A SMALL RESEARCH IN SCHIZOPHRENIA

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OUR RESEARCH began eight years ago in a part of medicine mainly concerned with classification and empirical treatment based on a study of symptoms. The scientific method has been applied to medicine comparatively recently and there are places where it penetrates rarely. Specialties whose scientific background is poorly developed or in which science proves difficult to apply lag behind the more fortunate. Psychiatry is one of the laggards. Yet it was among the first to emerge, for by the 1850's it had its own journals in both Britain and North America, while men had devoted themselves solely to its practice even earlier. Unluckily the sciences required to nourish and fertilize psychiatry did not develop as quickly as those which proved useful to other specialties. Psychology, sociology, anthropology, biochemistry, pharmacology, neurophysiology and neuroanatomy are in the main children of the 20th century. Starved of scientific guidance and stimulation, psychiatry fell back on the descriptive study of symptoms, dogma, system building and empiricism which is the fate of medicine without science.

SCHIZOPHRENIA

Among the ills which afflict mankind today few are more formidable, more universal, more persistent, more damaging, more mysterious and more elusive than schizophrenia – the shattered mind. How many of those who use this sinister and enigmatic word know what it means and what it implies? It is one of the gravest and one of the most tragic illnesses. Nowadays it kills rarely, but so savagely does it cripple that at the present time one out of every five hospital beds in the western world is occupied by a schizophrenic. What is schizophrenia? It is a group of illnesses which include those labelled dementia præcox by Emil Kraepelin, the German psychiatrist, at the end of the 19th century. In 1910, a Swiss, Eugene Bleuler, rather to Kraepelin's disgust, enlarged his ideas somewhat and introduced the name schizophrenia. Dementia praecox (madness of the precocious or parboiled) is not a satisfactory name for an illness which can start far into middle years. Bleuler's word gained ground and has now almost swallowed up its predecessor.

During a lifetime, at least one person in a hundred will become schizophrenic and perhaps one-third of that number will be permanently harmed. Young men and women struck down in their prime form the bulk of the victims, and mental hospitals are crammed with tens of thousands, many of whom have been shut away for years. Even those who work with this monstrous illness are surprised at its vagaries. Within a few weeks a cheerful and active young man can become so deranged that he will eat his own excrement: while in the space of another few weeks a long forgotten "hopeless madman" may, without any special treatment, return to sanity. This does not often happen, but that it happens at all is astonishing. Slow and insidious illnesses in which the sick person becomes almost imperceptibly more and more seclusive, odd, shy and unable to hold his place in society are most usual.

What, then, makes the schizophrenic person behave in this way? The literature on this alone is vast. Briefly he experiences changes in perception, thinking, mood and sometimes bodily posture, occurring separately or in concert, which can last a few days or a lifetime. These changes in experience are understandably accompanied by altered behaviour. The sick person usually recognizes his surroundings and his memory is unimpaired. He is not always aware that he is ill, because like the rest of us he tends to believe the evidence of his senses, and although actual hallucinations (false perceptions) are comparatively rare, distortions and alterations in reality are frequent. These strange and disturbing experiences readily lead to false beliefs –delusions.

THE CAUSE

Everything from lack of mother love to a specific inherited weakness of constitution, from the unkindness of an industrial society to invasion by yeast-like organisms has, or has had, eloquent and industrious advocates. None has yet been proved, but in spite of this the more partisan vehemently denounce those who disagree with them.

Kraepelin held that the glands (possibly the gonads) produced poisons which affected the brain. Bleuler seems to have believed this too, though lukewarmly. Carl Jung seceded from psychoanalysis in 1913 largely because he could not support Freud's contention that schizophrenia was due to difficulties in early childhood. At 83, Jung, a lively and unrepentant heretic, still reaffirms his belief in a toxine-X, whose secretion is somehow connected with emotion. Freud changed his mind in later years and talked of curing mental illness with a syringe.

Jung published his views in 1906, and since then the hunt for the brain poison has not gone well. It has been sought zealously. The searchers—patient, unrewarded scientists—have continued in the face of repeated discouragement and open hostility from many clinicians. Toxine-X remains undiscovered. It has had many swan songs in the last half century. The most recent and possibly most definitive was that given by M. Bleuler, son of Eugene, in 1950. "Looking over these and other

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works in the pathological physiology of schizophrenics one is forced to make this negative statement. These works have failed to bring us even one step closer to the possibility of finding behind the psychological psychosis of schizophrenia a definable, specific, pathological, somatic schizophrenia. We have no evidence of any disturbance which would neatly differentiate it from other psychoses, somatic disorders, or the norm. It is possible that as a result of these negative results the search for a specific somatic basis for schizophrenia will be given up for a long time to come, if not permanently." This authoritative and unambiguous statement represented the opinion of many psychiatrists at the start of the second half of this century. It rests on the ruins of many high hopes.

NEW APPROACH

Observation is the gateway to discovery. In May 1950, our colleague, Dr. John Smythies, while reading Rouhier's book "Le Peyotl" noticed something which lifted a latch and allowed exploration to begin. Peyotl is the Mexican cactus *Anhelonium williamsii*, a small succulent which has been studied by psychologists, psychiatrists, anthropologists, chemists and many others since the 1880's. This interest stems from the fact that it contains among other things mescalin, an alkaloid isolated in the 1890's, which induces visions and other changes in awareness in some people. Many years ago Louis Lewin, the father of psychopharmacology (the science which studies the relationship of drugs to psychological change), hinted that mescalin and similar substances could be used as tools for exploring the mind in health and disease. This hunt was taken up, but only in a limited way. Many did not agree that any mental illness, quite apart from schizophrenia, and the mescalin experience were closely related to each other; but perhaps more important, no consistent biological disturbances were found in schizophrenia. Smythies observed that mescalin looked familiar and after consulting Dr. Julian Redmill (then a medical student, who had been a biochemist) we learnt that it resembled, amongst other things, adrenaline (epinephrine). This observation we learnt later was unoriginal, but when combined with a second observation that there was a resemblance between the mescalin experience and that of some schizophrenics we had the makings of a hypothesis which could be used and tested. To get beyond the gateway, hard work, money, much luck and a long period of time would be needed.

FIRST STEPS

We had no money, but we had luck. Dr. J. Harley-Mason of Cambridge confirmed Redmill's view that mescalin and adrenaline resembled each other and agreed that intermediate compounds might exist. We did a small number of experiments with mescalin and found—as Guttman and Maclay and Tayleur Stockings had found before us—that some cases of acute schizophrenia closely resembled some mescalin experiences. The controversy which surrounds this often disputed point resolves itself if one recognizes that the mescalin experience and that of some people suffering from schizophrenia can be studied in terms of similarity or difference, depending upon one's purpose. This allowed us to emphasize what had never so far as we can discover, been stated clearly before, that it is stupid to compare a single experimental taking of mescalin with every sort of schizophrenia. One should compare very acute cases of schizophrenia where onset is rapid so that secondary elaborations play a lesser part. When this is done, as Table I shows, the illness and the experiment have much in common.

TABLE I.—A COMPARISON BETWEEN THE PSYCHOLOGICAL EFFECTS OF MESCALIN AND THE SYMPTOMS OF ACUTE SCHIZOPHRENIA*

	Mescalin		*Acute schizophrenia*	
	Illusions	*Hallucinations*	*Illusions*	*Hallucinations*
Sensory disorders				
Vision	+++	++	++	++
Hearing	+	+	++	++
Synæsthesia	+++	—	?	—
Motor disorders				
Catatonia		++		+++
Behaviour disorders				
Negativism		++		+++
Withdrawal		++		+++
Thought disorders				
Pressure		++		++
Disturbed association		+++		+++
Blocking		++		+++
Conceptual thought replaced by visual images		+++		+++
Neologisms		+		++
Disorders of interpretation				
Ideas of influence		++		+++
Paranoid ideas		+++		+++
Heightened significance of objects		+++		++
Delusions		++		+++
Depersonalization		++		++
Mood disorders				
Fear and terror		+++		+++
Depression		+		+
Indifference and apathy		++		+++
Manic symptoms		+		+
Insight	Sometimes absent		Sometimes present	

+ = occurs: ++ = marked when it occurs: +++ = marked and frequent: — = not relevant.
*From Osmond, H. and Smythies, J.: *J. Ment. Sc.*, 98: 309, 1952.

Our small number of experiments not only made us more convinced of our hypothesis, but provided us with a surprising clue. We had assumed that we would work from mescalin towards adrenaline. Retrospectively this gigantic task was far beyond our capabilities either then or now. A severe asthmatic, listening to a recording of a mescalin experience, remarked that things like that sometimes happened to him. He told us that if, as he sometimes did, he took very large amounts of adrenaline, the outside world became changed; he had coloured visions with his eyes shut and feelings of unreality. Perhaps if one could in some way cut out the pressor effects of adrenaline so that large quantities could be taken, we would have our natural mescalin-like compound—M-substance as we called it. So we began to consider the immediate derivatives of adrenaline.

PINK ADRENALINE

In 1951 our work began in Saskatchewan. After Bleuler's comments, toxic theories of schizophrenia were at about their lowest ebb. Without new methods we could expect no support. We searched the literature to find how many hallucinogens were known—defining these as being substances with a mescalin-like action which did not produce clouding and confusion of consciousness or major bodily disturbances. We could only find four in the United States and British pharmacopœias whose structural formula was known. These are mescalin itself, lysergic acid diethylamide, harmine and ibogaine. The status of the two last was shaky though it was later confirmed. Hashish was left out because its active principle was in doubt and it is still uncertain.

We found several asthmatics who had perceptual changes after taking adrenaline; at least two had associated this with deteriorated adrenaline. It seems likely that this is not infrequent but that asthmatics simply get some more adrenaline if they notice it.

Dr. Asquith of Regina told us that when, during the war, pinkish adrenaline which had lost its pressor effects was used during anæsthesia, "disturbances" which included hallucinations occurred when the patient revived. It seemed to us that substances close to adrenaline might be worth investigation.

Early in 1952 when we had a little money we called upon scientific colleagues at the University Medical School in Saskatoon, Professors MacArthur and Hutcheon, and Dr. V. Woodford, and asked for their help. When we mentioned pinkish adrenaline, Professor Hutcheon suggested adrenochrome. Professor MacArthur showed that it could be related to every hallucinogen then known. Professor Hutcheon made some of this brilliant red stuff for us.

An advantage of a small research is that one is spared many difficult decisions. We had no animals with which to experiment and so were not lured into that treacherous region where so much research has floundered – animal catatonia. Great effort has been spent in equating the fixed postures of a variety of animals with human schizophrenia. The relationship is still unclear. In man, catatonia is not very frequent and is usually a transient episode in the illness. In *October 1952* we undertook preliminary tests with adrenochrome on ourselves, our wives and some colleagues. We found that changes in perception, thinking and mood occurred, not of the extreme kind one sees with mescalin but mildly and insidiously, not unlike those seen early in schizophrenia. Had we found our M-substance in so short a time? We were quickly undeceived. In the next few months we not only lost our source of adrenochrome, but could find no other. Those who tried to repeat our work were equally unfortunate, for while we now know that chemists could not make pure, stable adrenochrome, because of professional pride none was prepared to admit this. We and many others had frustrating experiences with more or less impure or deteriorating samples. In *July 1954* our luck turned when we received 200 mg. of adrenolutin from Dr. Harley-Mason. This is a greeny-gold relative of adrenochrome. This too was encouraging, but it was hard to experiment with because its effects would sometimes persist for a week or more. We thought that it would be easier to synthesize than adrenochrome. This was a mistake and we have only recently had pure stable adrenolutin. In 1956, we worked with inhaled, mixed adrenaline by-products of a pinkish colour. These are very powerful but seem too dangerous to work with. They confirm that there are several adrenaline derivatives of which we are ignorant. Our direct search for M-substance reached a stalemate in an unexpected way. The limitations of synthetic chemistry rather than those of psychiatry proved to be our gravest obstacle.

OTHER WORK

It might appear too bold to build a hypothesis of schizophrenia about a group of substances not demonstrated in the body. However, the evidence for the potential presence of adrenochrome as reviewed by Boeg was strong. It would be strange indeed for adrenochrome to be absent from a system containing the substrate (adrenaline) and the enzymes that could convert the substrate into adrenochrome.

Adrenaline is oxidized by plasma into a substance which has a peak absorption in the DU spectrofluorometer at 395 μ. (Leach and Heath). Hoffer and Kenyon showed that the new substance was adrenolutin. Adrenochrome was readily transformed into the greenish fluorescent adrenolutin.

The reaction was enzymatic because of cœruloplasmin (Leach and Heath). Isolation studies with schizophrenic cœruloplasmin led to the discovery of taraxein. This substance is closely associated with cœruloplasmin. Injected into monkeys it produces marked changes in behaviour and in the depth electroencephalogram. In man it produces transient schizophrenia-like symptoms and alters the metabolism of adrenaline. No taraxein has been extracted from non-schizophrenic persons.

The hypothesis subsumes that the increased production of adrenochrome will cause some change, either qualitative or quantitative, in the urinary indoles. These changes have been found (McGeer), but so many indoles are present that it is difficult to interpret the findings. However, schizophrenic fluids do interfere with growth of cells, both plant and animal, as do many indoles.

The hallucinogenic properties of adrenochrome placed in close proximity to brain tissue (in the ventricles) was demonstrated. Adrenaline under these conditions produces anæsthesia and analgesia. There is a lag period of 30 minutes after adrenaline.

Adrenochrome acts more quickly; this suggests that some of the activity after adrenaline injection was due to the formation of adrenochrome in cerebrospinal fluid where it is quite stable.

Thus at the beginning of 1957 the hypothesis was strengthened by the observation: (1) that plasma could convert adrenaline to adrenochrome and then adrenolutin; (2) that this reaction was enzymatic; (3) that taraxein was closely associated with these enzymes; and (4) that adrenochrome in the brain is hallucinogenic.

1957: THE BREAK-THROUGHS

In 1957 and in the early months of 1958, Drs. N. Payza and R. Heacock of our team have achieved successes which are changing the tempo of our research. In mid 1957, Payza discovered how to synthesize pure adrenochrome. In spite of the gloomy who claimed that it would never be made and was "inherently" unstable, once the contaminating silver ions have been removed it keeps well. Payza then began to develop an assay method for adrenochrome to measure it in blood, spinal fluid and urine. He succeeded after much initial difficulty. At the same time he has been studying the mechanisms, apparently enzymatic, by which adrenochrome becomes either the apparently harmless leuco-adrenochrome, or the powerfully persistent adrenolutin. Heacock meanwhile has found how to purify adrenolutin, and is now searching fo. more aminochromes, as these derivatives of adrenaline have been called.

Using our assay, we have been able to show that when the enormously powerful L.S.D.-25 is given to normal subjects, if psychological changes occur there is usually a dramatic and coincident rise in the levels of adrenochrome in the blood, and that adrenochrome injected intravenously is destroyed much less rapidly. From this we have found that schizophrenic people seem less able to remove adrenochrome from blood than normals. Much work is now in progress, for we now have a working hypothesis and a method which allows us to test, refine and explore it.

WHERE WE STAND NOW

We have not yet found our M-substance. We consider that we have two worthy candidates, adrenochrome and adrenolutin, while we have evidence that there are other powerful substances of which we know very little.

Not everyone agrees with our views, and clearly it will take them some time to learn to work with adrenochrome. However, there is now something a little more specific to disagree about than unidentified toxins, degenerative processes or even psychodynamic formulations. There is also a chance that this massive and elusive illness may, before long, become easier to diagnose and that with this will be made the first steps towards treatment of a rational rather than empirical sort. Perhaps the body with its usual parsimony uses the hormone concerned with flight and fright to modify perception, thinking and mood. If this is so, one can see many teleological advantages to such a scheme. But to do this the sustained effort of research is needed. So far, moneys to enquire into the workings of the brain, the organ of mind, have been generally meagre. Money is readily available for every other organ, but the brain which as the vehicle of mind makes all else possible is grievously neglected.

Our work has been on a small scale and perhaps lacking in refinement. We have tried to do as Helmholtz once advised, "to trust the inadequate and act on it". We hope one day to be able to add as he did in his aphorism "Then it will become fact."

RÉSUMÉ

L'auteur trace dans leurs grandes lignes des recherches qui ont pris place dans le domaine de la schizophrénie. L'étincelle jaillit un jour de la lecture d'un livre sur le peyotl (*echinocactus Williamsii*) et les anomalies qu'il produisait chez ceux qui se servaient de son suc. On découvrit bientôt que la mescaline en était l'ingrédient actif. Alors qu'on cherchait à établir un rapport entre l'intoxication à la mescaline et la schizophrénie aiguë on se rendit compte du rapprochement qui existe entre la constitution chimique de cet alcaloïde et celle de l'adrénaline. D'une part, certains asthmatiques chroniques déclarèrent avoir été sujets à d'étranges sensations après administration d'adrénaline, d'autre part on se rappela avoir remarqué qu'en anesthésie pendant la guerre, l'emploi d'adrénaline rosée avait coïncidé dans la période postopératoire immédiate avec des altérations du comportement chez les opérés. Des recherches montrèrent qu'un des produits de cette forme altérée d'adrénaline était l'adrénochrome qui lorsque administré à des sujets normaux produisit des altérations insidieuses de la sensation assez semblables à celles que l'on observe dans la schizophrénie. Les recherches à ce point furent temporairement ralenties par l'impossibilité de produire l'adrénochrome sous une forme stable et pure. On découvrit cependant que l'adrénolutine était un autre produit de l'oxydation de l'adrénaline et que cette réaction se produisait dans l'organisme sous l'effet de l'enzyme céruloplasmine. Cette substance mena à la découverte de la taraxéine que l'on a jusqu'à présent isolée uniquement du sérum des schizophrènes. Une méthode a depuis été mise au point pour synthétiser l'adrénochrome en forme pure et d'en faire le dosage dans le sang, le liquide céphalo-rachidien et l'urine. Il semble que le L.S.D.-25 agisse en retardant la destruction d'adrénochrome et permettant son accumulation dans l'organisme. Il est intéressant de noter que toutes ces découvertes ont été effectuées dans des conditions matérielles et financières des plus modestes.

EFFECT OF HEPARIN UPON TOTAL OXYGEN CONSUMPTION OF ATHEROSCLEROTIC INDIVIDUALS

Total basal oxygen consumption and respiratory quotient were determined by Engelberg (*Am. J. M. Sc.*, 236: 175, 1958) in 46 atherosclerotic patients before and after injection of heparin. In 20 there was an average increase in oxygen consumption of 32.7%; in three there was an average decrease of 15.3%, and in 23 there was no change after heparin. There was no increase in oxygen consumption after saline placebos or oral anticoagulants. The respiratory quotient showed no characteristic change, although more frequently it fell after heparin injection.

The author suggests that the increase in oxygen consumption results from the lipæmia-clearing action of heparin.