TOWARD AN INTEGRATED THEORY OF SCHIZOPHRENIA

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EVIDENCE is accumulating that schizophrenia is a disease involving "immuno-allergic" sensitization of the tissues of the central nervous system. Variations in its symptomatology may in part depend upon the altered ability of the sensitized nervous tissue to bind or release serotonin, and perhaps other endogenous catechol amines. Accumulation of these products; their rates of turnover; the presence of endogenous enzyme enhancers or inhibitors; specific endocrine dyscrasias; blood-brain barrier conditioners; as well as cellular changes in electrolytes, may all play a part in the process. Genetic defects; lags in maturation; autonomic imbalance and pre-psychotic personality structure may lurk in the background.

That these are not primary is indicated by the fact that the disease process is frequently reversible in response to non-specific immuno-allergic desensitization in much the same way as are somatic allergic conditions.

Conason and Ryberg (1) discuss results of an empirically developed desensitizing regimen in the treatment of 98 mentally disturbed patients, 22 of whom were diagnosed as chronic schizophrenics. This empirical treatment has evolved over the course of some twenty-five years during the treatment of several thousand patients.

Beginning in 1931 with the use of adrenal cortical extract (ACE) in the treatment of a depressed patient suffering with Addison's hypoadrenalism, the procedure was extended to non-Addisonian patients suffering with depression accompanied by marked hypotension. Further extensions involved a wide variety of mentally and emotionally disordered patients. Among these were an increasing number diagnosed by competent psychiatrists as schizophrenics, who had failed to respond to conventional therapies. Assessment of the results obtained with ACE replacement therapy in psychotics was disappointing. Improvement did occur in a fair proportion of patients. It was neither complete nor long-lasting. Relapses were frequent after treatment was discontinued. The rationale for treatment had rested on the notion that these patients suffered from adrenal-cortical refractoriness following long-continued unremitting stress stimulation, with a resulting disturbance in salt and water metabolism. It appeared worth while to see whether the temporary improvement obtained with the ACE replacement therapy might be augmented and prolonged by stimulation of the pituitary-infundibular-adrenal axis. Progressively increasing doses of non-specific-protein was the technique of stimulation selected.

By 1948 clinical results seemed to warrant freezing the procedure to facilitate assessment of the results of treatment. The treatment so fixed consists of

giving 3·0 ml. adrenal cortical extract intramuscularly daily for 12 days followed by weekly intramuscular injections of a non-specific-protein mixture containing 2% solids derived from non-pathogenic micrococci, casein, and purified endotoxin, the mixture having proved more reliable in its clinical effect than any one of numerous single pure antigenic substances tried. Beginning with a sub-reactive dose of 0·2 ml. this antigenic mixture is increased progressively by a weekly increment of 0·2 ml. to doses which in the absence of tolerance are shock-producing (3·6 to 5·0 ml.). Given as outlined the treatment caused no observable side reactions except for occasional warmth and soreness at the site of injection, which was considered a signal to repeat the dose the following week. The response of some psychotic patients to this regimen was impressive. In those patients who responded well to the treatment mental fogging lifted; normal feeling tones and optimism replaced depression; agitation and severe anxiety-tension became less persistent and gradually faded; catatonic posturing and indifference disappeared; disabling phobias and obsessions were submerged and then given up; active hallucinating together with paranoia and delusional thinking were gradually replaced by rationalizations and finally by insight. As the patients improved they began to display interest in the outside world, responded to suggestion, were able to concentrate and make decisions and began to initiate activities of their own. Finally they lost their sense of isolation and depersonalization and with little pressure or urging returned to their normal activities to the point of undertaking responsibilities they had been unable to handle. Only those patients who were able to return to full-time work or school activities were considered to have recovered.

Treatment as outlined above resulted in complete clinical and social recovery in half the psychotic patients. An additional quarter of these patients were symptomatically improved, but failed to recover completely. Despite lessening of many of their difficulties, they did not regain steady normal feeling-tones, could not initiate their own activities, or return to work activities in a consistent manner. The remaining quarter failed to respond or regressed while under treatment. About one in five of those successfully treated relapsed within a year of cessation of treatment. In most of these a second course of treatment resulted again in remission, but in view of their previous relapse they were placed on "maintenance therapy" consisting of a perennial series of "booster shots" given at 21 day intervals, much as are given in the treatment of hay fever on a perennial basis. On several occasions attempts were made to step-up the speed of treatment by either increased increments of the medication or by decreasing the interval between injections. Both resulted in agitation and hyperactivity to such an extent that they were not pursued. On one occasion, three patients who were each making excellent progress were precipitously thrown into severe relapse by the substitution of an oily menstruum for the usual aqueous one, in a single injection. At the time, 1949, no satisfactory explanation for these relapses presented itself. In the light of our present theory it seems possible that the "adjuvant effect" of the oil or its depot action may have caused resensitization of the brain.

Success or failure in treatment could not be accounted for by age, sex, length of illness, severity of initial symptoms, pre-psychotic type of personality structure or clinical diagnosis. Attempts to relate prognosis to evidence of change in pituitary or adrenal output failed to show any consistency. The reaction of patients to the Randolph or Thorn eosinophile test, or their titre of urinary steroids, varied irregularly and gave no reliable clue to the probability of recovery. The only phenomenon which showed up with consistency

was that displayed by patients who had presented definite evidence of salt and water imbalance. These patients consistently signalled oncoming recovery by rapid increase in weight which was interpreted as due to hydration.

Patients with such endocrine dyscrasias as hypo- or hyperthyroidism, Cushing's syndrome or marked hypogonadal states combined with psychosis were treated with appropriate endocrine therapies as well as with non-specific desensitization. These patients were not included in statistics for purposes of appraisal of results of treatment. The lack of a satisfactory rationale of treatment discouraged earlier publication. Recent findings combine to suggest such a rationale. Even though the findings are not conclusive they map out a promising line of study. Thus recent publications show that:

(*a*) The sedating effects of the active rauwolfia alkaloids are mediated through the release of serotonin from its binding to brain tissue (1b and 3).

(*b*) Lysergic acid diethylamide-like excitation and hallucinogenic hyperactivity accompanies excess serotonin turnover or accumulation in the brain (3). Such excess may be experimentally induced by feeding the serotonin precursor, 5-hydroxytryptophane (2) or by blocking the serotonin inactivator monoamine oxidase (3).

(*c*) This has led to the suggestion that disturbances in brain serotonin level are basic to schizophrenia (2). Wooley is testing this theory by feeding 5-hydroxytryptophane to a group of schizophrenics to raise their serotonin brain levels. Unlike serotonin itself, the precursor passes the blood-brain barrier, enters the brain and is there decarboxylated to form serotonin. Free serotonin having discharged its function is instantly inactivated by monoamine oxidase (4). Serotonin bound to tissue escapes inactivation, providing a protected depot for release of the active free form in response to normal needs or to homeostatic feedback demands. The mechanism for the release of serotonin from its binding to normal brain tissue is not known. Its release from somatic tissue-binding (*in vivo* and *in vitro*) in the course of immuno-allergic or anaphylactic reactions suggests that a similar mechanism may induce its release from brain tissue. H. Weissbach *et al.* (5) review some of the evidence of immuno-allergic or anaphylactic release of serotonin from somatic tissue. They call attention to:

(*a*) The release of serotonin from normal rabbit platelets in plasma on addition of purified antigen or antibody (6).

(*b*) The relationship between tolerance to serotonin and desensitization in the guinea pig (7).

(*c*) The release of serotonin in the blood of rabbits during anaphylactic shock (8).

(*d*) The blocking of serotonin-induced and antigen-induced uterine contractions in the sensitized mouse uterus (Schultz-Dale reaction) by reserpine and lysergic acid diethylamide. The author shows that antigen causes uterine contractions by release of serotonin (9).

The suggestion follows that schizophrenia may involve immuno-allergic or anaphylactic brain sensitization, with secondary disturbances in serotonin brain levels. Such a postulation finds further support in the following:

I. The reported rarity of asthma, hay fever, and acute rheumatic arthritis among populations of mental hospitals as compared to the general population or to non-psychotic hospital personnel (10) together with the sharp alternation

between asthma (and other so-called psychosomatic illness) and psychosis in some psychotics, suggests the likelihood that competition between allergenically sensitized nervous tissue and similarly sensitized somatic tissue for a common incitor is involved.

II. Varying sensitivity of schizophrenics to adrenalin and noradrenalin has led to controversial theories of autonomic imbalance as crucial to schizophrenia (12 and 13). The findings are as susceptible to explanation by immuno-allergic sensitization of the psychotic (with accompanying adrenalin and noradrenalin hyper-reactivity) as they are to theories of autonomic imbalance.

Funkenstein *et al.* (12), for example, classify their patients according to their pressor response to a standard dose of adrenalin together with their ability to resist the hypotensive action of methacholine. They claim to be able to predict success or failure in electroshock therapy by these reactions. Patients with very marked adrenalin sensitivity as shown by excessive pressor response and concomitant good resistance to the hypotensive action of methacholine, doing poorly, while those with lessened sensitivity to adrenalin as shown by a small transient pressor response and profound and prolonged hypotension after methacholine, respond to the electroshock treatment with recovery.

Similar sensitivity to adrenalin can be experimentally induced in rabbits by sensitizing them to bacterial endotoxins (14). Rabbits made sensitive to endotoxins are found to be also sensitive to adrenalin and noradrenalin. In these animals the catechol amines trigger repeated immuno-allergic reactions. Unlike normal untreated animals who react to an intradermal injection of adrenalin by transient skin blanching, sensitized rabbits develop severe haemorrhagic necrosis in response to intradermal adrenalin or noradrenalin. This necrosis is antagonized by such catechol amine inhibitors as chlorpromazine and dibenzyline, as well as by treatment of the sensitized animal with cortisone for several days. This inhibitory action of cortisone contrasts sharply with the fact that treatment of normal untreated rabbits with cortisone renders them sensitive to bacterial endotoxin so that a single dose of endotoxin following cortisone acts like a challenging dose, producing a generalized Schwartzman reaction as well as sensitization to adrenalin and noradrenalin (14 and 15). Thomas calls attention to the striking parallel between this sensitizing effect of cortisone and the occasional precipitation of psychosis in the course of cortisone therapy implying a similarity in mechanism. The parallel is sharpened in the light of our proposed theory of the pathogenesis of schizophrenia by Thomas's recent suggestion that the generalized Schwartzman phenomenon as well as accompanying adrenalin and noradrenalin reactions are mediated through serotonin release (17).

Thomas was able to induce a "temporary immunologically non-specific state of tolerance" in his sensitized rabbits by repeated daily injections of small doses of bacterial endotoxin. This induced tolerance to adrenalin and noradrenalin as well (14), (15 and 16).

III. Recent findings of organ-specific auto-antibodies in the blood of patients suffering with Hashimoto's thyroiditis, thyrotoxicosis, and Addison's disease (18, 19, 20 and 21) suggest that auto-antibodies to nervous tissue be sought in the blood and C.S.F. of schizophrenics. The induction of schizophrenic-like states in non-psychotics by injection of "taraxein" from the serum of psychotics brings to mind the "passive transfer" of the allergist. The persistence and life-long course of schizophrenia might find explanation in such mechanisms as are encountered in genetically determined iso-immune or auto-

immune states in which iso-antigens or auto-antibodies trigger repeated cycles of immuno-allergic reactions (23).

IV. The tranquillizing effects of an increasing number of anti-allergic drugs of varying chemical structure, such as phenergan, benadryl, chlorpromazine, bonamine, hydroxyzine and others (23 and 24) raises the suspicion that their tranquillizing effects may be related to their anti-allergic action.

V. The reversal of the schizophrenic process by the non-specific desensitizing regimen in 50 per cent. of chronic schizophrenics discussed above adds plausibility to the theory that the disease primarily involves immuno-allergic sensitization of the nervous system, with secondary disturbances in the brain turnover of the catechol amines, more especially noradrenalin and serotonin.

It is suggested that the homeostatic mechanisms which operate to maintain sanity in the normal mind, are blocked in the psychotic by immuno-allergic brain tissue alterations, just as the homeostatic mechanisms regulating somatic tissue metabolism are blocked by such alterations in hay fever, asthma, serum sickness, angioneurotic oedema, contact dermatitis and other so-called atopic allergic states.

References

1a. Conason, E. G., and Ryberg, P. E., *Dis. Nerv. Syst.* (Monograph Suppt.), July, 1957, **18,** 3.
1b. Brodie, B. B., Shore, P. A., and Pletscher, A., *Science*, 1956, **123,** 992.
2. Wooley, D. W., *Science*, 1957, **125,** 752.
3. Shore, P. A., and Brodie, B. B., *Proc. Soc. Biol. Med.*, 1957, **94,** 433.
4. Brodie, B. B., and Shore, P. A., *Ann. N.Y. Acad. Sci.*, 1957, **66,** 631.
5. Weissbach, H., Waalkes, T. R., and Udenfreind, S., *Science*, 1957, **125,** 235.
6. Humphries, J. H., and Jacques, R., *J. Physiol.*, 1955, **128,** 9.
7. Herxheimer, H., *J. Physiol.*, 1955, **128,** 435.
8. Waalkes, T. R., *et al.*, *J. Pharmacol. Exptl. Therap.*, 1957. In Press.
9. Fink, M. A., *Proc. Soc. Exptl. Biol. Med.*, 1956, **92,** 657.
10. Ehrentheil, O. F., *Arch. Neurol. Psychiat.*, 1957, **77,** 178.
11. Funkenstein, D. H., Greenblatt, M., and Solomon, H., *J. Nerv. Ment. Dis.*, 1951, **114,** 1.
12. *Idem*, *Scientific American*, 1955. May.
13 Perrin, G. M., and Altschule, M. D., *New Eng. J. Med.*, 1957, **256,** 682.
14. Thomas, L., *Ann. Rev. Physiol.*, 1954, **16,** 467.
15. *Idem*, *Bull. N.Y. Acad. Med.*, 1955, **31,** 485.
16. *Idem*, *J. Exptl. Med.*, 1956, **104,** 865.
17. *Idem*, *Ciba Medical News*, 1957. 20 May. Press release.
18. Anderson, J. R., *et al.*, *Lancet*, 1957, *ii*, 1123.
19. Witebsky, E., and Rose, N. R., *J. Immunol.*, 1956, **76,** 408.
20. Rose, N. R., and Witebsky, E., *ibid.*, p. 417.
21. Roitt, I. M., *et al.*, *Lancet*, 1956, *ii*, 820.
22. Leach, B., and Heath, R. G., *Ciba Medical News*, 1957. 3 June; *Amer. J. Psychiatry*, 1957. July.
23. Raffel, S., *Immunity*, 1953. New York: Appleton Century Croft.
24. Bender, L., and Nichtern, S., *N.Y. State J. Med.*, 1956. 15 September.