

SCHIZOPHRENIA : A NEW APPROACH.

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INTRODUCTION.

Mr. Gladstone, with that candour which a great Statesman can afford, once said, " Government is a rough business, and the results are most unsatisfactory." Unfortunately no great psychiatrist has described the present state of our knowledge and treatment of schizophrenia in an equally robust phrase ; but surely, " rough business and unsatisfactory results " would not be an unfair summing up ?

We have now known of this illness for nearly half a century, and yet our understanding of it is slight and our useful information scanty. This is not because we have been idle, but because our efforts have been poorly rewarded. Thousands of papers are written every decade ; tens of thousands of observations are made ; there is no lack of opportunity for studying patients when about one hospital bed in five in this country is occupied by a schizophrenic, yet we are still entirely ignorant of the cause of this disease. There are, it is true, numerous theories, but none is generally accepted. We have one form of treatment, deep insulin, which produces remission of symptoms in some cases and what seems to be a cure in others, but even the value of this treatment is hotly disputed. Because deep insulin is a purely empirical procedure the psychiatrist is always tempted to become preoccupied with details of technique so that he forgets, or at least becomes less aware of our fundamental ignorance.

THE PRESENT SITUATION.

Since Bleuler (1), over forty years ago, defined schizophrenia in his great monograph, and advanced the hypothesis that it was a metabolic disorder with manifestations in the psyche, the bodily functions of schizophrenics have been studied intensively, but these investigations have not, with few exceptions, been illuminating, and where some abnormality has been found this can usually be accounted for by the poor condition of the patients. This is no place to catalogue the extraordinary efforts of nearly two generations of research workers, but an observer is astonished by the ill-rewarded zeal and activity. No stone has been left unturned ; indeed showers of stones seem to have been thrown up indiscriminately. From Bellak's (2) extensive survey it is clear that not everyone agrees with Bleuler that schizophrenia is a metabolic disorder. The psychoanalysts hold with more or less tenacity that the illness is largely psychogenic. In their view, so far as an uninitiated person can summarize it, the schizophrenic, unable to adjust to difficulties occurring in very early childhood, retires into a fantasy world when confronted with some insupportable situation later in life. Between these polar opposites there is plenty of scope for theorizing, and there has been no lack of it. Nutritional disorders, head injury, infections including syphilis and tuberculosis, hereditary and various endocrine deficiencies have all been implicated, and either in concert or separately have their supporters.

TREATMENTS.

Where causation is obscure, treatment is usually varied. In this illness it extends from the highly intensive and often non-verbal psychotherapy used by Rosen, through more formal psychoanalysis, to a whole range of physical therapies including electrical and insulin shock, freezing and over-heating, increased oxygen intake and nitrogen inhalations. Psychosurgery is also used, and at the other end

of the scale are those who believe in custodial care and eugenic advice. Insulin shock alone has received some measure of general approval, but even here there is no agreement as to how it works, and some disagreement about whether it works.

THE FUTURE.

Future campaigns planned include sociological studies, special psychoanalytic techniques, refined shock therapies, more accurate surgery, and fuller endocrinological and biochemical investigations. Gjessing's (3) scheme is an example of the type of prolonged study from every angle which it is hoped will solve the problem. He suggests that a group of schizophrenics should be studied in every conceivable way for an indefinite period ; at the end of some long time he believes something valuable will emerge : but are these hopes justified ? The body is prodigal in its chemical syntheses, and an experiment of this sort might go on indefinitely, bringing nothing but discouragement. The toxic substance, if toxic substance there is, may not be easily identifiable because its effects may be largely psychic and there may be only slight physical disturbances in animals. It is difficult to be sure when a guinea-pig is deluded. A substance whose most important properties were only discoverable by human experiment would remain long hidden until someone happened to know what he was looking for, which no one at present does.

A NEW APPROACH.

It is possible, however, to approach the illness from another direction. Suppose that we start with the signs and symptoms and natural history of schizophrenia and ask ourselves how these could be produced, refusing to be diverted by the existing schools of thought.

There are no constant physical findings, but Hoskins (4), who has had a unique opportunity to study the illness, agrees with many others that disorder of the adreno-sympathetic system is one of the most constant features. Mott (5) some years ago observed some peculiarity in the adrenal medulla in schizophrenics, but he became more interested in the gonads and the matter seems to have been dropped. Early in the illness physical symptoms of anxiety are often found, but these die out as the illness progresses. It is as well to emphasize that the majority of authorities are agreed that there is no physical pathology known in schizophrenia.

The psychic symptoms are disturbances of association, thought, mood, and behaviour without dementia. Delusions and hallucinations occur frequently, and disturbances of bodily function lumped together as catatonia are important. The illness may sweep down in a few hours or may be very insidious. It may last a few days or a whole lifetime. Acute onset is usually considered a good prognostic sign, but it is not a certain one. An early response to treatment is also looked on as a good augury, but people who have been degraded lunatics for years have been known to recover long after treatment has failed. Now that schizophrenics are surviving longer than in the past, more cases are being seen in which the illness has died out in late middle age, leaving behind a socially crippled person who is not, however, a schizophrenic.

There is evidence that shy, shut-in people are more liable to schizophrenia than outgoing folk, but this is disputed, and some psychiatrists maintain that the "shut-inness" is just an early stage of the illness. What is certain is that people who apparently enjoyed excellent physical and mental health have been struck down by it. Most doctors agree that long thin people are more likely to develop it than short fat people.

No age is exempt, but the first attack usually occurs in young adulthood. Psychological investigation has yielded little except that clever and stupid people are equally affected.

Its association with difficulties in early life is uncertain and by no means proved ; it is often hard to decide when the illness began, because the childhood disturbances may only be early symptoms. Psychoanalytic evidence is vitiated by the lack of an objective standard due to the paucity of published analyses of normal people. We have therefore no sure means of telling whether the schizophrenic usually has a more unhappy childhood than the non-schizophrenic, but it is certainly not unknown for schizophrenics to have histories which suggest a happy and contented childhood.

We must therefore account for a situation in which a person of any age, but usually a young adult, in response to stress or with little evidence of it, becomes

slowly and insidiously, or with overwhelming speed and accompanied by acute confusion, subjected to disturbances of association, changes in affect, thought disorder, hallucinations and delusions and catatonic symptoms to such an extent that life outside a mental hospital becomes impossible. The sick person, on the other hand, may never even need to visit a doctor but may simply appear odd and eccentric. The illness may terminate quickly either with or without medical aid, or may be completely resistant to any form of treatment and continue for years without any pathognomonic physical changes being demonstrable. It must be influenced by a wide variety of treatments, such as psychoanalysis, deep insulin, metrazol, E.C.T., thyroid therapy and leucotomy. Occasionally events such as a severe physical illness or a psychic or physical shock may affect it favourably. It must be possible for the patient to recover after years of illness without measurable evidence of intellectual impairment, and to appear remarkably normal in spite of a long period of incarceration. The illness should bear some understandable relationship to the manic-depressive disorders, and not infrequently be indistinguishable from them at an early stage. It would be in keeping with our present knowledge if an inherited constitutional basis could be provided for its occurrence.

THE SYNTHETIC ILLNESS.

The first question that one asks is whether any known substance could produce results of this sort; not merely confusion with secondary delusions, but a disturbed mental state which could be mistaken for schizophrenia. It has been known for over fifty years that mescaline, the alkaloid extracted from the peyotl—*Anhelonium Lewinii*, an American cactus—produces symptoms almost identical with schizophrenia, including catatonia and thought disorder. The symptoms differ in different subjects, but not more markedly than different cases of schizophrenia differ. No account of the effect of altering the dosage of mescaline in the same subject has come to our notice, so that it is impossible to decide whether the difference in symptoms is due to differences in rates of absorption, or the ratio of body weight to dose, or to other factors. It has been taken for years by psychiatrists who wish to experience schizophrenic symptoms and to investigate synaesthesia. From time to time investigators have mentioned that it is unfortunate that more is not known about it. Klüver (6) in America and Eric Guttman (7) in this country drew attention to our ignorance on this subject and to its importance respectively; but are we really so ignorant? The formula of mescaline has been known for at least twenty-five years, and probably much longer. It had not, however, been published in a psychiatric paper for many years until Mayer-Gross's recent lecture (8). Unfortunately in this paper the formula was misprinted, and in addition the structural diagram was so arranged that its most remarkable quality was obscured. Organic chemists have, of course, known its biochemical affinities for many years, but they have rarely been interested in its psychological properties.

There are many other hallucinogenic drugs, but none has either such striking properties or such a simple chemical constitution as mescaline. It would therefore be an excellent candidate for a schizophrenic agent, if there were any likelihood of its appearing in the body.

Before discussing this question it is necessary to examine a widely held view whose most recent proponent is Mayer-Gross. To quote his own words: "The symptoms of mescaline intoxication have been compared to those of schizophrenia, but it is much more the strangeness experienced by the patient suffering from schizophrenia and the difficulties of describing what is happening in the two conditions which is similar. Many typical schizophrenic symptoms, especially in sub-acute and chronic states, are never seen in mescaline intoxication. Early psychotic phenomena in acute schizophrenia show certain analogues, especially in the field of hallucinations and other sense abnormalities" (8). Surely, in trying to lump together acute and chronic schizophrenic reactions and compare them with the laboratory observations of trained psychiatrists taking mescaline voluntarily, Mayer-Gross is comparing two innately different situations. It is highly unlikely that the unheralded schizophrenic psychosis of indefinite duration in an unprepared victim, and the experiences of a voluntary mescal taker who knows what to expect and how long his ordeal will last, would be exactly similar. The remarkable thing is that these acute reactions have so much in common. In the accompanying table it will be seen that mescaline reproduces every single major symptom of acute schizophrenia, although not always to the same degree.

TABLE I.—*A Comparison between the Psychological Effects of Mescaline and the Symptoms of Acute Schizophrenia.*

	Mescaline.		Acute schizophrenia.	
	Illusions.	Hallucinations.	Illusions.	Hallucinations.
1. Sensory disorders :				
a. Vision	xxx	xx	xx	xx
b. Hearing	x	x	xx	xx
c. Body image	xxx	—	xx	—
d. Smell and taste	xxx	xxx	xx	xx
e. Skin sense	xx	—	xx	—
f. Temperature	xx	—	xx	—
g. Synaesthesia	xxx	—	?	—
2. Motor disorders :				
a. Catatonia		xx		xxx
3. Behaviour disorder .				
a. Negativism		xx		xxx
b. Withdrawal		xx		xxx
c. Antisocial violence		(big doses) Reported		xx
4. Thought disorder :				
a. Pressure		xx		xx
b. Disturbed association		xxx		xxx
c. Blocking		xx		xxx
d. Substitution of <i>primitive thinking</i> in the form of visual images for conceptual thought		xxx		xxx
e. Neologisms		x		xx
5. Disorders of interpretation :				
a. Ideas of influence		xx		xxx
b. Paranoid ideas		xxx		xxx
c. Heightened significance of objects		xxx		xx
6. Delusions		xx (time factor)		xxx
7. Splitting		xx (time factor)		xxx
8. Depersonalization (a)		xx		xx
Derealization (b)		xxx		xxx
9. Mood disorders :				
a. Fear and terror		xxx		xxx
b. Depression		x		x
c. Indifference and apathy		xx (time factor)		xxx
d. Manic symptoms		x		x
e. Euphoria		xxx		xx
f. Schizoid humour		xx		xx
10. Insight		Sometimes absent (time factor)		Sometimes present

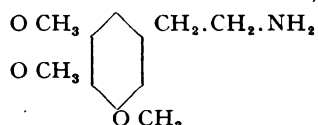
o, does not occur. x, occurs. xx, marked when it occurs but not always present. xxx, marked and frequent. —, not relevant.

We have actually noted in our six subjects all these effects of mescaline except 1(b) reported by Rouhier (15) and Tayleur-Stockings (16) and 3 (c) reported by Hey (17).

Subacute and chronic schizophrenia cannot be compared legitimately with acute mescaline poisoning, but should be compared with chronic mescaline intoxication. Very little seems to be known about this condition, and one of the few references to it known is quoted in Mayer-Gross's lecture. It reads: "The use of the drug was, and probably still is, a problem to the Christian Missionaries who insist that its regular intake leads to increasing laziness and impairment of will-power." Surely a lay person might describe a chronic schizophrenic in such a phrase? May it not be that to use his own words, "the strangeness experienced by the patient suffering from schizophrenia and the difficulties of describing what is happening in the two conditions" constitute an essential similarity? Language is not designed to depict the weird world of the mescaline taker and the schizophrenic. Only very rarely is the latter willing or able to describe his experiences coherently. When he does, as in Henning's (9) astonishing book *The Witnesses*, the world which he describes is more like that of the mescaline taker than any other.

The objection that all the symptoms of schizophrenia are not found in acute mescaline poisoning is not valid. So far as one can judge from the little evidence available, the effects of mescaline vary as much as but not more than the symptoms of schizophrenia, which unhappily for psychiatrists allows a wide range of variability.

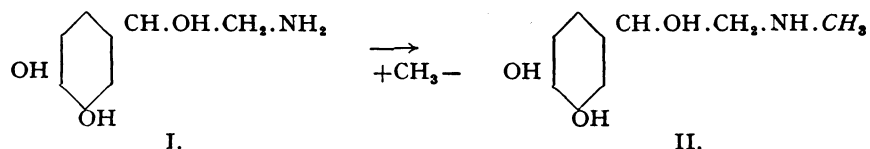
To return to the chemical constitution of mescaline, which is—



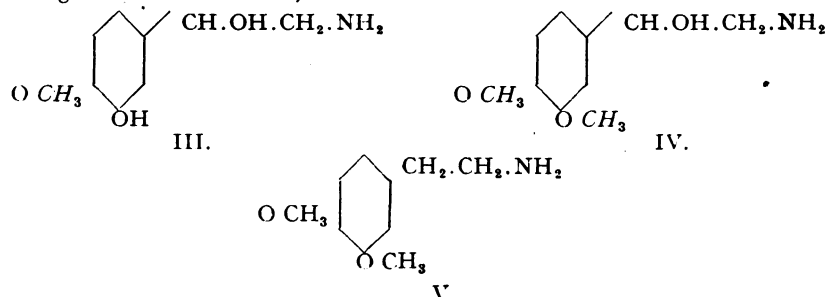
it is a fairly simple compound, and those with biochemical knowledge will realize that it is not very dissimilar from adrenaline. This observation was made by one of us in June, 1950, with the assistance of Dr. Julian Redmill, then a medical student at St. George's Hospital. The adrenergic qualities of mescaline and many similar drugs were investigated by Dr. J. Harley-Mason, M.A., F.R.I.C., University Demonstrator in Organic Chemistry at Cambridge. He has been good enough to allow the following biochemical observations on this aspect of the subject to be published.

BIOCHEMICAL NOTE.

He writes: "It is extremely probable that the final stage in the biogenesis of adrenaline (II) is a transmethylation of nor-adrenaline (I), the methyl group arising from methionine or choline.



It is just possible that a pathological disordering of its transmethylation mechanism might lead to methylation of one or both of its phenolic hydroxyl groups instead of its amino group, leading to the formation of (III) and (IV). Methylation of phenolic hydroxyl groups in the animal body is of rare occurrence, but a significant case has been reported recently by Maclagon and Wilkinson (10). It is particularly interesting to note that out of a series of phenylethylamine derivatives tested by Noteboom (11), 3,4-dimethoxyphenylethylamine (V) was the most potent in producing catatonia in animals, and that this substance



differs from (IV) only in the absence of its side chain hydroxyl group. It is however doubtful, in view of the relatively high dosage of (V) required to produce a catatonic effect, whether enough of a compound such as (IV) could be elaborated in the body to produce mental symptoms, having regard to the normal capacity for adrenalin production. It may be, however, that in chronic intoxication smaller amounts would be effective.

"The extremely high activity of lysergic acid diethylamide is remarkable, the dosage level of 30-50 mgm. being one-tenth the amount of adrenalin or thyroxin required to produce an observable response. The compound bears no relationship to any substance at present known to occur in the animal body and the mechanism of its action is wholly obscure."

Surely it is significant that a single biochemical failure could occur in the stress mechanism and produce these dangerous toxins, one of which is already known to be a powerful catatonic agent? Mescaline itself is not, of course, the toxic agent in schizophrenia. It is not nearly active enough, and the adrenals could not possibly make 500 mgm. or more daily, which would be necessary to produce symptoms. It is, however, thought that mescaline itself is non-toxic, and that the toxic agent in mescalism is a breakdown product.

We therefore suggest that schizophrenia is due to a specific disorder of the adrenals in which a failure of metabolism occurs and a mescaline-like compound or compounds are produced, which for convenience we shall refer to as "M substance." The striking implications of the relationship between the bizarre Mexican cactus drug and the common hormone have, so far as we know, never been recorded before. Psychiatrists appear to have been unaware of its biochemical structure, biochemists to have been uninterested in its production of an artificial psychosis. The close clinical connections between schizophrenia, anxiety states and stress have been known for a long time, and the process involved may be that in certain people when the adrenals are overworked (due perhaps to an inherited latent fault as Kallman has suggested) (12) the process of methylation becomes disturbed and highly toxic substances are produced. This M substance, once produced, would naturally set up a vicious circle, since one of the prominent features of both the mescal "psychosis" and of many cases of schizophrenia is the stress and terror experienced by the victim. There is already a certain amount of evidence for the presence of such an agent (13). This hypothesis could also account for the somatic manifestations of schizophrenia—the excessive adrenocortical activity perhaps generated by Vogt's mechanism, the vascular changes, the disturbances of carbohydrate metabolism, the overloading of the detoxicating mechanisms of the liver, and the pigmentation (melanin and adrenaline metabolism are linked).

The result of these endogenous disturbances in sensation, feeling and thought upon the sick person would depend on the age of onset, the rate at which M-substance is produced, the patient's previous personality and special mode of reaction to M-substance, and the cultural setting in which the illness occurs. These variables allow for the enormous range of different reactions such as is actually observed in schizophrenia, which could thus appear to have many and various "precipitating causes."

Similarly, many forms of treatment could be expected to alleviate the condition to some extent—acute physical illnesses with their general metabolic upset: psychotherapy, where the attempt made to help the patient adapt to his strange new environment might serve to break the vicious circle by alleviating the stress experienced and thus depressing the production of M-substance; leucotomy, which might break the circle at the level of cerebral reaction to stress; and lastly and most significantly the only generally accepted treatment, insulin, is itself an anti-adrenaline agent. Further, since it is known that mescaline produces its effects by interfering with the glucose metabolism of the brain, the beneficial effects of insulin treatment may be produced, not so much by the comas, as by the large amount of glucose that is forced into the bodily metabolism. It is of interest that Mayer-Gross (14) reports that high doses of glucose raising the blood sugar above 200 mgm. inhibit the action of lysergic acid (LSD. 25).

Many of the results of schizophrenia have little to do directly with disturbances of brain function, but depend on factors which are, in the anthropological sense, cultural. The isolation and dislike which the patient experiences in our community forces him to retreat into his private world. The schizophrenic regresses because, faced with an incomprehensible change in his external and internal sur-

roundings, his painfully learned patterns of behaviour suddenly become useless and he is left isolated and enmeshed in his own fantasies and the phantasmagoria produced by M-substance. He is literally and not figuratively out of touch with his environment. In societies different from our own the results of this universal metabolic abnormality (the production of M-substance) may be socially beneficial to the individual. For instance the Shamans in Siberia and the Mystics in Tibet are in fact leaders of society though undoubtedly having schizophrenic experiences.

DISCUSSION.

It is easy enough to speculate about an illness which has been the subject of so much investigation and remains so barren in established aetiology, but the first essential for any directed programme of research is a hypothesis based on fact, otherwise observation hardly progresses beyond the stage of cataloguing. It seems to us that the advantage of this new approach lies in its combination of the clinical and the biochemical, which allows one to substitute a definite plan of campaign in place of the present state of speculation about unknown substances. Mescaline is the simplest agent producing a schizophrenic-like psychosis, and the only one that closely resembles a substance found naturally in the body. The proper course of action to test this hypothesis is clear. It would consist in the pharmacological investigation of mescaline, its breakdown products, and the range of compounds between it and adrenaline (especially 3,4-dimethoxyphenylethylamine), and the attempt would have to be made to isolate these substances from the body-fluids of acute schizophrenics. Once these investigations have been done our hypothesis will either join the large number of plausible theories which have failed to stand up to the test of experiment and are now to be found on the scrap-heap of psychiatry in the pages of old journals, or the cause of schizophrenia will be known.

SUMMARY.

After a brief survey of the present state of our knowledge regarding schizophrenia we have drawn attention to the close biochemical relationship between adrenaline and mescaline. This, taken in conjunction with the clinical relationship between acute mescaline intoxication and acute schizophrenia, and between the latter condition and stress, appears to us to be significant. The clinical and biochemical implications of this are discussed.

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