BIOCHEMISTRY AND SCHIZOPHRENIA

By

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IT is presumptuous for a clinician to embark on this subject, and I hasten to apologize for my boldness in doing so. My excuses are many. The first comes from clinical experience. Since my student days, when I observed malignant schizophrenia in a young girl for the first time, and watched its relentless progress despite all therapeutic efforts, I came to the belief that this was an illness of body as well as of mind, and this belief has led me to maintain a continuing interest in the medical, as distinct from the purely psychological, investigations of this disease throughout my professional years. Next has been the observation of experimental or model psychoses produced by drugs. An LSD or mescaline psychosis is not schizophrenia, any more than curare poisoning is myasthenia gravis, but there is enough similarity between the dissociation states produced by psychotomimetic drugs and the real thing to stimulate one's curiosity, at least.

Physical treatment methods of schizophrenia, including insulin and electro-convulsive therapies, as well as the new pharmacological agents, especially the Rauwolfia fractions and the phenothiazines, have made their impression on me as well, as they have on many of you. Their ability to bring about cessation of the schizophrenic process is far from consistent, but enough gratifying results have occurred to catch the fancy of any student of this disease, and to make him wonder about the ways in which they exert their effects. My final excuse for tackling this subject of biochemistry and schizophrenia is the one of good fortune. It has been my privilege to come to know many of the people working in this field in the United States and Canada in recent years, and to listen to them in both formal and informal moments. I come, therefore, as a reporter of work in progress from the hands of some of my colleagues in North America. This is an account of some of the straws they have thrown into the wind, and of the directions in which they seem to be blowing.

The search for a biochemical "lesion" in schizophrenia is a long story and needs no review here. I shall confine myself to more recent investigations. At the present time there is a renewed search for an endotoxin or for multiple endotoxins, produced through metabolic error, as the answer to the riddle of schizophrenia. This hypothesis holds that the patient afflicted with the disease, possibly because of an abnormality in his or her genes, comes into the world with a chemically determined predisposition, and that it may flower into clinical symptoms at varying age levels from one case to another. It is generally held that the basic difficulty is in enzyme systems, and that as the result of such enzymatic fault, chemical substances poisonous to the brain are generated, and that the patient literally stews in his own juice as a result.

If such a derangement of one's juice is present in schizophrenia, it should be possible to transfer body fluids from the healthy to the sick, and to note behavioural changes. This has been done, and with occasional suggestive results. Reiter (1938) performed exchange transfusions on four schizophrenic patients, using blood from non-psychotic subjects as donors. Three of the four showed

improvement, which was impressive in two cases, and it lasted for three to four weeks.

Recently Freedman and Ginsburg (1957) have repeated Reiter's experiment in four cases. The first was one of identical twins, aged 5½ years. They were suffering from childhood schizophrenia. The sicker twin underwent exchange transfusion, while the less sick twin acted as a control. The donor blood came from a non-psychotic adult. It was estimated that 55 per cent. of the child's total blood was exchanged. As the transfusion proceeded, the child's initial restlessness changed to tranquillity. He became more aware of his surroundings in succeeding days, attempted to play simple games, showed evidences of affection towards others he had never exhibited before, and began to babble, although he had never talked previously. The improvement began to recede after the third week, and he reverted to his former severe schizophrenic state in the fifth week. The other twin, living under identical conditions, showed no change during the experimental period. These investigators were unable to obtain benefit in three chronically ill *adult* patients in which this procedure was followed.

What occurs when we look at the other side of the coin, when blood or a blood extract from schizophrenics is introduced into the circulatory system of normal non-psychotic recipients? This brings us to the studies of the Tulane University group under the direction of Dr. Robert G. Heath (1957a). Recently they have made rapid injections of 450 ml. of plasma from schizophrenic patients, to which 50 ml. of citrate has been added, into the veins of non-psychotic volunteer prison inmates after 500 ml. of their own blood had been withdrawn. With the help of a hand pump it was possible to effect this intravenous plasma injection within a space of 2 to 3⅔ minutes. All of four volunteers receiving plasma from schizophrenics developed symptoms, described as being characteristic of schizophrenia, which persisted for 15 to 45 minutes. The reactions were not intense, but all subjects showed lessening in facial animation, and all described symptoms of depersonalization, blocking and thought deprivation. One showed a mild degree of posturing. Although the reactions were mild and without clear-cut secondary symptoms such as hallucinations, they were all definite. Two subjects receiving plasma from non-psychotic donors showed none of these aberrations. The experiments were conducted under double-blind conditions.

In addition to this experiment of rapid whole plasma injection from schizophrenic patients into non-psychotic normals, the Tulane group has been occupied during the past two years with the study of serum concentrates injected in the same fashion. They have made a protein extract from the blood serum of schizophrenics (Heath *et al.*, 1957b) which they call taraxein.* This extract has been given to 21 human non-psychotic volunteers. The dose administered in each case was that quantity of taraxein which could be derived from 400 ml. of schizophrenic serum. Similar extracts from non-schizophrenic blood were used as controls, and a double-blind technique was used to assess results. All subjects who received the concentrate from patients ill with the disease developed symptoms which have been described for schizophrenia. Fundamental symptoms such as blocking and deprivation of thought, depersonalization and autistic feelings developed consistently, and persisted for two hours or longer. Each of the classical symptoms, such as catatonic stupor and excitement, hebephrenia, ideas of reference, delusions of grandiosity or persecu-

* From the Greek *tarasso*, to throw into turmoil or disturb the mind; similarly the term ataractic is applied to drugs with the opposite effect.

tion, and auditory hallucinations appeared in one or more of the test subjects. No visual hallucinations were reported. Heath informs me that these observations have been duplicated by Swedish investigators recently.

Another recent report on the behavioural effects which result from the injection of schizophrenic blood plasma is worthy of account. In this case the albino rat (Holtzman strain), a less complicated creature from the standpoint of behaviour than his human cousin, was used as the recipient. Winter and Flataker (1951) developed a rope-climbing test for rats in order to compare their responses to various anti-histaminic drugs. The rats were trained to climb a vertical rope approximately five feet high (172 cm.). They were fasted overnight, and a dish of food placed on a platform at the top of the rope served as an inducement for climbing the next morning. As an immediate stimulus to climb the rope, mild electric shocks were applied to the rats' feet through a wire grid on the floor of the cage. After a week to two weeks of such training, these laboratory rats learned to climb the rope in approximately four seconds after the electrical stimulus was applied, and there were only minor variations from rat to rat and from trial to trial.

This technique lends itself to accurate timing within 0·1 second intervals and to the expression of the rats' response in quantitative terms. Climbing-time was measured at intervals after injection of the drug over a 3-hour period.

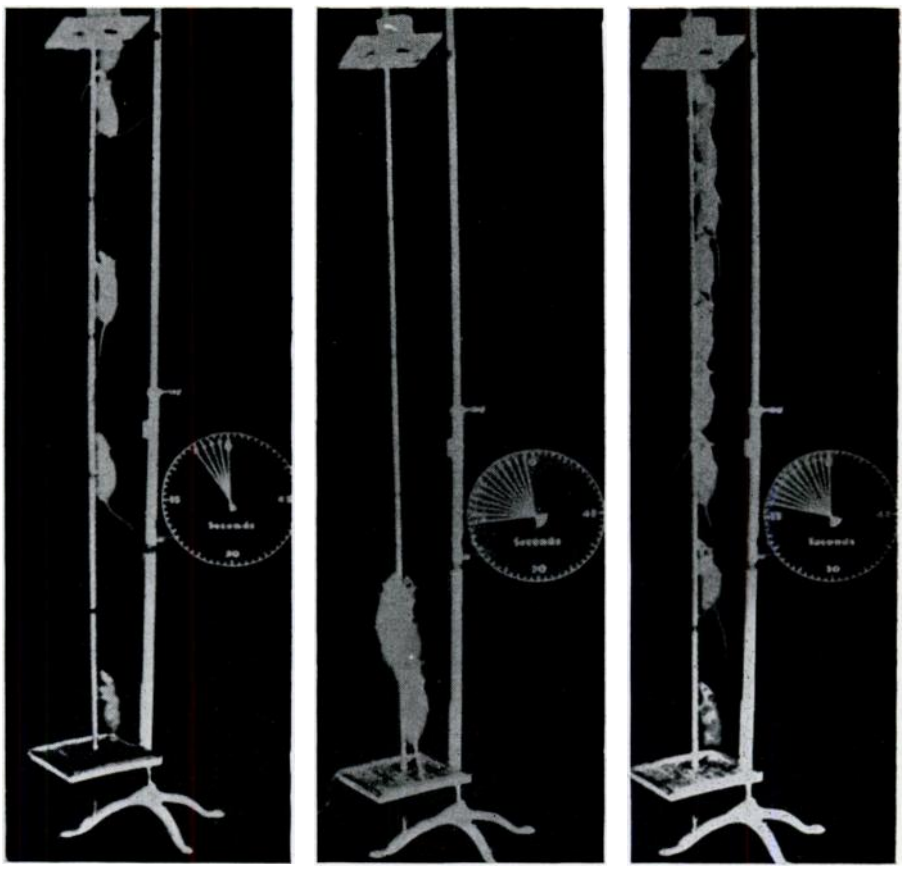

FIG. 1.

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When the climbing time was plotted against the time after injection of a drug, an accurate measure of the degree and the duration of the drug's effects could be obtained in units which they called "minute-seconds".

Winter and Flataker (1956) also found this rope climbing test to be an efficient quantitative method for expressing LSD effects in the rat, and more recently (1957) they have turned to the study of extracts from the blood of humans in health and disease. Heparinized plasma from psychotic patients not on treatment with ataractic drugs (Fabing, 1955) was obtained from three mental hospital populations and from a group of non-psychotic volunteers, part of whom were in good health and part of whom were patients suffering from medical and surgical disorders. Animals were given 1 ml. injections of plasma under blind experimental conditions in which the experimenter was unaware of the diagnosis associated with the plasma samples. Three rats were injected in each test. Seventy-eight psychotic patients and seventy non-psychotic subjects provided plasma specimens for these studies. The following table summarizes their results:

Group	Diagnosis	No. of Patients	Average C.T.D.* min.-sec.
I	Schizophrenia, paranoid	17	1,073
II	Schizophrenia, catatonic	10	720
III	Schizophrenia, childhood	3	800
IV	Schizophrenia, hebephrenic	4	249
V	Schizophrenia, undifferentiated or not specified	11	920
VI	Miscellaneous	8	991
VII	Alcoholic psychosis	3	514
VIII	Mental deficiency with psychosis	4	274
IX	Manic depressive	4	485
X	Schizoid personality	3	155
XI	Emotionally unstable	2	67
XII	Brain trauma	1	164
XIII	Volunteers, normal health	44	147
XIV	Non-psychotic medical and surgical patients	26	149

* C.T.D.=Climbing Time Delay.

The delay in climbing times in the rats who were injected with plasma from psychotic patients, and especially from the schizophrenic groups, is demonstrated clearly by the table. The data have been subjected to various kinds of statistical analysis, and it is concluded that the differences are highly significant. In addition to the stark objectivity of these figures, the investigators have described profound behavioural changes in the rats receiving intraperitoneal injections of the more potent plasma specimens from schizophrenic patients. Instead of being frisky and anxious to be handled, the rats retreated to the back of the cage, huddled together and became quiet and withdrawn. Their climbing technique was clumsy and was often interrupted, while the animals seemed to stare into space. If they achieved the platform at the top of the rope, they often hung their heads over the food box without eating. Much of this behaviour appeared reminiscent of the activity of the same rats under intoxication with LSD. Experiments were also carried out with injections made subcutaneously, but effects were lacking. Similarly, intraperitoneal injections of cerebrospinal fluid from schizophrenics failed to produce climbing time delay and changed behaviour.

Let us go back to our original question. Is the schizophrenic patient stewing in his own juice? It seems that the experiments detailed above give a

hint that when much of the blood of at least some schizophrenics is washed out and replaced by blood from non-schizophrenics, there is a temporary amelioration in the psychotic process. The obverse of this type of experiment seems more convincing. The juice of schizophrenics, in the form of blood extracts, appears capable of producing transient schizophrenic symptoms when it is incorporated into the circulation of normal rats and men. This should not surprise us, because it is considered with other findings of biological differences between schizophrenic and normal blood sera, such as the finding almost 30 years ago (Lazell and Prince, 1929) that the serum of schizophrenic patients kills the tadpoles of *Rana catesbiana* in three days, whereas these tadpoles lived in normal serum, plus Macht's (1948, 1950) observation that schizophrenic serum inhibits the germination of the seeds of *Lupinus albus*, Fischer's (1953) observation that it is toxic to larvae of *Xenopus laevis*, and Federoff's (1956) recent observation that it is toxic to the "L" fibroblast derived from mouse derma in tissue culture preparations. At Zurich last week we learned about another of these biological differences. Workers in Gyorgi's laboratory have found schizophrenic serum toxic to mycelia of certain moulds and fungi.

Perhaps none of these experiments alone is totally convincing that a biochemical difference between the blood of schizophrenics and of the remainder of our race exists, but the sum of the evidence is strong enough to have set a great many minds into motion among our colleagues in the field of chemistry. The most revealing creatures seem to be the rats climbing their ropes. Winter plans to continue his observations and to expand his technique into other areas of biochemical inquiry in mental illness. The happiest aspect of the rat climbing test is that it can be studied quantitatively. One of the difficulties which has impeded research in psychiatry is that there has been so little that we could weigh and measure, and all science suffers when these things cannot be done.

If, then, we accept the above data optimistically and say that there is a toxic substance or that there are toxic substances in the blood of schizophrenics, what is its nature or what are their natures? There, of course, is the rub. Nobody has brought the culprit to heel.

It may be worth while, however, to list the major areas where abnormal compounds have been sought for in this quest in recent years:

1. Adrenal cortex (Pincus and Hoagland, 1950).
2. Imidazoles (Young *et al.*, 1951).
3. Adrenal medulla (Funkenstein *et al.*, 1952).
4. Glutathione (Altschule *et al.*, 1952).
5. Adrenochrome (Hoffer *et al.*, 1954).
6. Adrenoxin (Rinkel *et al.*, 1954).
7. Serotonin (Erspamer, 1954; Brodie *et al.*, 1957, *inter alia*).
8. Indoles (Hoffer *et al.*, 1954; Fabing, 1955).
9. 5-hydroxyindoles (Wooley and Shaw, 1954).
10. Aromatic compounds (McGeer *et al.*, 1956).
11. Tryptophane metabolites (Sherwood, Riegelhaupt, 1956).
12. Serum copper (Leach *et al.*, 1956; Akerfeldt, 1957a; Abood, 1957a).
13. Histamine (Lovett Doust *et al.*, 1956).
14. Catechol amines (Abood, 1957b; Sulkowitch and Altschule, 1957).

The list, though not complete, is a formidable one, and represents a prodigious amount of effort on the part of many workers. It is interesting to look down this list and to note, especially during the last three years, the number of investigations which concern themselves with compounds containing

benzene rings. Among them are all the indoles, including the 5-OH indoles such as serotonin, adrenochrome and other catechols, and tryptophane itself, as well as other aromatic compounds. It is noteworthy that the human

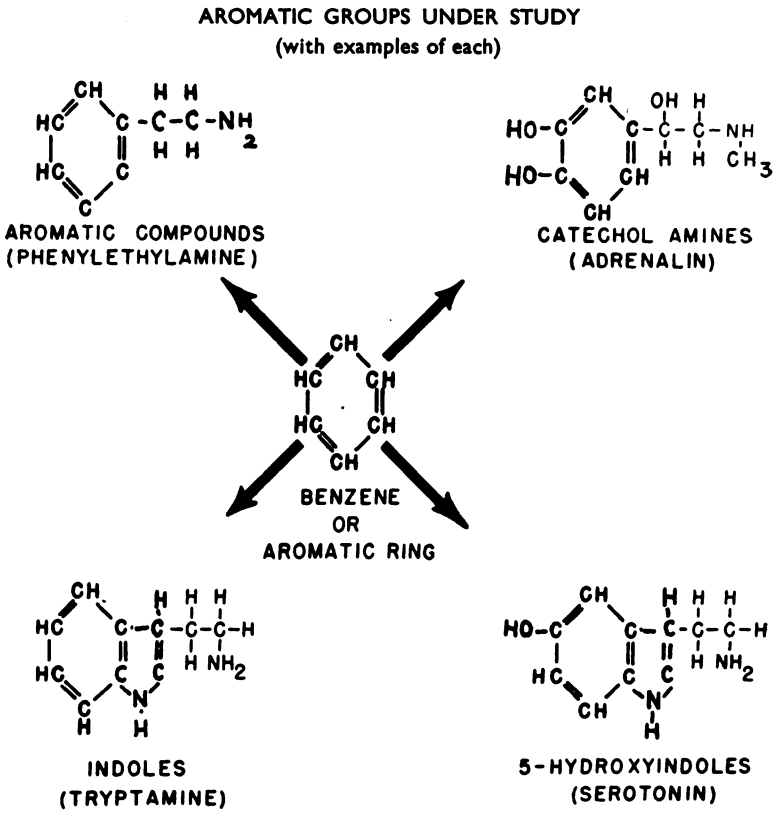


FIG. 2.

body, despite its constant and amazing accomplishments in synthesis, does not seem to be able to make the benzene or aromatic nucleus *de novo*, and that it must be introduced in our food. The usual food sources for this ring structure in our diet are in the amino-acids phenylalanine and tryptophane. We get these in our protein intake.

I am reminded of a remark which Romola Nijinsky made to me twenty years ago. Her whole life was dedicated to the search for a cure for her husband, the renowned Russian dancer, and she became a close student of his illness. She said, "Why do so many schizophrenics quit eating meat? Doctors never take note of this fact, but it is so. Could it be that the patients sense that it is harmful to them and avoid it in an almost instinctual way?" It would seem that if her observation is correct, a good many people are trying to answer her question at the present time.

The great majority of the hallucinogenic or psychotomimetic or psychodelic (Osmond, 1957) drugs which have been undergoing intensive study in recent years contain the benzene nucleus, either as indoles or as aromatic amines. The dramatic episode of Hofmann's (Stoll, 1947) stumbling upon the effect of LSD, a benzene-ring-containing indole, in himself in 1943 has undoubtedly

focused the attention of many investigators on this group of compounds (Fabing, 1956c). The story of his accidental swallowing of a small quantity of lysergic acid diethylamide, inadvertently sucked into his mouth from a pipette, and the consequent temporary schizophrenia-like psychosis it produced, has been told many times. There are two other laboratory accidents of this kind which have never received common notice.

The first concerns W. K. Sherwood (1956), of Monterey, California, a student of tryptophane metabolism. He was working with a peroxidated derivative of tryptophane produced by the mould, *Neurospora crassa*. He assigned the term "B.G.E." to the oily yellow compound which he was extracting, because it produced a blue-green colour when Ehrlich's reagent was added. When the substance was heated, fumes were generated which, when inhaled, produced schizophrenia-like symptoms. Under these circumstances he became intoxicated on repeated occasions. He became withdrawn, uncommunicative, dissociated from the world of reality, and incapable of normal activity. His thought processes became blocked and he sat and stared at his laboratory bench for long periods, involved in a jumbled tangle of thoughts. He experienced depersonalization symptoms in that he felt that an "Outside Talker" was doing his thinking and speaking for him. Auditory hallucinations, in the form of conversations with the Outside Talker, occurred. These disturbed states of thought and behaviour persisted for as much as four to seven days, and he found that he had to get away from his laboratory and its fumes for periods of as long as a fortnight before he recovered fully. His wife came to recognize the onset of his symptoms before he did. She would announce, "You've been smelling things again", and would insist that he stay away from his laboratory until he had recovered.

The second instance of accidental model psychosis occurred in a commercial laboratory which was interested in the electronic sterilization of foods. In the case of meats it was found that they developed an offensive odour of skatole when processed in this manner. A chemist was assigned the task of irradiating tryptophane and otherwise manipulating it in order to come more closely to grips with the problem of the development of skatole, since tryptophane is the parent substance from which skatole is derived. On two occasions this chemist developed acute catatonic schizophrenic symptoms which lasted for some days and required hospitalization. It is presumed that his disturbance occurred, as in the case of Sherwood, from the odoriforous breakdown products of tryptophane he had been inhaling. Perri (1957) has been pursuing this problem further, and finds that tryptophane undergoes many ill-defined oxidative changes upon irradiation as well as upon heating. When submitted to high voltage Roentgen rays, 80 per cent. remains as tryptophane, 7 per cent. goes to identifiable compounds such as indole acetic acid, indole pyruvic acid, etc., and 13 per cent. goes to unknown compounds among which is a large yield of red-brown pigment.

Shortly before his untimely and tragic death three months ago, Sherwood (1957) came to the conclusion that he had found a similar pigment in schizophrenic urine. He believed it to be N-hydroxy-indoleacetic acid, and he was in the process of pursuing this idea more fully when his death came. He found, as did E. L. Ross (1913a) many years ago, that urines of patients suffering from dementia praecox contained significantly more indole acetic acid than did urines of normal persons or those suffering from other mental diseases. This significant observation had been relegated to almost a half century of oblivion because of the belief that this substance was manufactured by intestinal bacteria,

and that its increased level of excretion in Ross' patients was due to the fact that they were chronically constipated. The weight of evidence today is against this notion, and supports the contrary idea that indole acetic acid is derived from the endogenous metabolism of tryptophane, as Ross (1913b) contended originally.

Sherwood confirmed Ross' finding by chromatographic analysis of more than 1,000 urines from normals and from mental patients from two California hospital populations. His findings may be tabulated as follows:

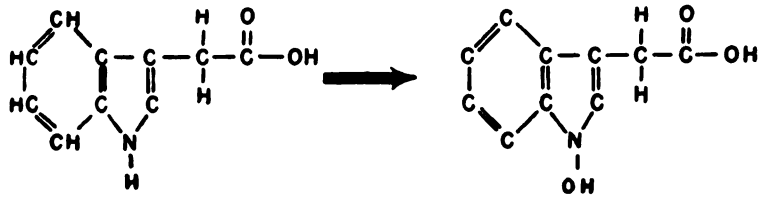
Excretion of Indole Acetic Acid by Normal Humans and Patients with Various Diseases (Sherwood)

Type of Patient	IAA Expressed in mg./litre Urine
Normal adults	2·0–5·0
Stress diseases (allergies, trauma, etc.)	·1–1·2
Growth (carcinoma, pregnancy)	·1–1·2
Terminal cancer and/or radiation sickness	more than 8·0
Phenylketonuria	more than 8·0
Schizophrenia	more than 8·0

The lowered IAA content of the urine of patients with stress diseases was of interest to Sherwood because a similar lowering can be obtained by giving normal persons cortisone intravenously or orally. He suspected that the cortisone secreted by patients suffering from stress diseases alters the metabolic pathway of tryptophane to IAA. He was interested in the disorders characterized by rapid growth, namely pregnancy and malignancy, as well. The plant physiologists (Skoog, 1950) have found indole acetic acid to be a hormone, or auxin, and Sherwood felt that rapid growth in animal tissues required large quantities of this substance, too, and that they used it up to the extent that little of it was left over to spill out in the urine. When patients with malignancies were near death, however, their tumours no longer took up IAA, he thought, and then it spilled out in the urine in large quantities.

His chief interest in this substance, however, was in the case of schizophrenia. He wrote "Although we have listed schizophrenia among the diseases in which massive urinary excretion of IAA occurs, we believe that there may be an important difference between schizophrenic IAA and ordinary IAA. If one does, as we have done repeatedly, a regular ether extraction of schizophrenic urine at pH_4, one gets out a reasonably high amount of IAA. The same urine, however, turns crimson upon addition of acid to pH_1. It is N-OH indole acetic acid . . . One must not get the impression from the above that indole

SHERWOOD'S SURMISE



DONCCNACATEDELIII -HYDROXY-INDOLEACETIC ACID

FIG. 3.

acetic acid, or its N-OH derivative, is the only substance in the urines of schizophrenics. As all of us know, who have handled specimens of these urines, they are almost as heavily laden with malodorous phenyl compounds as are the urines of phenylketonurics. This is also true of the urines of terminal cancer patients and/or cancer patients suffering from radiation sickness. In all three instances, there appears to exist a massive derangement of metabolism of all of the aromatic amino acids. One common factor to all is the excretion of extraordinary amounts of indole acetic acid."

This brings us to the last area of inquiry concerning biochemistry and schizophrenia—the urinary constituents. In addition to Sherwood's confirmation and extension of Ross' earlier observation, fourteen investigators have found various kinds of differences in the excretion of aromatic compounds in schizophrenics and in the normal population. Of these, the recent studies of McGeer *et al.* (1956a, b) deserve special mention. Using a paper chromatographic technique they found considerable day-to-day variation in the excretion of aromatic compounds in all humans tested, whether normals or schizophrenics. To get round this fact, they studied pooled specimens of urine from normals, schizophrenics, and other psychotics. The urine pools were adjusted to a common specific gravity (1·023). Extracts were prepared by adsorption of aromatic metabolites on charcoal, followed by elution with aqueous phenol, and concentration of the eluate with riddance of the phenol by evaporation, after the method of Dalgliesh (1955).

Chromatograms of pools of urine extract from acute schizophrenics and from "debilitated" chronic schizophrenics (those too sick to be housed on an open ward) showed at least ten spots which did not appear in the chromatograms of pooled extracts from normal urines. These spots seemed to correspond to abnormal aromatic compounds which either do not appear in normal urine or which are present in imperceptibly low concentrations. Pooled extracts from other types of psychotic patients, chiefly depressives, yielded four spots on chromatographic analysis which did not appear in the normal extracts but did appear in the schizophrenic ones.

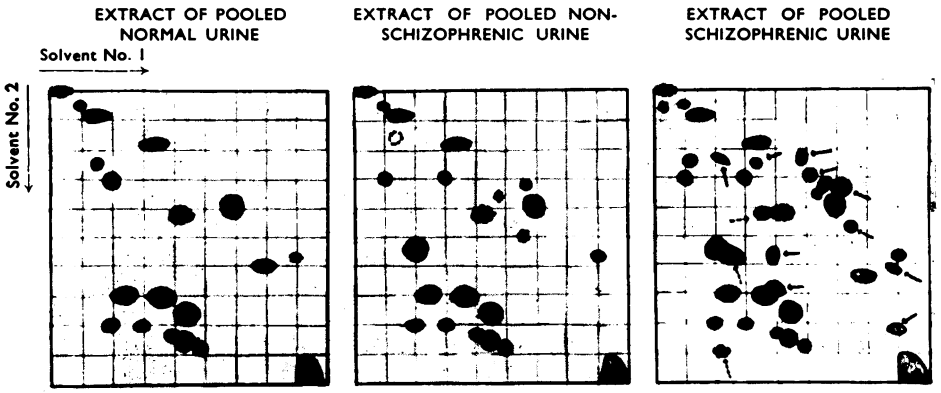


FIG. 4.

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SAMPLE CHROMATOGRAMS OF SCHIZOPHRENIC AND NONSCHIZOPHRENIC URINES

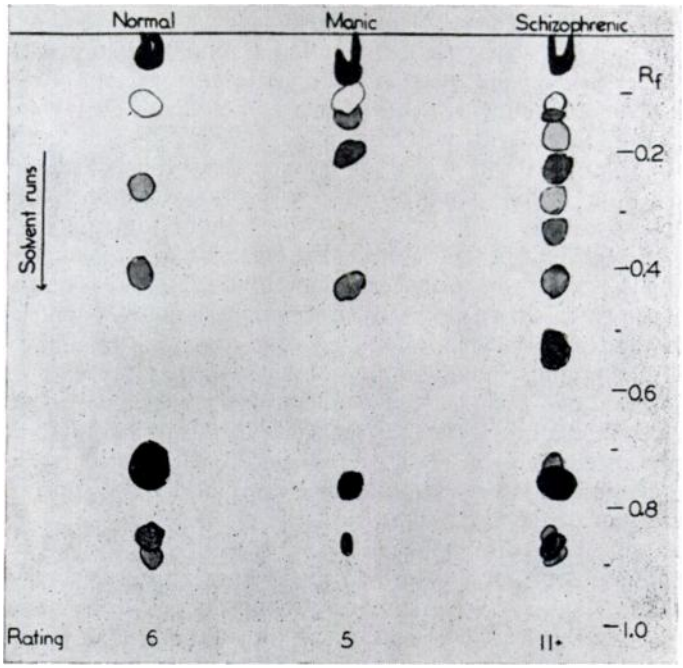

FIG. 5.

The University of British Columbia group of investigators is now at work trying to identify the abnormal compounds which McGeer and McGeer have captured on their chromatograms. Meanwhile, these extracts have been subjected to biological study. Wada (1957) has injected them intracisternally or intraventricularly into cats and monkeys. In cats rage reactions, running reactions, withdrawal reactions and what appeared to be fear reactions resulted from schizophrenic extracts, whereas cats injected with normal extracts did not exhibit these changes. In some of the monkeys a catatonic state lasting for five to eight hours developed following intraventricular or intracisternal injection of schizophrenic extracts, but not in the case of normal extracts. In both cats and monkeys such injection of schizophrenic extracts produced EEG changes in cortical and subcortical leads which were not present when normal extracts were used.

Winter (1957) has made preliminary observations on the effect of intraperitoneal injection of the McGeer extracts on his rope-climbing rats. Preliminary findings are to the effect that the rats injected with schizophrenic extracts stumble and fumble and cannot climb the rope quickly, and they behave oddly while they are trying to do so, whereas those injected with normal extracts climb it with their accustomed speed and precision.

Much more might be said. Hoffer (1957) has succeeded in isolating adrenochrome in a stable crystalline form, and is pursuing his studies of this adrenaline metabolite and its possible role in the aetiology of schizophrenia. The Tulane group is pressing forward in their study of taraxein and its mode

of action. Akerfeldt (1957c) is enlarging his inquiry into the chemical dynamics of the oxidation of colourless N-N-diphenylenediamine by various kinds of sera, including the schizophrenic, to a red compound. Riegelhaupt (1956, 1957) is probing more deeply into the reason why the urine of many schizophrenics produces a red-violet colour in the presence of glyoxylic acid and sulphuric acid. He is on the trail of an indole compound which seems to provoke the colour reaction. These are by no means all the people who are at work on related problems.

Is it likely that this will all lead to a single lightning-flash of understanding which will solve the riddle of schizophrenia? It would not take a crystal ball to predict that the answer will not come about in such a fashion. Every clinician senses that we are not dealing with a single disease process in this illness. Eugen Bleuler, the father of the name of this disorder, implied this point of view in the very title of his masterly monograph on the subject. He labelled it, *Dementia Praecox, or the Group of Schizophrenias.* The key word here is the word *group.* Because we are dealing with a group of diseases, it is more likely that our knowledge about exact aetiology will come in parts, and perhaps even in bits and pieces.

When this knowledge comes (and I feel confident that it will, now that so many eyes and so many new tools of inquiry are being put to work), it is probable that Bleuler's term, which has served us so well and so long, will fade out of existence and will be replaced by newer, more precise nosological entities based on more exact aetiologies. Think back a hundred years to a perhaps happier Mid-Victorian time. Many a discourse was given from this historic rostrum about the fevers. At the time these terms served the members of this great Society of Medicine well, and helped them in their understanding of the sick. But as Victoria's long reign drew slowly towards its close, and as the latter half of the nineteenth century unfolded, the bacteriologists came into being. With their guidance, the fevers ceased to exist as they became more exact entities, the infectious diseases.

Will schizophrenia bend and break into its component aetiologies during the second half of our century as did the fevers during Victoria's century, on this occasion under the intellectual weight of a new breed of medical scientists, the biochemists? And will a more rational group of therapies, based on the aetiologies they discover, be forthcoming for these unfortunate sick? The straws blowing in the wind give me confidence that these things will come to pass.

References

ABOOD, L., Brain Research Inst. Conf., Chicago, Ill., 1957a. 12 January, p. 12.

Idem, "Biochemistry and Mental Illness", 1957b. Read at Conf. on Biochemistry and Mental Illness, Univ. Brit. Col., Vancouver, B.C., 20 June, 1957.

AKERFELDT, S., *Science*, 1957a, **125**, 117.

Idem, Brain Research Inst. Conf., Chicago, Ill., 1957b. 12 January, p. 7.

Idem, Read at 113th Meeting, A.P.A., Chicago, Ill., 1957c.

ALTSCHULE, M. D., SIEGEL, E. P., and HENNEMAN, D. H., *Arch. Neur. and Psych.*, 1952, **67**, 64.

BLEULER, E., *Dementia Praecox or the Group of Schizophrenias*, 1911. English translation (1950) by Zinkin, J. New York: Internat. Press.

BRODIE, B. B., TOMICH, E. G., KUNTZMAN, R., and SHORE, P. A., *J. Pharmacol. and Exper. Therap.*, 1957, **119**, 481.

DALGLIESH, C. E., *J. Clin. Path.*, 1955, **8**, 73.

ERSPAMER, V., *Pharmacol. Rev.*, 1954, **6**, 425.

FABING, H. D., *Neurology*, 1955a, **5**, 603.

Idem, *J.A.M.A.*, 1955b, **158**, 1461.

Idem, *J. Nerv. and Ment. Dis.*, 1956, **124**, 1.

FEDOROFF, S., *J. Lab. Clin. Invest.*, 1956, **48**, 55.

FISCHER, R., *Science*, 1953, **118**, 409.

FREEDMAN, A. M., and GINSBERG, V., "Exchange Transfusions in Schizophrenic Patients", 1957. Read at Soc. Biol. Psych. Meeting, Atlantic City, N.J.
FUNKENSTEIN, D. H., GREENBLATT, M., and SOLOMON, H. C., *Amer. J. Psychiat.*, 1952, **108,** 652.
HEATH, R. G., MARTENS, S., LEACH, B. E., COHEN, M., and FEIGLEY, C. A., "Behavioural Changes in Non-Psychotic Volunteers following the Administration of Taraxein, the Substance obtained from the Serum of Schizophrenic Patients", 1957a. Read at 113th Meeting A.P.A., Chicago, Ill.
Idem and ANGEL, C., *Amer. J. Psychiat.*, 1957b, **114,** 14.
HOFFER, A., OSMOND, H., and SMYTHIES, J., *J. Ment. Sci.*, 1954, **100,** 29.
Idem, Personal communication, 1957.
LAZELL, E. W., and PRINCE, L. H., *U.S. Vet. Bur. Med. Bull.*, 1929, **5,** 40.
LEACH, B. E., COHEN, M., HEATH, R. G., and MARTENS, S., *A.M.A. Arch. Neur. and Psych.*, 1956, **76,** 635.
LOVETT DOUST, J. W., HUSDEN, H., and SALNA, M. E., *Nature*, 1956, **178,** 492.
MCGEER, P. L., MCGEER, E. G., and GIBSON, W. C., *Science*, 1956, **123,** 1029.
Iidem and BOULDING, J. E., *ibid.*, 1956, **123,** 1078.
MACHT, D. I., *Cincinnati J. Med.*, 1948, **20,** 616.
Idem, South M.J., 1950, **43,** 1049.
OSMOND, H., *Ann. N.Y. Acad. Sci.*, 1957, **66,** 418.
PERRI, G., "Irradiation of Tryptophan", 1957. Read at Conf. on Biochemistry and Mental Illness, Univ. of Brit. Col., Vancouver, B.C., 20 June, 1957.
PFEFFER, A. Z., and PESCOR, M. J., *Arch. Neurol. and Psychiat.*, 1944, **52,** 131.
PINCUS, G., and HOAGLAND, H., *Amer. J. Psychiat.*, 1950a, **106,** 641.
Idem, ibid., 1950b, **106,** 651.
REITER, P. J., *Zischr. f. d. ges. Neurol. u. Psychiat.*, 1938, **160,** 598.
RIEGELHAUPT, L. M., *J. Nerv. and Ment. Dis.*, 1956, **123,** 383.
Idem, "Indolic Excretion of Schizophrenics", 1957. Read at Conf. on Biochemistry and Mental Illness, Univ. Brit. Col. Vancouver, B.C., 20 June, 1957.
RINKEL, M., HYDE, R. W., and SOLOMON, H. C., *Dis. Nerv. Syst.* 1954, **15,** 259.
ROSS, E. L., *Arch. Int. Med.*, 1913a, **12,** 112.
Idem, ibid., 1913b, **12,** 231.
SHERWOOD, W. K., *Trans. Soc. Biol. Psychiat.*, 1956, **10,** 53. Cincinnati: Merrell.
Idem, "Urinary Excretion of some Tryptophan Metabolites in Health and certain Diseases", 1957. Unpublished MS.
SKOOG, F., *et al.*, "Symposium on Plant Growth Substances", 1950. Univ. of Wisconsin Press.
STOLL, W. A., *Schweiz. Arch. Neurol. u. Psychiat.*, 1947, **600,** 279.
SULKOWITCH, H., and ALTSCHULE, M. D., *The Excretion of Urinary "Epinephrines", in Psychiatric Disorders.* In press.
WADA, J., "Behavioural and EEG changes induced by the Injection of an Extract of Schizophrenic Urine", 1957. Read at Meeting of Soc. Biol. Psych., Atlantic City, N.J., June, 1957.
WINTER, C. A., and FLATAKER, L., *J. Pharmacol. Exper. Therap.*, 1951, **101,** 156.
Idem, Proc. Soc. Exp. Biol. Med., 1956, **92,** 285.
Idem, "The Effect of Blood Plasma from Psychotic Patients upon the Performance of Trained Rats", 1957. Read at Soc. Biol. Psychiat. Meeting, Atlantic City, N.J.
YOUNG, H. K., JR., *et al.*, *Univ. of Texas Publ.*, 1951, 5109, 189.

DISCUSSION

By **Dr. D. Stafford-Clark**

As the British contributor to this meeting with the privilege of opening the discussion of the last paper of the two-day symposium, I would like to precede such observations as I have to make on this most stimulating and interesting paper by echoing what I know is in the hearts and minds of all British members present at this meeting. It is this: We have all at some time or another had occasion to recognize and appreciate the warmth, generosity, and above all the unassuming friendliness and kindliness of American hosts, some of whom are included in our guests here today. Many of us have travelled in America, worked there, or enjoyed professional contacts which have placed us in the position of accepting American hospitality. And we cannot have failed to be touched by the sincerity and enthusiasm with which our American friends have set out to entertain us and to make us feel happy with them, and at home in their society. In the past two days it has been our privilege to extend what we hope has been a comparable hospitality, and certainly one motivated by a

comparable enthusiasm and delight in being on this occasion the hosts ourselves. May I say on behalf of all the British doctors present, and the two societies who have jointly arranged this meeting, how delighted we have been to have you, our American guests, with us; how stimulated we have been by what you have told us; and how deeply we hope that you will go back to your own country, taking with you memories as warm, happy, and lasting as those which you in your turn have given us.

In moving to a discussion of the paper we have just had, I have had to make some alterations in the general gist and arrangement of what I had planned to say, because Dr. Sargant has just given us the welcome news that Drs. Humphrey Osmond and Hoffer are present here today, and will both say a few words in the context of this paper.

I shall therefore omit all specific reference to their remarkably stimulating contribution to our knowledge and speculations about the Biochemistry of Schizophrenia, since although this must inevitably form an important aspect of any survey of this work as a whole, they can be left to speak about it for themselves. There remain a number of points whose brief consideration may be relevant and helpful in discussing this topic.

Dr. Fabing was modest enough to say that it might be thought presumptuous of him as a clinician to make noises like a biochemist. I do not entirely share his modesty, and indeed fear that I may even exceed what he would regard as his own presumption; for I intend, being also a clinician, to make some noises like a communication engineer, some noises like a cyberneticist, and even a bashful cheep or two like a mathematician; and in truth I can claim to be none of these things.

In one sense, the cardinal features of schizophrenia may perhaps be regarded as respectively:

1. A failure to make the usual interpretation of external or internal events; for example, to understand what is going on in the world outside, or indeed what might be going on in one's own body.
2. A failure to communicate in the usual way with other people.
3. A failure to integrate interpretation and communication, within oneself, or with others, in a way which will even allow the first two difficulties to become apparent in their full nature to any but the trained observer.

There is in fact, as far as brain function is concerned, a failure of communication and control. This is of course a common feature of breakdown or disruption of function in communication engineering, and is one of the ways in which electronic computers themselves can be described as going wrong. The brilliant and exciting work of Grey Walter and Ross Ashby in this country, and of MacCulloch in the United States, has shown with what relevance we may make models of the brain in terms of various types of electronic computer.

These practical experiments in cybernetics can bridge, to some extent, the gulf separating our knowledge of brain biochemistry and electrophysiology, from our knowledge of actual behaviour. Apart from the elementary insight into the relationship between brain function and behaviour which such models can provide, we remain confined to the conception of brain, in mathematical terms, as a "black box"; that is a system whose detailed nature is unknown, but whose behaviour can be described in terms so formulated as to accept the unknown as a part of the whole system, which does not necessarily interfere with the consistency of that system's external behaviour.

Regarding the brain as a "black box" of this kind, Ashby has pointed

out that one of its characteristics would seem to be that of ultra stability. Ultra stability may be roughly defined as the capacity to change the general field of behaviour in conformity with a change in external circumstances, brought about by the effect of signals from the outside world upon the black box itself, in such a way that the behaviour of the black box remains able within its own limits to deal with every possible variation in signal information, and to make responses which remain in a varying degree appropriate to the external changes which have been imposed.

There is of course a great deal of evidence to support our analogy of the brain in this sense as an electronic computer; albeit an electronic computer of possibly immeasurable complexity, which provides for its remarkable flexibility and wonderful precision. The electroencephalogram, crude though its information must yet remain, at least supports the view that it is in its electrical function that we must seek the practical key to the work of the brain. Its communication is by electrical signals, and their transmission from neurone to neurone through synapses is probably the way in which patterns of activity are regulated and controlled. It is indeed possible to build up a mathematical theory of communication within the brain, using concepts of this kind.

But all models which have so far been constructed have taken the source of their electrical power for granted. Such power has in fact been piped in from the local mains supply in the laboratory, or stored in accumulators hitched on to the working model.

I am sure that we must never forget that the brain is the only electronic computer which manufactures its own electricity biochemically as it goes along. In studying the functions of the brain, therefore, we have to remember that we are at least two removes both from the subjective experiences, and from the output in terms of behaviour, which we seek to explain. At one remove there is the electrical network, in all its wonderful complexity and beautiful intricacy; and at the second remove there is the biochemical process, also wonderfully intricate and many sided, whereby the brain continues to live, to breathe, to gain its nourishment, and to make its power. It is in the biochemical aspects of brain function in health and illness that we see those changes which may affect both the conductivity and the availability of electrical power within the system. And it is the ultimate translation of this power into electrical signals, which are themselves the only measurable accompaniment to thought and feeling, which presumably alone makes these processes possible.

Nevertheless, though we operate necessarily at these two removes, we can see a simple biochemical correlation beginning to appear in terms of behaviour and experience, which relates the normal stresses of anxiety at one end, to the delusions and hallucinations and disordered thinking of schizophrenia at the other. I have attempted to work this out in another place, in a contribution to the symposium on schizophrenia recently published by a group of British workers under the general title of "Schizophrenia: Somatic Aspects". In briefest outline the theory is this.

The normal adrenergic response to stress includes the subjective feeling of anxiety as one of its components. Another component is the increased concentration of adrenaline in the circulating blood and probably in the brain itself. This has been shown experimentally to affect synaptic transmission within the brain and nervous system, and may well account for the tendency in anxious and apprehensive subjects to misinterpret or misidentify marginally, external experience. The worried sentry, crouching in his foxhole, tends in his accumulated fear and tension to mistake a tree for a crouching enemy,

a creaking bough for the sound of a crawling man. This misinterpretation, amounting to a transitory illusion, is caused by nothing more toxic or abnormal than a high adrenaline concentration.

The next stage towards a pathological condition may be postulated as exhaustion caused by protracted loss of sleep, wherein actual hallucinations and disorder of thinking may be seen symptomatically, as exemplified by observations of volunteers who have taken part in sleep deprivation experiments and subsequent tests. One stage further on, the toxic confusional states, and episodes of delirium show us how exhaustion plus circulating toxins or metabolic errors can produce profound states of mixed psychotic and dementing symptoms, characterized by gross interference with the patient's interpretation of reality. It is but a short step from these to the manifestations of the group of schizophrenias with which we are concerned.

Smythies, Osmond and Hoffer have suggested that we can bridge this gap by a study of the so-called model psychoses which can be brought about by a number of hallucinogens, and of which they will doubtless have something to say themselves. We thus have, as it were, an ascending scale of disordered brain function from apprehension at one end to schizophrenia at the other, biochemically related to and mediated by the effect of circulating chemical substances upon the electrical conductivity and synaptic pattern of brain function.

An interesting sidelight on this is provided by an observation which you may have noticed in the exceedingly interesting work on the climbing performance of rats, quoted by Dr. Fabing in his paper. May I remind you that of the 14 groups of rats tested, the only group whose speed of performance in climbing was *greater* than that of the normal group, was the group of rats (No. 11) treated with serum from emotionally unstable patients? Their average climbing time delay was shown by an index of 67, less than half that of the rats who had received injections of serum from volunteers in normal health. If this can be taken as indicating anything significant at all, it surely indicates that emotional tension may actually facilitate speed of reaction, and increase the capacity for this *above that normally existent*. It is only when such apprehension passes over into chronic exhaustion, toxic confusion, or the biochemical disturbances of schizophrenia, that the reverse and pathological effect upon speed and facility of response are produced. But I repeat, there is evidence that these are all stages along the same ascending scale of biochemical interference.

It remains important to remember that in studying brain function we must never allow our relative technical proficiency in measuring biochemical changes to blind us to the fact that these are of ultimate importance only in their effect upon patterns of electrical activity, conduction, communication, and control in the electrical functioning of the brain; but as clinicians we must not forget that communication remains the ultimate key to the treatment of schizophrenia, or indeed of any other kind of illness.

Clinically, it is the failure of communication and control which brings the schizophrenic to the doctor. However skilful and appropriate our physical treatment of schizophrenia may become as the result of refinements in our knowledge and understanding both of the biochemical processes which may underly it, and the electrophysiological processes whose secondary disturbance ultimately brings about the syndrome, it remains true that we can only treat patients successfully, and restore them to true health and happiness, if we gain contact with them at a human and personal level, and give them

thereby the bridge over which they may cross back into normal harmony and understanding with their fellows. Both Dr. Fabing and I admitted at the outset that we spoke as clinicians; and it should be the badge of the clinician that he deals with his fellow human beings, whether at the bedside or in the consulting room, and whatever the nature of the sickness which afflicts them, in relation to their whole life and happiness. The foundation of clinical work must remain contact between doctor and patient; contact to which clinical psychiatry deservedly pays great attention, and may further specify and define in terms of rapport. Whether we regard this as the harmonious and flexible communication between two systems, symbolized by two separate black boxes, or whether we regard it in philosophical terms as a universe of discourse between two minds, it remains true that it is upon the flexibility, imaginative sympathy and understanding of the doctor that the control of the communication system, and so in the long run the security of whatever life-line can be extended to the patient, must ultimately depend.