaldosteronism. Finally, is the marked therapeutic effect of electroconvulsive therapy mediated by the adrenal cortex? The results of an investigation by Hodges, Jones, Elithorn and Bridges (100) on plasma cortisol levels following therapy make this seem unlikely. Although the values at half-an-hour after therapy are significantly raised, the increase is not great, and at 1 and 2 hours after treatment the mean values of plasma cortisol concentrations of a group of depressives do not differ from their pre-treatment levels.

It is appropriate to consider, under the heading of endocrine disturbance, the changes in carbohydrate metabolism that have been reported by many investigators (see review, for example, by Sourkes (175)). The most consistent finding has been a decrease in glucose tolerance during states of depression, which some authors find improves with clinical recovery (152, 153, 94). Possible explanations that have been put forward have been the increased adrenal cortical activity or changes in the gastrointestinal absorption of glucose, but it seems that an important factor may be deficiencies in the patients' diet before the patients were tested. A recent series in our unit (96) gave no evidence of impairment in glucose tolerance when depressed patients were given diets high in carbohydrate for three or four days before testing, and no change in their glucose tolerance on recovery.

In summary, although a great deal of effort has been directed to unravelling the endocrinological basis of depression, it seems that the few variables selected for investigation have shown little abnormality. It is improbable that the changes in corticosteroid production are anything else than the normal accompaniments of the emotional turmoil that the patients experience, and indeed it appears that the decline that occurs in adrenal cortical activity on settling down after admission to hospital is as great as the decline that occurs when the patients recover from their depressive illness.

Summary and Conclusions

There is evidence that in affective disorders there are biochemical disturbances in three main areas: in amine metabolism, in electrolyte distribution and in adrenal cortical activity. There is growing evidence of a causal association between brain monoamines and affective disturbances; if brain monoamines are depleted by reserpine a significant proportion of mentally normal subjects suffer from a depression not distinguishable from severe endogenous depression. There is good evidence that drugs such as imipramine and the monoamine oxidase inhibitors, which increase the effective activity of brain monoamines, alleviate depression. Although 3, 4-dihydroxyphenylalanine (the precursor of the catecholamines) has apparently no antidepressive effect, whether given with or without a monoamine oxidase inhibitor, it has been shown that when tryptophan, the precursor of 5HT and tryptamine, is fed to depressed patients it will potentiate the antidepressive action of a monoamine oxidase inhibitor. There is also direct evidence that there are disturbances in amine metabolism in depression, as shown by the very significantly decreased excretion of tryptamine, decreased levels of 5-hydroxyindoles in cerebrospinal fluid, and changes in the metabolism of noradrenaline. There is therefore a reasonable case of supposing that these monoamines are involved in the aetiology of depressive illness, but monoamine deficiency is not the sole cause of the disorder, and although patients do respond to monoamine oxidase inhibitors and tryptophan they do not do so as quickly or effectively as with E.C.T.

Turning now to the changes in electrolyte distribution, are these causal or are they secondary phenomena? We cannot say yet, but the therapeutic effect of lithium salts in affective disorders suggests that electrolyte changes may play a part, although the matter will not be settled until we determine the underlying causes of the change in electrolytes and learn how to restore them to normal. It might be envisaged that alterations in the electrolyte distribution could produce two changes in the brain: (1) a direct change in excitability of neurones and (2) a change in the production of monoamines, such as 5-hydroxytryptamine, which are presumably used to "modulate" synaptic transmission. This would be of especial importance when cerebral function is already impaired by changes in electrolytes.

If the underlying abnormalities in electrolyte distribution are endocrinological, it must be confessed that so far only small changes in adrenal cortical activity have been demonstrated and that these seem unlikely to be of much aetiological importance. Apart from cortisol and thyroid hormone, few other endocrine functions have been adequately examined. As well as extending the scope of endocrinological investigations, it seems that it would be fruitful to make the investigations more specific and to measure the effects of various hormones, *in vivo*, on the distribution of electrolytes and on amine metabolism. Very little is known about these questions, which are now of importance in the study of affective disorders.

Finally, we must face the very real possibility that we are far from the primary disturbance in depression. The changes may all be secondary to other abnormalities which have not been taken into account at all, and we may be in the position of investigators of pernicious anaemia before anything was known about vitamin B_{12}. In spite of all the numerous investigations and very exciting leads that are now opening up, we are perhaps only in a slightly better position than Sanctorius of Padua, who can be regarded as the father of metabolic studies in man. He summarized the position some 300 years ago in words which are still relevant today when he said: "Where the bond of union is between the mind and the animal fluids God Almighty

alone knows, but there is no one theory better confirmed by experience than that they mutually influence one another."

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