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PHYSIOLOGICAL EFFECTS OF SCHIZOPHRENIC BODY FLUIDS

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INTRODUCTION

CONTROVERSY has raged for over half a century as to whether schizophrenia, the most severe of all mental illnesses, could have an organic basis or whether its origin lay strictly in the psyche. Over the years, physiologists have probed into almost every aspect of the soma in the quest for some abnormality which would account for the schizophrenic syndrome. Many possibilities have been considered, investigated to a degree and then abandoned when definitive answers were not forthcoming. A dominant approach throughout has been the search for some psychotoxic material circulating in schizophrenic body fluids. Activity has been spurred by the recurrent recognition that chemical agents such as the ergot alkaloids, mescaline, bulbocapnine and lysergic acid diethylamide (LSD-25), could induce in normal persons transient mental disturbances similar to those seen in schizophrenia.

Almost every decade of the present century has witnessed a fresh surge of activity in the search for a schizophrenic psychotoxin, particularly among the aromatic constituents of the body fluids. Around 1916, Holmes (58) suggested that the symptoms might be due to a toxic aromatic amine elaborated by intestinal bacteria. In the 1920s Buscaino (12) supported that view and, by analogy with mescaline and bulbocapnine, believed that the toxin was a phenylethylamine derivative. Hoffer, Osmond and Smythies (56), in 1954, used similar reasoning based on the structures of mescaline, LSD-25, harmine and ibogaine, to propose that the schizophrenic psychotoxin might be an indole derived from adrenaline. Stimulating hypotheses as to the exact nature of the schizophrenic psychotoxin have also been put forth recently by Woolley (121),

Fabing (27) and others. Both old and new hypotheses postulate some aberration in aromatic metabolism, originating either in the body or in the intestinal tract and resulting in the production of a psychotoxic material.

Attempts to demonstrate the validity of this psychotoxin hypothesis have traditionally followed two major lines. The first is the attempt to show some abnormality in the aromatic content of schizophrenic body fluids by application of chemical techniques. These have ranged from crude tests, such as that for indican used by Townsend (106) or Buscaino's "black silver nitrate reaction" (13), to the more refined chromatographic techniques applied to the problem today. The end result of the chemical work to date has been the demonstration of a probable quantitative and a possible qualitative dysfunction in aromatic metabolism in schizophrenics. The nature and importance of this dysfunction are unknown and its very reality is still seriously questioned by many. The second approach has been the attempt to demonstrate abnormal physiological (i.e. psychotoxic) effects of schizophrenic body fluids. This paper is intended to review some of the many reports in the literature dealing with this second approach to the problem. The reviewers have not attempted to include all the material on the subject, nor have they restricted the scope only to reports containing substantial experimental evidence to back the conclusions. The chief criterion in selection has been the probable interest to researchers currently working in the field.

The difficulties inherent in devising a meaningful test for "abnormal" effects of schizophrenic body fluids cannot be over-emphasized. The symptoms of schizophrenia and the criteria for diagnosis are almost exclusively psychological, whereas most animal tests are essentially physiological. This combination lends itself poorly to definitive investigation. Psychiatrists still debate as to what constitutes the clinical entity schizophrenia; it is not surprising, therefore, that the subjects of experimental psychosis and psychotoxicity are extremely controversial, and that the requisites for an appropriate test of these phenomena become almost a matter of personal conviction. Over the years many different kinds of tests have been used and, for convenience in discussion, they have been classified as:

(*A*) Elicitation of "catatonic" symptoms in animals.
(*B*) Occurrence of other "C.N.S." effects in animals such as a change in a trained response or in behaviour.
(*C*) Toxic effects towards animals, plants, cell cultures and other organisms.
(*D*) Hyperglycaemic effect in animals.
(*E*) Toxic effects on enzyme systems *in vitro*.

The relationship to the schizophrenic problem in some of these groups seems remote. The assumption is usually made, however, that the test is of significance if differences between schizophrenic and normal body fluids can be demonstrated. Based on this assumption, there have been many reports of "successful" tests using blood, bile, C.S.F. and urine. The results have been variable, and there has been much question as to the reality of the effects observed (cf. Table I). Part of this inconsistency may be attributed to the necessity for subjective evaluation in many of the tests and part to variation in biological sensitivity of the test organisms. Much of the inconsistency, however, results from shortcomings in experimental design. Certain of these weaknesses should be emphasized at the outset because they apply so generally to the tests reported to date.

TABLE I

Physiological Effects of Schizophrenic (as Compared with Normal) Body Fluids

Test	Body Fluid	Workers Reporting "Abnormalities" for Schizophrenic Fluids: Positive Findings	Negative Findings
I. Catatonic Symptoms in:			
Mice	Urine	Nieuwenhuyzen (1934)	Tinel and Eck (1933)
Mice, pigeons, etc.	Urine	Baruk and Camus (1933-49)	Tomesco (1937)
Monkeys and cats	Urine extracts	Wada and Gibson (1957)	
Mice, pigeons or cats	Blood	Baruk and Camus (1933-49)	Guilmot (1952)
Mice, pigeons, etc.	Bile	Baruk and Camus (1933-49)	
Mice	Bile	DeNigris and Mariani (1936)	
Mice and cats	Bile	Guilmot (1952)	
Rats	C.S.F.	LeGrand and Annee (1938-39)	Shapiro (1956)
Guinea pigs	C.S.F.		Sogliani (1938)
II. Schizophrenic Symptoms in:			
Monkeys and man	Serum fraction	Heath *et al.* (1956)	Smith (1958)
III. Behavioral Changes in:			
Siamese fighting fish	Urine		Smith *et al.* (1956)
Spiders	Urine extract	Rieder *et al.* (1957)	
Rats	Serum	Winter and Flataker (1957)	
IV. Lethalness to:			
Rabbits	Urine	Bouchard (1887)	
Rabbits	Urine	Juschtschenko (1909)	
Guinea pigs	Urine	Loewe (1911)	
Mice	Urine and C.S.F.	Gamper and Kral (1934)	
Rabbits	Urine extracts	Moya *et al.* (1956-58)	
Mice	Urine extracts	Kemali *et al.* (1957)	
Mice	Serum	Weichbrodt (1922)	
Mice	Serum	Kastan (1926)	
Mice	Serum	Baldi (1926)	
Mice	Serum	Wahlstrom (1936-37)	
Mice	Serum	Miyakawa and Yamasita (1937)	
Mice	Serum	Wilczcowski (1946)	
Mice	Serum	Sjovall (1947)	
Mice	Serum fraction	Mall (1958)	
V. Toxicity to:			
Tadpoles	Serum and urine	Lazell and Prince (1929)	
Tadpoles	Serum and urine	Malis (1947)	Edisen (1956)
Tadpoles	Serum and urine	Fischer (1952-56)	Georgi *et al.* (1954)
Yeast cells	Serum, urine, C.S.F.	Rieder (1953-57)	
Paramecium	Urine extracts	Weber (1953)	
Cell cultures	Serum	Federoff (1956-58)	Reiter (1938)
Plants	Serum, urine, C.S.F., sweat	Macht (1924-56)	
Plants	Urine	Herz and Weichbrodt (1924)	
Plants	Urine	Tscherkes and Mangubi (1931)	Freeman and Looney (1934-39)
Plants	Urine	Hoffer (1955)	
VI. Inflammatory Action in:			
Rabbit's eye	C.S.F.	Gamper *et al.* (1932-34)	Scheid (1937)
Rabbit's eye	C.S.F.	Dussik and Pichler (1938)	Reiter (1938)
Rabbit's eye	C.S.F.		Persic and Feric (1957)
VII. Hyperglycaemic Effect in:			
Rabbits	Serum	Hall (1938)	Goldner and Ricketts (1942)
Rabbits	Serum	Meduna *et al.* (1942)	Harris (1942)
Rabbits	Urine extracts	Meduna and Vaichalis (1948)	
Rabbits	Urine extracts	Morgan and Pilgrim (1952)	
Rabbits	Urine extracts	Shiraishi (1955)	
Rabbits	Urine extracts	Moya *et al.* (1955-58)	
VIII. Inhibition of Glucose Utilization by:			
Rat diaphragm	Serum	Walaas *et al.* (1954)	
Rat neural tissue	Serum	Hukuda (1936)	
Rat neural tissue	Serum	Haavaldsen *et al.* (1957)	
Rat neural tissue	Serum	Streifler and Kornbluth (1957)	

1. The number of tests run is often too small to eliminate entirely the factor of chance.
2. Schizophrenia is usually presumed to be a single disease entity which runs a constant course. Adequate description of the criteria for original diagnosis, severity and acuteness of the symptoms, stage of the disease and physiological status of the individuals comprising the schizophrenic group are seldom given.
3. Diet, stress and similar factors are frequently not comparable between the schizophrenic and the control groups, and what part such factors may play in the test results is unknown. Horwitt (59) believes that inattention to such information is the greatest weakness in all physiological research in schizophrenia.

4. Specificity of the test to schizophrenia is seldom shown. Comparisons are usually made between schizophrenics and either non-schizophrenic mental patients or normals. Other common disease processes, with no associated mental symptoms, are usually not shown to give negative results. This objection seems particularly important when the significance of most tests to schizophrenia must be assumed.
5. The possibility that the test results may be due to differences in pH, tonicity, electrolyte distribution, buffering action or similar "artefacts" is not always considered. One might assume that the schizophrenic and control fluids would average the same in these respects but this assumption may be erroneous, particularly in work with urine.

Review of Experimental Work

A. *Production of Experimental Catatonia in Animals and Humans*

Catatonia is probably the only biological effect which can be readily associated with schizophrenic symptomatology. The association may, perhaps, be too easily made, since the catatonic effect is notoriously non-specific. De Jong (16), in an excellent review of this phenomenon, describes it as a general reaction form of the central nervous system. Catatonia, with its most significant component, catalepsy, can be induced in many animal species by drugs such as bulbocapnine, cannabis, mescaline and substances related to adrenaline, by asphyxiation, by gases such as carbon dioxide and by neurosurgical, physical and other means.

Non-specific as the effect may be, catatonia has been reported as being produced in animals and in man through the use of schizophrenic but not normal body fluids, and this stands out as the most dramatic evidence so far advanced that schizophrenia may involve the production of psychotoxins.

De Jong and his group (18, 21) did some of the earliest work on the production of catatonia in animals, using human body fluids. They found that a benzene extract of urine contained a substance, tentatively called "catatonine", which was much more potent than mescaline, bulbocapnine, adrenaline or acetylcholine in evoking catatonic symptoms in rats and mice; it was ineffective in rabbits. "Catatonine" was found to exist in less than normal amounts in the urine of mental patients, and from this it was originally argued that "catatonine" was retained by schizophrenics. Injection into rats of urine extracts containing "catatonine" led to catalepsy of the rear paws. Similarly active extracts could also be obtained from blood (22). A quantitative bio-assay was worked out and "catatonine" was isolated from urine. It proved to be chemically identical with nicotine (37), and in retrospect it was established that the mental patients tested smoked less than the normals. This is a good illustration of one of the many pitfalls plagueing investigators in this field.

Later Nieuwenhuyzen in de Jong's group found that, if the urine of non-smokers was used, there remained a catatonogenic agent which appeared in greater amounts in the urine of schizophrenics than of non-schizophrenics. This agent was not identified. It could be demonstrated in benzene extracts of mildly alkalinized urine in 14 out of 24 (58 per cent.) of schizophrenics; the method of obtaining and testing the extract was critical (17, 83). Nieuwenhuyzen also showed that the "oxyproteic acid fraction" of schizophrenic urine, which is obtained by precipitation as a barium salt, led to catalepsy and hyperkinesis when injected into mice. About 6 mg. of this preparation was required as compared to about 2 mg. of histamine, 6 mg. of tryptamine, 0·04 mg. of nicotine and

150 mg. of urea (84). This oxyproteic acid fraction of urine was examined by Gullotta (49) in his studies on aromaturia in schizophrenics.

Tinel and Eck (104) reported a catatonogenic, thermolabile and easily oxidized lipoid in human urine which occurred to about an eight-fold greater extent in normal than in catatonic urine. They indicated that this material was not identical with "catatonine" but details are lacking and the report is unconfirmed.

More recently, Kemali (65) has found occasional evidence of catatonic symptoms when a "chromogen" fraction of schizophrenic urine is injected into mice; death, however, is the more frequent result (see Section C).

Baruk, one of de Jong's early collaborators, went on to explore the catatonogenic properties of schizophrenic body fluids in a whole series of investigations (5, 6, 14). Baruk and Camus reported that they could induce catatonia with typical posturing by subcutaneous injections of urine, blood or bile from schizophrenics; they found that bile gave the most consistent results (cf. 102). The effects were variable and depended on the animal species used. Clear catatonia lasting episodically for several hours, or even days after injection, was produced in mice given ½–1 c.c. of bile. Cats given 8–10 c.c. showed variable effects and guinea pigs (4–6 c.c.) showed little reaction. Some birds, such as pigeons (3–4 c.c.), also showed catatonia; other species showed only torpor. During non-catatonic intervals there was frequently ferocity, excessive salivation, muscular twitching and hyperreactivity of tendon reflexes. However, bile from some cases of serious migraine, icterus catarrh, chronic rheumatism or "hepatic-intestinal intoxication" sometimes also proved catatonogenic. Normal human or animal bile never produced anything more than torpor and somnolence. Tests showed that these minimal effects could be attributed to known bile constituents (bile salts, sodium taurocholate, sodium glycocholate, cholesterol, amino acids, gastric sugar, etc.); none of these normal bile constituents tested in pure form produced anything more than torpor and sometimes dyspnoea. Cholesterol seemed to inhibit the catatonic effect of active biles. Biles from anxiety patients produced dyspnoea but no catatonia. The active agent seemed to be thermolabile and benzene-soluble. Baruk and Camus believed that the toxin was produced by intestinal coliform bacteria and, following this lead, DeNigris and Mariani (19) reported that filtrates of the cultures of such bacteria obtained from the faeces and bile of catatonics produced acute and chronic catalepsy with periods of exaltation in animals.

Tomesco and his co-workers (105) also followed Baruk in demonstrating catatonia, as evidenced by maintenance of unstable equilibrium in white mice, after intra-peritoneal or subcutaneous injection of filtered, colibacillus-containing urine from a catatonic schizophrenic. The effect lasted 1–3 hours depending on the dose used (½–3 c.c.) and was consistent in the numerous mice tried. C.S.F. from the same schizophrenic was not active and no sign of catatonia was evoked in any of the 15 animals injected with physiological saline, 2 normal urines or 2 schizophrenic urines in which colibacilli could not be demonstrated. The toxic urine retained its activity for 3–4 days at room temperature; heating the urine to 120° C. for 30 minutes resulted in an increase in toxicity but a modification of the catatonic action. The intestinal intoxication hypothesis, held by these various workers, would seem untenable today. Intestinal sterilization of schizophrenics, which has become possible since the time of Baruk and Camus, has not produced notable clinical benefits.

More recently, Guilmot (48) injected bile subcutaneously into the abdominal region of cats (10–20 c.c. dose) or mice (½ c.c.). He used persistent

placement of paws, a lack of response to stimulation and a conservation of attitude in unstable equilibrium as the three signs of catalepsy. He treated 17 animals with bile from catatonic schizophrenics, 3 with normal bile and 4 with bile from miscellaneous non-schizophrenic mental patients. Somnolence was a common symptom with both schizophrenic and non-schizophrenic biles. None of the non-schizophrenic biles caused death and only one of the 7 evoked any sign of catalepsy. By contrast, 9 of the 17 animals receiving catatonic bile showed all three signs of catalepsy, another 4 of these 17 showed one or two signs of catalepsy and 3 of the 17 died. Although the group is small, the distinction between bile from catatonics and from normals seems clear. Blood from a catatonic produced no effect, and none was obtained with 50 mg. of progesterone or with 0·5 mg. of nicotine. This last is surprising in view of de Jong's findings. The effects with bile came on ½ to 1½ hours after injection and sometimes lasted 12 hours or more. There was a great variation from animal to animal.

LeGrand and Année (67) found that catatonic symptoms could be produced in rats by subcutaneous injection of lyophilized material from schizophrenic C.S.F.; the symptoms lasted 48 hours and were elicited by samples from 10 out of 13 schizophrenics and by 0 out of 6 normals and epileptics. The activity was destroyed by heating to 45° C. (but not to 40° C.) for 30 minutes. There was no loss of activity on dialysis, filtration or ultracentrifugation. Shapiro (96) attempted to repeat this work using C.S.F. from chronic schizophrenics of 6 to 25 years duration but found no such consistent effects; he found the main reaction was listlessness due to hypertonicity of the injected solutions and was elicited by C.S.F. from mental defectives as consistently as with C.S.F. from schizophrenics. The difficulty may have been in his choice of chronic cases since almost all investigators have found that the body fluids of acute cases show "abnormal" physiological effects more strongly than do the body fluids of chronic schizophrenics. Sogliani (101) also reported minimal reactions in guinea pigs or rabbits injected with schizophrenic C.S.F.; these animal species proved insensitive in the hands of de Jong and of Baruk. In contrast to Guilmot, Sogliani found that schizophrenic blood caused symptoms identical with those produced by bulbocapnine but that the same reaction could often be obtained with the blood of normals.

Interest in catatonogenic effects has recently been revived by the dramatic reports of Heath and his co-workers (53, 68). They found that catatonic and other "schizophrenic" symptoms could be produced in monkeys and man by injection of a material from schizophrenic serum. The material, named taraxein, is an enzyme related to but not identical with the copper-containing enzyme ceruloplasmin. Both enzymes oxidize adrenaline; *in vitro* tests show that schizophrenic serum oxidizes adrenaline (added in approximately 1,000,000 times physiological concentrations) more rapidly than does normal serum (52). According to Hoffer and Kenyon (55), the oxidation product in this *in vitro* system is adrenolutin or some related hallucinogenic material. Attempts by Leach and Heath to isolate the oxidase enzymes in serum led at one stage to a blue precipitate being found in schizophrenic but not in normal serum. It is this fraction that yields the taraxein which, on injection, leads to profound EEG and behavioural changes in monkeys and to "schizophrenic" symptoms in man. About 400 ml. of serum must be processed to obtain the material for one test. The material is unstable, being inactivated by a number of factors.

The number of tests reported so far is small and the results somewhat variable. Material which was screened for activity in monkeys has been given to

17 non-psychotics and to 3 psychotics in remission; the experiments were double blind with a number of inert substances serving as controls, including enzyme preparations which proved inactive in the monkey screen. The effects of taraxein on psychotics were more pronounced than on normals. In normals the peak effect occurred 15–40 minutes after injection and lasted 4 hours at most; in psychotics the effects lasted in some cases for four days. Although taraxein appears to be absent in normal serum, its presence or absence has not been reported for other disease states in which rapid *in vitro* oxidation of adrenaline by serum has been shown.

One argument raised against Heath's work is that transfusions of schizophrenic blood do not elicit the reactions reported for taraxein*. It can be argued, however, that the difference resides in the speed of administration of the toxic material. It is known, for example, that the effects of bufotenine depend on the speed of injection as well as on the dose given (28). Heath has given rapid transfusions of schizophrenic serum to 4 non-psychotics and reported the production of transitory mental disturbances. As Bond (9) points out, this is a simple experiment which should open for other laboratories a way to confirm Heath's work. Although the response of normals to this procedure may be transitory, the effects on psychotics in remission should be more intense and thus readily observed. Early efforts to confirm the work in humans have been disappointing (99, 122), although Melander *et al.* (125) have recently reported reproducing Heath's findings "on several occasions". As yet, detailed data are not available from these other laboratories working with taraxein. Judgment as to the significance of this work must wait on a great many more experiments. The special problems associated with defining schizophrenia and its symptoms, as well as the relationship of such factors as stage of the disease, stress and nutritional status to the effects observed, make an early answer unlikely. Certainly the promise of the work justifies exploration by many laboratories.

Wada and Gibson (111) have studied behavioural and EEG changes in cats and monkeys injected intracisternally or intraventricularly with extracts prepared by McGeer *et al.* (71) of the aromatic constituents of normal and of schizophrenic urine. Both types of extract caused some degree of docility, somnolence or torpor in animals. The schizophrenic extract brought about various unusual behavioural patterns, ranging from rage states (5/10 cats), and automatism-like states (3/10 cats) to recurrent stuporous and catalepsy-like episodes (1/10 cats, 5/10 monkeys). Except for one brief stuporous episode in one monkey, none of the 9 cats or 11 monkeys showed such unusual behaviour following injection of a normal extract even at higher dosage level. The amount of schizophrenic extract used corresponded to 1–5 ml. of urine. Most of the experimental animals were used for both normal and schizophrenic extract in order to minimize the effect of differences in sensitivity. EEG changes were also much more pronounced after injection of schizophrenic extract.

B. *Occurrence of Other Essentially C.N.S. Effects in Animals*

1. *Behavioural Changes.* Winter and Flataker (117) developed a rope-climbing test for rats in order to compare responses to various antihistaminic drugs. Trained rats will climb a vertical rope in a given time with only minor variations from trial to trial. The "climbing time" can be measured to 0·1 second. Injection of the hallucinogen, LSD-25, into these rats leads to a delay

* Two groups report therapeutic benefits in schizophrenics treated by blood transfusions (8 of 12 in one series and 5 of 6 in the other (44, 123)), but another group found such treatment useless in their series of 5 cases (86) (cf. 128).

in climbing time (118), as does intra-peritoneal injection of 1 ml. of plasma. The average delay caused by plasma from 46 normals or from 35 non-psychotic medical and surgical cases was very slight and only about one-sixth that caused by plasma from 80 psychotics, the majority of whom were schizophrenics. The difference between the normal and schizophrenic groups is statistically highly significant. The rats receiving active schizophrenic plasma also showed behavioural changes; they retreated to the back of the cage, huddled together and became quiet and withdrawn. Their climbing technique was clumsy and the animals often stopped and hung "bewildered" on the rope. Subcutaneous injection of plasma or intra-peritoneal injection of schizophrenic C.S.F. produced no such effects. Ceruloplasmin, but not albumin, potentiated the effect of serum in rats. Adrenergic blockade modified the serum effect markedly but cholinergic blockade did not (119).

Another attempt to produce an LSD-like effect in animals has been made by Rieder (92). Following a report of Witt (120) that administration of LSD-25 and other hallucinogens to spiders led to characteristic changes in the type of web, Rieder induced similar, but not identical, changes by giving extracts of the basic components of both normal and schizophrenic urine. The active material(s) in normal urine could be extracted into chloroform while that in schizophrenic urine appeared principally in a butanol extract of the aqueous residue from the chloroform extraction. Rieder and others (126, 127) feel that this spider web "test" does not reflect the effect of a single "psychotoxin" but probably the combined action of a number of substances.

Smith and her co-workers (100) reported that the characteristic response of Siamese fighting fish to LSD-25 (26, 108) was not produced when the fish were exposed to 25–50 per cent. solutions of urine from either schizophrenics or normals.

Bulle and Konchegul (11) found that the C.S.F. of all 17 schizophrenics tested resembled 5-hydroxytryptamine (serotonin) in altering the pain response and knee jerk of dogs on injection into the internal carotid artery; C.S.F. samples from manic depressive or neurotic patients had some, but dissimilar, effects, and C.S.F. samples from normal persons had no effect.

EEG changes in normal humans are reportedly induced by intravenous injection of 10–20 ml. of epileptic or schizophrenic C.S.F. (89). The reality and meaning of this effect must await further details and confirmation.

2. *Modification of Adrenaline Effect.* Local application of adrenaline to the parietal lobe of a dog leads to an increase in blood pressure which apparently depends on liberation of a hypertensive agent by action of the hypothalamus; this reaction is strongly modified by chlorpromazine or reserpine. Dogs injected with schizophrenic serum do not show this response to parietally applied adrenaline (though i.v. adrenaline still causes a rise in blood pressure). Dogs injected with normal serum do show response to parietally applied adrenaline. The refractoriness of dogs after schizophrenic serum is believed due to a polypeptide substance P. The brains of normal dogs contain about 23 units of substance P per gram of tissue; the brains of dogs injected with schizophrenic serum contain 43–116 units per gram with local concentrations of 275–312 units/gram in the hypothalamus (76).

C. *Toxicity to Animals, Plants, Cell Cultures and Similar Organisms*

1. *Work with Mice, Rabbits and Similar Animals.* A number of reports are in the literature indicating that schizophrenic body fluids are more toxic than

normal towards various animals. Unfortunately the information available from some of the early work does not make clear what criteria of toxicity were used or how many experiments were performed with fluids from what type of patient.

(*i*) Work with urine. In 1909 Juschtschenko (63) reported that the urine of psychotics was more toxic than that of normals and correlated this with a "decreased somatic oxidizing ability" as measured by a decreased excretion of phenol after a test dose of benzene. Previously Bouchard (10) had reported that both the urine and blood of psychotic patients was more toxic than that of normals to rabbits. In 1911 Loewe (69) found that the urine of schizophrenics, and particularly of catatonics, was more toxic towards guinea-pigs than was normal urine. Some toxicity was noted in the urine of demented alcoholics, persons with progressive paralysis and epileptics. The "toxic factor" in urine was non-dialysable.

Abely *et al.* (1) reported that injection of psychotic urine into guinea-pigs resulted in weight loss and histological changes in the seminal vesicles but that psychotic C.S.F. had no consistent effect (cf. 15, 129, 130).

In 1934 Gamper and Kral (39) found that many samples of both normal and schizophrenic urine were toxic to mice on subcutaneous injection. In contrast to Abely, however, their major effort was on the toxic effects of C.S.F. (Section C-1 (*iii*)). Very recently, Moya has noted, as an incidental finding, a high percentage of deaths in rabbits injected with schizophrenic urine extracts (see Section D).

Kemali (65) has isolated a "chromogen fraction" from overnight urine by adsorption on to carbon and elution at 100° C. with an ammoniacal organic medium. Portions of this extract corresponding to 10–30 c.c. of urine were injected intra-peritoneally into mice. Schizophrenic extracts invariably caused restlessness, ataxia, hypotonia and death; normal extracts, even at double or triple the dose, caused only temporary restlessness and a short prostration with complete recovery in about one hour. Fractionation of the crude schizophrenic extracts by column chromatography has yielded several very highly toxic fractions.

Pfeiffer and Albrecht (87) reported that schizophrenic urine was much more "toxic" than normal urine; they used the temperature decrease produced in experimental animals multiplied by the time of temperature deficit as a measure of "toxicity". Urechia and his co-workers (110) were not only unable to confirm this report but they found a completely opposite effect. According to them, all urines examined contained a pyretogenic substance, believed to be a polypeptide with sugar and chondroitin sulphate components, but the excretion of this substance was markedly increased in schizophrenia as well as in pregnancy and in kidney disease.

(*ii*) Work with serum. In 1922 Weichbrodt (115) found that the blood and serum of many patients suffering with endogenous psychoses caused death in immature white mice when injected intra-peritoneally but not when injected subcutaneously. The toxic factor was destroyed by heating at 56° C. for 30 minutes. The blood of menstruating women and of epileptics before and during attacks was also toxic but no toxicity was found in blood from paretics, arteriosclerotics, senile psychotics or hysterics.

Kastan (64) and Wilczcowski (116) both confirmed Weichbrodt's results although the former found toxic sera in senile psychotics as well as in schizophrenics and epileptics. The mice injected with toxic sera showed increased neutrophiles according to Kastan. Wilczcowski found that serum was more

toxic than whole blood and that the toxicity was destroyed by heating to 35° C.

Wahlstrom (112) and Sjovall (98) also confirmed Weichbrodt except that they used different routes of injection. Wahlstrom found that only 10–12 per cent. of mice injected subcutaneously with sera from 60 normals died as compared to 34 per cent. injected with sera from 561 schizophrenics. As reported by Weichbrodt, the toxicity was destroyed by heat. Ether-extracted serum was not toxic, nor was the extract itself, but a combination of the ether extract plus a non-toxic serum was toxic. This indicates that two serum components are needed for toxicity. A similar indication was found by Federoff (29) in work with cell cultures (see Section C-4). Mice treated with toxic sera showed pathological changes in the liver and brain. Histological changes have also been noted in the livers of guinea-pigs injected with schizophrenic C.S.F. (20) and in the brains of dogs injected with blood from "acute psychotics" (8).

Sjovall (98) felt that Wahlstrom's conclusions were questionable on statistical grounds, particularly because Wahlstrom had used a varying number of mice per serum. Sjovall therefore repeated the work using sera from 24 unmedicated, male, hebephrenic and catatonic schizophrenics and 24 male hospital attendants. Physical and laboratory examinations were made to ensure that all were somatically healthy. Each serum was tested in 30 mice at an i.v. dosage of 0·025 ml./gram. Mice injected with lethal sera died within 24 hours. The mean number of deaths per sera was 23 out of 30 for the schizophrenic sera and only 15 for the normal sera. The standard dosage was below the LD_{50} for only 6 of the schizophrenic sera, including four from inactive cases, whereas 12 of the 30 normal sera were below the LD_{50}. Rapidity of death, which seemed to be connected with a haemolytic principle, was also greater with the schizophrenic sera. Sjovall concludes that the difference in toxicity between schizophrenic and normal sera is statistically significant.

In independent work, Miyakawa and Yamasita (77) also found that schizophrenic sera on intra-peritoneal injection were lethal to mice in a high percentage of cases while sera from normals or non-schizophrenic psychotics were not. Sera from acute schizophrenics were much more toxic than those from chronic cases but there was no significant difference between sera from hebephrenics and catatonics. This latter detail conflicts with the report of Baldi (4) who found that while 3–5 c.c. of catatonic serum per kilogram were needed to evoke a toxic reaction on intravenous injection in rabbits, sera from hebephrenics (6–7 c.c./kg.) and paranoid schizophrenics (8–10 c.c./kg.) were progressively less toxic. Similar toxicity in a mild form was shown by sera from some medical cases including patients with haematuria and liver disease.

Mall (124) found that trypsin-digested sera of some acute or catatonic schizophrenics, as well as epileptics, cause convulsions and death on injection into mice. Untreated sera or trypsin-digested normal sera had no such activity. The toxic material seems to be associated with the α-2-globulin fraction and there is some indication that normal sera may also contain the toxic component which is inactivated by a protective component of the albumin fraction.

Injection of schizophrenic sera into salamanders leads to an increase in capillary permeability which is indicated by a disappearance of fluorescein from the blood stream. Normal sera had no effect but similar changes were found with sera from cases of acute nephritis or severe infections. The effect was compared to that of histamine (25), which is interesting in that a significant hyperhistaminaemia has been reported for schizophrenics (46).

(*iii*) Work with C.S.F. Gamper and his co-workers found that C.S.F. from

many schizophrenics caused death on subcutaneous injection into immature mice and inflammation when injected into the anterior chamber of a rabbit's eye. There was a clear distinction between the toxicity of schizophrenic C.S.F. and that from normals, manics or other types of non-organic psychoses. Toxic C.S.F. was obtained from epileptics, alcoholics, senile psychotics, cases with various organic brain disorders and some carcinoma patients. Two per cent. saline was non-toxic. The C.S.F. samples from hebephrenic and catatonic schizophrenics were generally much more toxic than those from paranoid schizophrenics. Several hundred samples were apparently studied in a number of experimental series (39, 40, 41).

In a smaller series of 18 schizophrenics, most of whom were paranoid, Dussik and Pichler (23) found that the C.S.F. caused less inflammation than reported by Gamper and Kral but that there was a clear reaction elicited by 61 per cent. of the samples. In 9 of 10 cases studied serially, the direction of change of the inflammation reaction paralleled the clinical change under insulin treatment.

Unfortunately, neither Scheid (95), nor Reiter (90) could confirm Gamper and Kral on the toxicity of schizophrenic C.S.F. to animals. Persic and Feric (85) tested C.S.F. samples from 42 schizophrenics and from 20 patients with other nervous disorders in the anterior chamber of rabbit eyes. They found a severe inflammatory reaction with 34 per cent. of the samples but this included a higher percentage of the non-schizophrenic than of the schizophrenic samples.

2. *Tests with Tadpoles.* Fischer (33, 35) reported a significant difference in toxicity to tadpoles between the serum and urine from acute schizophrenics and that from normals. The toxicity decreased as the schizophrenics improved under treatment. Lazell and Prince (66) found a similar difference in toxicity between normal and schizophrenic serum and Malis (73) is said to have obtained similar results; Edisen (24) reported inconclusive results using a tadpole test. Fischer (35) later said that the toxicity was related to the ammonia content of urine and that the test must be performed with urine of a standard salt concentration and at a standard barometric pressure. He felt that the test results correlated with the degree of stress.

The validity of this tadpole test has been the subject of a somewhat acrimonious polemic between Fischer and his erstwhile colleagues in Georgi's laboratory in Switzerland (42, 34). The latter group point out that the great variability in the data of Fischer collected in Georgi's laboratory, is not related particularly to weather conditions but probably depends on the reaction of tadpoles to various non-specific environmental factors (cf. 47). In their evaluation of Fischer's data on 34 schizophrenics and 34 normals, the schizophrenic urine and sera were not significantly more toxic than the normal (91).

3. *Work with Micro-organisms.* After discarding the tadpole test as of doubtful value for the demonstration of a specific toxic factor in schizophrenic body fluids, Rieder (91) tried yeast cells (*Saccharomyces cerevisiae*) as a test organism. He measured in a Warburg apparatus the oxygen uptake of the cells on exposure to dilute serum, urine or C.S.F. Care was taken to evaluate and minimize the effects of pH, solution tonicity and similar environmental "artefacts". His initial report was based on results with samples from 68 schizophrenics, 49 normals and 64 non-schizophrenic mental patients. Variability within the normal group was within acceptable limits and repeat tests on a single individual, whether schizophrenic or non-schizophrenic, gave closely similar results. On the average, the schizophrenic samples of urine,

C.S.F. or serum showed highly significant inhibition of yeast metabolism as compared to normals. Of the 64 samples from the non-schizophrenic mental group, only 8 per cent. showed significant inhibition and most seemed stimulatory. The non-schizophrenic samples came from 14 epileptics, 25 multiple sclerotics, 7 chronic alcoholics and 18 post-encephalic Parkinsonism patients. When more than one body fluid from a single patient was tested, there was good agreement between the values obtained for the different liquors. Overall, however, schizophrenic urine seemed slightly more inhibitory than either serum or C.S.F.

Weber (114) studied the toxicity towards *Paramecium* of basic fractions obtained from urine by absorption and elution from IRC-50 columns followed by electrophoresis. The fractions from schizophrenic urines were more toxic than those from normal urines with a highly significant difference in the fractions of ionic mobility comparable to that of mono- or dimethylamine. Fischer (34) implied that the toxicity factor tested for by Weber was ammonia, but ammonia, mono- and dimethylamine were excluded by testing the toxicity of solutions of the pure substances.

4. *Work with Cell Cultures.* Although Reiter (90) twenty years ago could not detect any significant differences between osteoblasts grown in schizophrenic and in normal sera, Federoff and his colleagues (30, 31) have recently shown an overall difference in toxicity to certain cell strains between schizophrenic and non-schizophrenic sera. The sensitivity of cell cultures towards schizophrenic sera varies greatly with the cell strain. Fifty-nine schizophrenic sera out of 80 showed very high toxicity to L strain cells compared with only 3 out of 29 normal samples. In another series the sera from 33 healthy adults, 32 non-schizophrenic mental patients, 98 schizophrenics and 28 surgical patients were examined. The normal sera were clearly less toxic than sera from any of the other groups. There was a significant difference between the schizophrenic and non-schizophrenic mental patients which seemed even more marked when the frequency of occurrence of the Lewis and Piotrowski "signs of schizophrenia" was compared with the toxicity score. The surgical patients as a group showed a toxicity comparable to that found with the schizophrenics but 10 of the 17 surgical patients whose sera were very toxic had urinary retention (32).

Although toxic sera could be stored at −20° C. or in the lyophilized state, toxicity was lost if the serum was heated to 56° C. for 35 minutes. The activity was not destroyed by dialysis or by mechanical shaking. Toxic serum which was deactivated by heating could be reactivated by addition of a non-toxic human (but not animal) serum. This indicates that at least one heat-labile and one heat-stable component are necessary for toxicity and that the former is also found in normal, atoxic human serum (29). The multiple nature of the toxic factor in sera, implied by this work and by that of Wahlstrom (see Section C-1), complicates considerably the problem of isolation and identification.

Federoff reported that the morphological changes resulting from the action of toxic sera on fibroblast-like cells in tissue culture are strikingly similar to the cytotoxic reaction produced by anti-serums but there is no conclusive evidence that the toxic substances in human serum are immunologically active (29, cf. 98, 109).

Georgi and Rieder (43, 93) have tested the effects on tissue cultures of chloroform and butanol extracts of alkalinized urine and of the desalted aqueous residue. The growth-inhibiting actions of the schizophrenic fractions were not significantly abnormal, although the schizophrenic chloroform

fraction may be slightly more toxic than the normal when compared on an equal "free base content". The butanol fractions of multiple sclerotic urine show a greater growth-inhibitory effect than do the corresponding fractions of either normal or schizophrenic urine. Multiple sclerotic urine was previously shown to have a stimulating effect on yeast cell metabolism as contrasted with the inhibitory effect of schizophrenic urine (91).

5. *Work with Plants.* Sera, red cells, C.S.F., urine, sweat and saliva from all types of psychotic patients have been reported to inhibit the growth of pea seedlings (*Lupinus alba*). A similar, but not identical, growth inhibitor is reported in the body fluids of patients with cancer, pernicious anaemia and certain other diseases, as well as in the body fluids of menstruating females. No such growth-inhibiting effect is found with fluids from normal, healthy persons or the general run of medical cases. Tests with indican and with various phenols known to occur in normal urine indicate that they have no effect. The toxicity of sera or other fluids from mental patients is destroyed by boiling or by X-irradiation but this is not true of the toxicity of fluids from cancer patients, menstruating females, etc. Whole blood is more toxic than sera or red cells alone, which is in contrast to the findings of Wilczcowski (116) who reported serum much more toxic than whole blood to white mice. Over 1,200 samples have been tested by Macht to reach these conclusions (72). Similar effects on root growth have been reported by Hoffer (57), by Tscherkes and Mangubi (107) and by Herz and Weichbrodt (54). This last group found a parallelism between the phytotoxicity of schizophrenic sera and the toxicity on intraperitoneal injection into mice. However, some other workers (36, 70) could not confirm the phytotoxicity of psychotic blood and urine towards *Lupinus alba.*

Jacobowsky (62) tested the phytoactivity of blood sera on a mould (*Aspergillus niger*). He studied sera from 59 individuals in one series and from 53 in a second series. All were male and somatically healthy. The 44 "normal" hospital attendants were eating the same diet as the 61 schizophrenics and 11 non-schizophrenic mental patients. Jacobowsky found that all sera stimulated growth; no toxic effect was detected. On an average, within each series, the sera from non-schizophrenic mental patients were more active than those from schizophrenics. There was no parallelism between the phytoactivity of the sera and their toxicity towards mice. The phytoactivity factor was insoluble in ether.

A disquieting factor in Jacobowsky's data is that the "phytoactivity index figures" were all much higher in the second series than in the first, even though the subgroups were in the same order in each series. The difference between the two series is unaccounted for, but probably depends on mould environmental factors or on the fact that different people did the two series.

Workers in Georgi's laboratory have recently reported that schizophrenic urine fractions were more toxic in mould sporulation tests than the corresponding fractions of normal urine (cf. 102).

D. *Production of Hyperglycaemia in Experimental Animals*

Interest in the role of glucose metabolism in schizophrenia stems from the empirical use of insulin coma as a therapeutic measure and the reports of abnormal glucose tolerance curves in some schizophrenics (3)

Hall *et al.* (50) initially reported on the occurrence of an anti-insulin (hyperglycaemic) factor in the blood serum of one schizophrenic woman. Meduna *et al.* (75) studied sera from 20 normals, 51 schizophrenics and 7

epileptics and found that an anti-insulin factor (AIF) was present in the blood of many schizophrenics which prevented the expected decrease of blood-sugar levels in rabbits following insulin injections. The average curve for blood-sugar decrease against time and the percentage of animals dying in hypoglycaemic coma was the same for epileptic and normal samples but "significantly less" for the schizophrenic samples. Each serum was tested in a separate animal because it was believed that the animal's response to insulin changed after one injection. The variation in individual blood-sugar loss curves was quite large in the schizophrenic group which was attributed to a great variation in the amount of AIF in schizophrenic blood.

Goldner and Ricketts (45) took exception to the conclusions of Meduna on the grounds that the variation between individual rabbits was so great as to render his data insignificant. Goldner and Ricketts used cross-over experiments in which the effect of schizophrenic blood plus insulin was compared with the effect of normal blood plus insulin and of physiological saline plus insulin in a single animal. Blood from 25 schizophrenics was compared with that from 20 staff and student members of the university. Both chronic and acute schizophrenics were included but all were seriously deranged at the time the blood was taken. Although Meduna *et al.* (75) had indicated that 9 such cross-over experiments in their hands gave results consistent with the data they reported, Goldner and Ricketts found no significant difference between the schizophrenic and the normal samples.

Harris (51) compared the effect in rabbits of schizophrenic serum plus insulin with a "standard" response to insulin alone. He found a significant anti-insulin effect in only 2 out of 7 schizophrenic bloods and there seemed to be no correlation with the clinical features.

In later work Meduna and his colleagues (74) studied urine rather than blood. Houssay (60) had reported that some anti-insulinic activity resided in normal urine and was increased in diabetic urine. Meduna used 24 hour urine samples from 21 normals and from 30 acute, untreated schizophrenics. The acidified urine was treated with kaolin, the filtered kaolin was eluted with ammonium hydroxide and the eluant treated with acetone to give a precipitate. The dry preparation from each 24 hour sample of urine was dissolved in about 10 ml. of water and injected intraperitoneally into a rabbit. With the control samples, the increase in blood sugar was generally maximal after one hour and averaged 37 per cent. of the fasting value; with the schizophrenic samples, the increase averaged 78 per cent. after one hour and 94 per cent. after two hours.

Moya *et al.* (82) repeated Meduna's work using intravenous injection of 2½ hour aliquots of extracts prepared from 24 hour urine samples from 10 healthy normals, 11 acute, untreated schizophrenics and 6 non-schizophrenic mental patients. All were female. They confirmed Meduna on the difference between the blood sugar versus time curves for normal and schizophrenic groups. The curve for the non-schizophrenic group was not significantly different from the curve for the normals. Sixty per cent. of the rabbits receiving a schizophrenic extract died 3 to 24 hours after the injection. Preliminary symptoms were diarrhoea, cold ears, shallow rapid breathing and limpness; these were followed by convulsions, screaming and death. None of the animals receiving any of the normal or non-schizophrenic extracts died. The same extracts gave minimal effects in rats and no effects in mice or frogs (cf. Section C-1 (*i*)). On the basis of earlier work in the same laboratory the transient and slight hyperglycaemic action of the normal extracts (which can be inhibited by

adrenolytic agents (79)) may be due to the hypotensive agent, kallikrein (81); schizophrenic extracts seem to contain less kallikrein than do normal extracts and hence their more potent and longer-lasting hyperglycaemic effect must be due to some other agent (80).

Morgan and Pilgrim (78) reported isolation of a hyperglycaemic factor from urine by acidification to pH 4·5 with acetic acid followed by centrifugation; the active material is in the precipitate. The same or a similar factor can be isolated from urine by adsorption on to benzoic acid. Treatment of aliquots of a given urine sample by the two methods yielded materials of about equal activity. The hyperglycaemic activity was assayed by intraperitoneal injection into fasted rats; the results are variable from rat to rat. The concentration of the hyperglycaemic factor is greater by about 20-fold in the urine of acute schizophrenic patients than in that of normals. Moya and his group have confirmed this report using the Morgan and Pilgrim procedures (80); the active material is presumably different from that in extracts prepared by Meduna's procedure which give minimal effects in rats. Morgan and Pilgrim tentatively concluded that the hyperglycaemic factor is a non-dialysable protein or polypeptide. It is not readily adsorbed on to carbon, gives a positive ninhydrin, biuret and Molisch test, is not soluble in ethanol or ether, but is soluble in water except at pH 4–4·5.

Shiraishi (97) has also reported an abnormally high excretion of a hyperglycaemic factor by psychotic patients. He indicated that the amount excreted is approximately proportional to the severity of the symptoms and decreases with clinical improvement.

E. *Effect on Enzyme Systems in vitro*

The anti-proteolytic activity of serum is reportedly increased in schizophrenia, during epileptic stupor, in progressive paralysis, in uraemia and slightly in alcoholism. The extent of increase in schizophrenia correlates with the severity of the symptoms (88). The positive finding in uraemia is of some interest to those postulating a dysfunction in aromatic metabolism in schizophrenia since the mental symptoms in uraemia have been attributed by some to an accumulation of toxic aromatic compounds in the blood (7, 38).

Schizophrenic serum is said to have only about half the stimulating effect of normal or animal serum on glucose utilization by the isolated rat diaphragm and a depressing effect is noted with some samples. Sera obtained from patients who had benefited clinically from insulin coma treatment showed a normal stimulating action (113). It has been hypothesized that the inhibitory effect noted with schizophrenic serum is due to pituitary or adrenal hormones; signs of increased adrenal cortical function are often observed in active phases of schizophrenia (2). Haavaldsen *et al.* (102) recently reported on a substance in the alpha-globulin fraction of serum from many psychotics (especially schizophrenics) which inhibits glucose utilization by the isolated rat diaphragm.

Streifler and Kornbluth (103) studied the effect of serum from 49 acute schizophrenics and 20 chronic schizophrenics on glucose uptake by rat neural (retina) tissue *in vitro*. They found that schizophrenic blood serum inhibited the glucose uptake more than did normal serum. No difference in this inhibitory behaviour was noted between acute and chronic cases, between the different forms of schizophrenia and between the various age groups. Sera from female patients, however, proved generally more inhibitory than those obtained from males.

Hukuda (61) studied the rate of glucose metabolism by rat brain tissue in a medium containing serum from normals or from schizophrenics. The 10 schizophrenic sera studied showed a significant inhibition of glucose metabolism and particularly of the conversion to pyruvic acid, as compared with the 6 normal samples. There was no significant difference between male and female sera.

Summary

The general conclusion which can be drawn from the numerous reports in the literature on the physiological effects of schizophrenic body fluids is that the subject is not yet on a firm experimental foundation. In many cases the experiments are inadequate to demonstrate the points they intend to prove. The cumulative weight of evidence would be impressive were it not for the disturbing number of conflicts amongst the various reports. Due allowance must be made of course for the unusual problems encountered in designing and executing convincing experiments, and encouragement can be taken from areas such as the toxicity of schizophrenic sera where there has been substantial confirmation of an initial report. Failure to obtain positive results on any particular test is not necessarily a setback to the psychotoxin concept of schizophrenia. Psychotoxic substances may exist but not be detected because of lack of suitability or insensitivity of the test, chemical alteration during the workup procedure or rapid detoxication by the bio-assay organism. The greater effect reported for taraxein in psychotics as compared to normal humans suggests that detoxication may be an important factor.

In each of the categories discussed, certain reports are particularly noteworthy. The work on experimental catatonia using schizophrenic bile is promising, but has not been followed up in recent years. Interest in bile may be encouraged by reports that LSD-25 or its metabolites are largely excreted through this medium (94). The recent work of the Tulane group on taraxein is dramatic, and, if confirmation can be obtained, considerable emphasis is bound to be placed on this lead. The method of rapid transfusions of schizophrenic blood should make confirmation possible in many centres.

In the area of non-catatonic C.N.S. effects, the experiments of Winter and Flataker stand out for methodology. They have been the first to apply to the problem a quantitative test which depends on a trained response.

Certain gratifying consistencies appear in the voluminous work on "abnormal toxic" effects of schizophrenic urine and serum. Although one must beware of assuming that various bio-assays are measuring the same or similar factors, many workers report such similar properties as the same percentage (60–70 per cent.) of "positive" tests with schizophrenic fluids and thermolability of the serum "factor".

The work of Rieder and others in Georgi's laboratory seems particularly convincing with regard to urine toxicity, since they have been at some pains to recognize and attempt to minimize the influence of artefacts. The report of Weichbrodt on the toxicity of schizophrenic serum to white mice has been confirmed by a number of workers. The experiments of Sjovall stand out from a statistical point of view and are impressive because of his care in the selection of schizophrenic and control groups. Federoff and his co-workers have provided interesting information concerning the apparent properties of the serum factor toxic to cell cultures.

In summary, the reviewers strongly feel that a spirit of optimism should prevail in this field. In general, criticisms are directed against the quantity of work reported (which is often a factor not entirely within the control of the investigator) rather than any lack of promise. There are a number of exciting leads in each of the categories discussed which merit contemporary efforts at confirmation and extension. Furthermore, there is not a large negative literature in this subject as there is in so many others, and its potential importance probably justifies an expanded research effort.

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