*The Sensitivity of the Sympathetic Nervous System to Adrenalin in Some Cases of Mental Disorder*[1]. By WM. MCWILLIAM, M.B., Ch.B., D.P.M., Senior Assistant Medical Officer, Inverness District Asylum.

LAST summer we had admitted to our hospital a case of the involution period in the female, which presented such notable features from the clinical aspect that I was stimulated to the discovery of the "whys" and "wherefores" it presented. An involution case, I found myself confronted with certain problems of an endocrinological nature, which are the experience of all psychiatrists.

These problems included the fundamental relationship of mind and body, the place of emotion in abnormal mental processes, and the old conflict of which the Lange-James theory is only one view-point. Disorders of emotion and consequent faulty judgments and beliefs are but the normal expressions of a "mind diseased," though such inconstant factors in the various psychoses. The importance of the sympathetic nervous system with its viscero-sensory relationships, and especially with the endocrine organs, could not but attract attention from the view-point of emotional disorder.

The further fact then obtruded itself that this same sympathetic system in its turn had as its master one of these endocrine organs, the adrenal gland, or to particularize, its chromaffin tissue. The question then arose: "How will the sympathetic nervous system in cases of mental disorder react to administration of extract of medulla of the adrenals?"

At this stage it might be of advantage to recall that Langley has differentiated in the vegetative nervous system that which he calls the autonomic from the sympathetic system. The former consists of a cephalic portion which proceeds from the mid-brain and the medulla oblongata and a sacral portion. It presents a functional antagonism to the sympathetic portion. Noting this antagonism and the different physical signs which arise on stimulation of the respective portions of the vegetative system, Eppinger and Hess have given the name of vagotonics to individuals in whom the activities of the autonomic predominate—of sympathetico-tonics to individuals in whom the sympathetic excels. Adrenalin, as the master of the sympathetic, is the sympathetic excitant, its injection producing a definite symptom-complex, the characteristics of which I shall later detail.

(1) A paper read at a meeting of the Scottish Division held at Inverness, June 5, 1925.

To-day I give you some of the results, in the hope that they may interest you from the scientific standpoint, and that I may later have the benefit of your opinion.

I would here admit that the fallacies of such a "reaction" are many and obvious. They arise chiefly from the complexity of the endocrine system. The adrenal cortex would seem to be associated with growth, but so are the pituitary and the pancreas. The pancreas, again, in addition to being one of the great factors in the metabolism of sugars, is the sympathetic depressant, in contradistinction to the supra-renal medulla, and so on. These factors make the symptom-complexes of "vagotonia" and "sympathicotonia" so unreliable, as in essence they are only "relative," and in them lie, too, the source of many of our fallacies.

As to the effect of the administration of adrenalin in the normal individual, may I quote Sharpey-Schafer?

"In man the subcutaneous injection of a dose of from ·5 to 1·5 mgrm. of adrenalin causes within a few minutes a slight elevation of arterial pressure with pallor of the face and extremities produced by peripheral vaso-constriction. The rise of blood-pressure, although slow in appearing, is long-lasting: it is accompanied by a quickening of the pulse."

In my series of cases, I injected subcutaneously ·5 mgrm. of a solution of adrenalin chloride, using in all cases the same preparation. As the blood-pressure varies in all individuals with the period of the day at which it is taken, the drug was administered at approximately the same hour in every case. These precautions were taken to obviate a few, at any rate, of the many possible flaws in technique.

The technique consisted of taking the subject's blood-pressure, and then injecting subcutaneously the dose of adrenalin I have mentioned. Ten minutes afterwards the pressure was again taken, and the process repeated at ten-minute intervals up to an hour.

During the course of the reaction, physical changes, *e.g.*, tremors, flushings, etc., and any change in the affective state were recorded.

The types of case for investigation were selected from the manic-depressive psychosis, dementia præcox, and various cases of melancholia, which did not belong to the manic-depressive group.

I give short notes on the several cases, with the types of reaction which were observed.

*Mrs. C—*, æt. 45, admitted May 29, 1924. A psychosis of the climacteric, characterized by depression, agitation and distress, arising in the course of an acute hallucinosis.

This patient remained acutely ill for five months, and then suddenly recovered from her hallucinations and depression. It was remarkable the change in her whole facies, and also that the recovery coincided with what would have been a menstrual period. Adrenalin reaction was first taken two days after recovery.

December 3, 1924 : Syst. bl. pr. rose from 180 mm. to 208 mm. in ten minutes, and by the end of thirty minutes had fallen to 166 mm. General physical reaction was marked by palpitation, tremors and flushing of the face. She felt very nervous.

December 5 : Syst. bl. pr. 164 mm. Reaction to adrenalin less intense—little erythematous flushing, less palpitation, less distress and less tremor. The improvement in patient's mental state has been progressive. Curve markedly depressed, syst. bl. pr. falling to 140 mm. in ten minutes and rising to 154 mm. at the end of 20 minutes, and remaining stationary.

December 8 : Syst. bl. pr. 160 mm. Reaction is less marked and the patient shows increasing mental stability.

December 11 : Patient had relapsed slightly on this occasion, having had an adverse emotional stimulus the previous day. General reaction showed increased distress and an increased state of *folie de doute*. Restlessness +, tremors +. Vaso-motor constriction and dilatation of pupils. The curve again showed a depressor trend, syst. bl. pr. falling from 160–140 mm. in 10 minutes, and coming to rest at 145 mm. at the end of 50 minutes.

December 18 : Little reaction shown, there being a preliminary fall followed by a short rise. Syst. bl. pr. 128 mm., falling to 120 mm. in 10 minutes and rising to 136 mm. at 20 minutes and remaining there. Mentally unstable, but has not relapsed to condition prior to December 3.

January 10, 1925 : Has again improved. Syst. bl. pr. 134 mm., rising to 156 mm. at end of 10 minutes, falling to 142 mm. at 20 minutes and remaining there.

This patient has, with several relapses—all of a very minor nature, and partly of psychic origin—shown progressive improvement, and would seem to be well on the way to a permanent recovery. I may add that her heredity is poor, and that at the great sexual crises of her life she had had minor mental attacks.

The psychic trauma which so coloured her relapses and the whole of the delusions and hallucinations of the acute state of her illness dated back to the patient's first physical and mental strain at the age of 13. The accompanying emotional shock gave the whole of her subsequent life a strong religious bias, and it was obvious that the whole atmosphere of the Sabbath was conducive to the mild relapses. She had also believed during the hallucinosis that her relatives were all dead and damned, and it was the visit of a sister which produced the first relapse.

The reactions in this case were more atypical than in any of the subsequent ones, and in the present state of our knowledge of the relationship of the sympathetic nervous system to the endocrine organs, and of the inter-relationship of these various organs, conclusions can only be grossly hypothetical, and of no real value.

I would only point out some important facts :

1. The relationship of the psychosis to the reproductive organs, as evidenced by the periods at which the illness recurred, and by the fact that sudden disappearance of the gross symptoms so closely coincided with menstruation.

2. The uniform " pressor " and " depressor " characteristics of the curves. These could hardly have been brought about by a previous injection of adrenalin, as two depressor curves followed one another at a week's interval without an intervening administration of adrenalin.

3. The progressive fall in the blood-pressure of the patient, both after the conclusion of each reaction and throughout the whole of the patient's convalescence.

4. During the first reaction there was vaso-motor dilatation

and flushing, and during the final ones of the series a normal vaso-motor constriction.

Regarding the depressor curve, I would again quote Prof. Sharpey-Schafer:

"The possibility of the same auto-coid substance acting under some circumstances as a hormone or excitant, and under other circumstances as a chalone or depressant, must be borne in mind."

In the literature of the adrenals I have found that small doses of the auto-coid of the medulla may produce depressant reactions, but this hardly accounts for the variability of the reactions in the present case, nor does, I think, the fact that extracts of most bodily tissues, in virtue of their histamine content, lower the blood-pressure, apply here.

The whole picture these reactions present bears to me a close analogy with the "flushings" and vaso-motor and cœnæsthetic experiences of the patient.

*M. M*—, or *F*—, female, æt. 37. This patient is a melancholic, and might be classified as of the "agitated" type. She shows depression plus great mental distress, and a delusional scheme based on sin, unworthiness and marital infidelity. Her reaction to adrenalin was short and sharp, and showed a marked secondary curve. Her syst. bl. pr. at the beginning of the test stood at 122 mm., rose within 10 minutes to 160 mm., and fell in the next 10 minutes to 118 mm. This was followed by a sudden rise of 10 mm. during the next 10-minute period, but at the end of 30 minutes the patient's systolic pressure was at 120 mm., and remained there.

During the reaction the patient showed an increase of psycho-motor excitement, pallor of the face, fine generalized tremor, and a picture of the emotion of "fear."

*A. M*—, male, æt. 50. Patient has been in a state of chronic mania during the past two years. He is elevated, noisy, abusive, destructive in his conduct, and full of the most nonsenical fancies. He is notoriously untidy, a humorist, and delights in his mannerisms and in exhibitionism. The patient's superficial circulation, too, is poor. He suffers from œdema of the lower extremities, and crops of boils and slowly-healing ulcers are signs of lowered vaso-motor tone.

His reaction to adrenalin was very similar to that of the preceding case (M. M— or F—). His syst. bl. pr. was at first high—140 mm.—and is accounted for by his age and arteries. Within 10 minutes it had risen to 166 mm., and by 20 minutes had reached its maximum of 172 mm. This was followed by a most abrupt fall to 120 mm. in 30 minutes. In the subsequent 20 minutes the pressure gradually rose to 144 mm., and by the end of the hour it had dropped to 138 mm.

Comparing the case of A. M— with M. M— or F—, we have the same abrupt rise and fall and the slight secondary curve. The first curve, I think, is due to the stimulation of an excitable sympathetic nervous system, and the second to a further out-pouring of adrenalin from the suprarenal under that same stimulation. The curves compare with the unstable emotional states of the patient. The chronic maniac shows a sympathetic which can be stimulated, but more slowly than in the acute condition; that it is readily exhausted, and that the secondary curve attains its height more slowly. Possibly the suprarenal itself is only slowly able to cope

with the work it has to do; that the secondary curve would seem to show. In brief, these two cases substantiate the observations of Cannon on the output of adrenalin in the *Bodily Changes in Pain, Hunger, Fear and Rage.*

*I. M. D*—, female, æt. 19; dementia præcox; katatonia. Adrenalin reaction is very slight, there being no emotional changes and no gross physical signs. The patient's vaso-motor circulation is very sluggish, limbs becoming swollen as the result of gravity. Curve shows a very slight preliminary fall and a very flat prolonged rise, ending in 50 minutes.

A reaction is produced compatible with the emotional picture of katatonia, with the vaso-motor condition and with the diminished coagulability of the blood described so many years ago by Dr. Lewis Bruce.

The pathological work of Sir Frederick Mott on the adrenal glands in dementia præcox gives further light on this abnormal curve.

*J. E. R*—, male, æt. 24. The patient is a youth of great stature. Height 6 ft. 2½ in., and with correspondingly large hands and feet. He almost suggests gigantism (hyperpituitarism at the adolescent period). Height at 17 years 6 ft. 1 in.

Reaction to adrenalin: Preliminary syst. bl. pr. 116 mm., and showing a very sluggish rise, only to attain its maximum of 140 mm. at the end of 30 minutes. There were no general symptoms. Pupils did not dilate until the end of 40 minutes.

Curve shows a sluggish excitability of the sympathetic nervous system.

This patient provides one of what may be an interesting series—interesting from the diagnostic standpoint. To me stupor is a clinical symptom-complex, which may arise in the course of both the dementia præcox and manic-depressive psychosis, and the difficulty often arises as to which psychosis the case belongs.

*D. B*—, male, æt. 20. Admitted November 17, 1923. Stupor. Heredity bad.

D. B— provides us with a typical picture of vagotonia. Among the symptoms he shows are profuse salivation, faulty habits, contracted pupils, increased gastric secretion and cold sweaty skin. His pulse is slow—60 per min.—and his oculo-cardiac reflex is vagotonic.

This patient was admitted in November, 1923. He was depressed and pre-occupied by hallucinations. He later lapsed into a condition of catalepsy, gradually becoming stuporose. He now shows the physical signs we have just noted, plus the mental ones of negativism and stupor. He will not speak, pays no attention to what goes on around him, and is depraved in his appetites.

Reaction to adrenalin: Preliminary syst. bl. pr. 114 mm. It then rises sharply in 10 minutes to 158 mm., and very slowly falls to 126 mm. This curve is very similar to those previously seen in the cases of A. M— and M. M— or F—.

A second case of stupor (M. J. G—) was one known definitely to belong to the manic-depressive type, and the type of curve corresponded with the previous result.

A further case of katatonia (J. McA—, male) shows in marked degree the vaso-motor accompaniments and the physical and mental signs of mild stupor. Here, again, the curve is of the same type as those seen in our other cases of dementia præcox.

*J. A*—, male, æt. 57, admitted May 30, 1924. This patient was obviously an involution case, his mental picture being that of extreme hypochondria.

On admission his bodily state showed the signs of auto-intoxication, *vid* the alimentary tract, plus atheroma of his vessels. His bowels were very constipated, and his tongue thickly coated. Refusal of food being persisted in on the grounds that he had no throat and could not swallow, and that his bowels were blocked up. His affective state was one of profound depression and subjective pre-occupation.

During the following year the mental picture varied little, and the patient remained depressed, introspective and deluded. All his food is digested, he says, in his throat, as he has no stomach or bowels.

In April, 1925, he developed an œdema of his forehead and eyes. This œdema began as a localized swelling in the middle line of his forehead, pitting on pressure. It gradually extended to fill the loose tissues round the orbits and then disappeared. The obvious diagnosis was that of an angio-neurotic œdema.

Angio-neurotic œdema is little more than a name, as the pathology of the condition is not known, though the present view is that it is a "local expression of the presence of a circulating toxin, prone to occur in persons of a nervous temperament." It is significant that the same authority states that patients show "other signs of vagotonia," and that treatment consists in giving either belladonna or adrenalin, attempts being made to stimulate respectively the parasympathetic and the sympathetic divisions.

Patient's reaction to adrenalin: We had a preliminary low syst. bl. pr. 128 mm. and diast. 96 mm. The curve showed a slow and gradual rise to a maximum of 148 mm. at the end of 30 minutes and a very rapid fall to normal—130 mm. in 10 minutes, and a slight rise in the next 20 minutes. There were no accompanying emotional or physical changes.

Observations on this case were:

(*a*) A slow reaction and a poor response with a relatively good secondary curve. (*b*) That the excitability of the sympathetic is below the normal, and that the output of adrenalin is relatively good. (*c*) That these facts are compatible with (1) the vaso-motor condition, and (2) the patient's mental state.

The affective state of J. A— depends on the weakness of the stimuli arising from the sympathetic and concentrated on the optic thalami, and his delusions on the misinterpretation of such stimuli being dependent on his emotional state.

Among other cases in which the test was employed were one of asthma with accompanying depression and one which strongly suggested Addison's disease.

*P. McK*—, æt. 65, admitted March 17, 1925. The most marked physical feature of this case is a deep pigmentation of the patient's trunk, being quite negroid in degree over her chest and abdomen. She is poorly nourished, and her syst. bl. pr. is 104 mm. She is listless and anergic, and complains of weakness. Mentally she is acutely depressed, groaning and crooning to herself, and is subjectively preoccupied. The pigmentation was first noticed a year prior to admission, following "influenza," and has progressively increased in depth. Family history and ancestry are negative.

Reaction to adrenalin: The auto-coid produced practically no change in patient's pressure curve, and there were no emotional or physical accompaniments.

The test was repeated on the following day. The syst. bl. pr. was found to be higher—116 mm.—and there was a slight reaction to 134 mm. after 10 minutes, with accompanying pallor of the face, tremors and feeling of nervousness. There was a further fall from the 15th–20th minutes, when the reaction would seem to have terminated.

This type of curve might be looked for in cases of Addison's disease, pointing to suprarenal deficiency; the analogy of the katatonic curve is noteworthy.

*J. McE*—, male, æt. 47. Has attacks of acute mental depression, which coincide with those of asthma. During some of his later and more severe attacks the patient has appeared to be more degraded in his habits, being very wet and dirty. In the intervals the patient is much brighter in mind, but there is an under-current of mild depression, which is explained by the patient's dread of future attacks, and by a belief that he will never be better. He supplies a good picture of the nervous type of asthmatic, with the attacks due to vagal crises and subsequent bronchial spasm. But the occurrence of incontinence of urine suggests that the pathological condition is not strictly limited to the vagus, but that it is rather a vagotonia, with the whole parasympathetic involved.

Reaction to adrenalin: (*a*) *During attack.*—Preliminary high syst. bl. pr. of 150 mm., falling in 10 minutes to 110 mm. Thereafter there was a slight rise to 118 mm., falling to 100 mm. at the end of an hour.

(*b*) *After attack.*—Preliminary syst. bl. pr. is low, 108 mm., rising slowly to 120 mm. at the end of 20 minutes and falling to 104 mm. at the end of an hour.

The injection of adrenalin produced rapid relief of the patient's symptoms.

Observations on this case were:

(*a*) Case shows a poor response of the sympathetic between attacks. (*b*) That the auto-coid readjusts an abnormal balance by stimulating the sympathetic, and so antagonizing the action of the vagus on the bronchial muscle. (*c*) With the readjustment of the balance to the patient's " normal " there is a marked reduction of the blood-pressure. There is a notable analogy here to the case of Mrs. C—.

### *General Conclusions.*

1. That the reaction to adrenalin corresponds to the excitability of the sympathetic nervous system, and the degree of emotional instability, or of emotional defect.

2. That there exist " negative " states of depression, which arise from inexcitability of the sympathetic.

3. That certain unknown factors, other than those of small dosage and histamin or cholin content of animal tissues, can cause a depressor adrenalin reaction.

### References.

(1) Prof. A. Sharpey-Schafer.—*The Endocrine Organs* (Part I).

(2) Langdon-Brown.—*The Sympathetic Nervous System in Disease.*

(3) Swale-Vincent.—*Internal Secretion and the Ductless Glands.*

(4) Laignel-Lavastine.—*The Internal Secretions and the Nervous System.*

(5) Bruce.—*Studies in Clinical Psychiatry.*