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Fact and Artifact in the Biology of Schizophrenia

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It appears important at this time to emphasize that many reports showing differences between patients with schizophrenia and normal individuals are based on environmental artifacts that are not related to the basic disorder. The practice followed by biochemical workers of requesting samples of blood or urine from subjects on psychiatric wards, with little more identification of the sample than that the patients have a mental disease, has many disadvantages.

We are now entering a period of renewed interest in biological research on schizophrenia. Nothing can be more harmful to this rejuvenation of the investigation of the biology of mental health than the publication of reports based on techniques of patient selection which do not meet the minimum standards accepted by other disciplines. Much of this conflict is due to a lack of understanding by some workers that the term *schizophrenia* is a general classification with many subdivisions, which are often only slightly related, and that the manner in which the patient chooses to manifest his difficulties may not be a function of his physiological status.

Symptoms that are usually considered artifacts in other studies are often erroneously accepted as biological aberrations in the evaluation of the schizophrenic patient. Year after year, papers appear which purport to distinguish between the state of schizophrenia and that of normalcy. The sum total of the differences reported would make the schizophrenic patient a sorry physical specimen indeed: his liver, brain, kidney, and circulatory functions are impaired; he is deficient in practically every vitamin; his hormones are out of balance, and his enzymes are askew. Fortunately, many of these claims of metabolic abnormality are forgotten in time with a minimum of polemic, but it seems that each new generation of biologists has to be indoctrinated—or disillusioned—without benefit of the experience of its predecessors. One is not certain where to place the blame for this weakness, but both editors and grant advisers could do well to insist on experimental design and interpretations of data which take into account some of the following, almost too obvious, variables.

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Variables

1) *Emotional stress, tension, and anxiety.* One does not obtain basal metabolic results during fever or exercise, nor should one expect to obtain basal samples during emotional stress. One of the basic characteristics of the schizophrenic patient is his peculiar emotional reaction to his environment. These reactions will vary in kind and intensity with the individual and with time. A supposedly basal sample taken from a physically quiet but emotionally disturbed catatonic subject may not be basal at all but may be a reflection of metabolism during intense adrenergic stimulation. Adrenergic stimulation has a marked effect on the levels of amino acids in the biological fluids.

To compare the results from such a blood sample with those from blood of normal subjects is like comparing data from blood samples obtained during grief or stress of battle with data from blood obtained during relaxed, basal conditions. With experience and knowledge of the individual patient, one may learn to distinguish between the presence or absence of some emotional stresses. But, even under optimal conditions, a preliminary period of at least 3 to 6 months may be required to evaluate the stability of subjects chosen for a metabolic study (*1*) in order to eliminate those that are unpredictable. Even when this precaution is taken, some subjects may occasionally leave a previous metabolic pattern because of a temporary emotional stress situation.

In such a situation, if one requires data from unstressed subjects, the tests are repeated at a later date. If basal data cannot be obtained from a subject, the results should not be averaged with those from subjects who are not disturbed. To show that there are differences between the reactions of a normal subject and those of a patient in the early, active stages of mental disorder may give good leads on the effects of emotional trauma on the biochemistry of a subject, but great care should be exercised in interpreting data obtained from such patients as being biological aberrations characteristic of the basic disease. Recent confirmation by McGeer *et al.* (*2*) of the observations by Young *et al.* (*3*) of the increased excretion of aromatic compounds in the urine of "schizophrenics" would have been more useful if their studies had included estimations of tension and anxiety (and possible nutritional imbalance) of the subjects studied.

2) *Nutritional state.* Emotional stress affects the appetite of all of us in different fashions. Even in the best managed hospitals, unless food intake is strictly controlled, the vagaries of psychotic behavior are such that they affect optimum nutrient consumption in some patients who tend to go in and out of negative nitrogen balance with varying interactions of their delusional states. Relatively unimportant food idiosyncracies may, in time, become manifest as mild nutritional disorders. The metabolic changes which take place with even mild and often unrecognized nutritional disorders are more severe than the biological variations being sought in mental disease.

Having studied such changes in mental patients for more than 15 years, I am at a loss to understand how some studies

of urinary excretion or of blood constituents can be performed without recourse to nutritional controls. My experience is that it may take 3 months (or the equivalent of 3 days of a rat's life) to achieve a nutritional steady state after a change in the dietary regimen.

3) *Liver dysfunction or suboptimal liver function.* It has been frequently claimed that some schizophrenic patients have decreased rates of clearance of bromsulfalein or hippuric acid. The study of liver function in such patients is well worth more attention, but only additional work can clarify whether such changes are related to diet, inactivity, training, slower circulation time, physiological hibernation, infection, or other factors. Although the pattern of urinary excretion is not expected to vary in a 24-hour sample from subjects with mild liver dysfunction, tolerance tests that can evaluate the *rate* at which a substance is absorbed or removed, or both, from the blood stream may show sluggish activity in some schizophrenic patients.

In one controlled study, which was designed to estimate the effects of a diet that provided borderline levels of protein, signs of liver dysfunction became apparent and were not repaired until after the protein intake was raised (*4*). Whether a schizophrenic patient is more susceptible to liver disorder during protein deficiency or whether the slower removal of injected compounds is a consequence of long-term inactivity cannot be determined with the data at hand, but whatever the cause of mild liver dysfunction in the mental patient, the possible presence of such defects should be evaluated more frequently.

4) *Training.* One does not have to be oriented in athletics to recognize that the cardiovascular efficiency of an individual can be markedly influenced by repetitive exercise or work, or conversely, by extreme inactivity. The activity of mental patients may vary widely, from prolonged states of fierce agitation that are acted out by considerable physical movement, to conditions of relative hibernation. Such differences make for important variations in studies of oxygen consumption, circulatory rates, and all related concomitants of biological efficiency. When one considers that the maximum oxygen uptake of a trained individual may be double that of the untrained subject (*5*, *6*), it is not surprising to note that data from most biological studies on mental patients have greater variations from the mean than are obtained from nonpsychotic subjects. In addition, in most mental institutions there are patients who do productive work and others who remain sedentary for years, and the differences in functional muscle mass between these subjects are considerable.

5) *Diurnal variations.* Those acquainted with mental hospitals are aware of the great differences in night restlessness that may exist in various wards. Many mental patients have a high level of nocturnal activity. (It is assumed that sedated or tranquilized patients are not used for basal studies.) The all-too-frequent practice of comparing overnight urine samples from mental patients with similar samples from normal individuals can lead to unwarranted conclusions that might not be made if full 24-hour samples were collected instead. In this connection, one should also be aware of the prolonged fasting period of more than 14 hours between supper and breakfast that is a characteristic of many of our institutions and of the possible effect of such a schedule on diurnal variations.

Conclusion

It is earnestly hoped that investigators who are impelled to study the biology of schizophrenia or of other mental disorders will attempt to control the variables mentioned so that we may better distinguish between the causes of schizophrenia and its effects. Admittedly such controls are expensive and difficult to administer, but they are worthy of incorporation into any research program where man is the experimental subject. Much has been said about the faults of psychiatrists who do not make sufficient use of the laboratory concepts of cause and effect in evaluating mental disease. Conversely, the biologist should not be so naive in the interpretation of his data that he loses cognizance of the fact that schizophrenia is not a simple entity, and that he, too, must beware of the trap of confusing cause and effect.

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Physical Mechanism of Bacteriophage Injection

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It is currently accepted by many that a bacteriophage attaches itself to its host at the tip of its tail (*1*). It has also been found that the outer part of the phage particle, the protein coat, is left outside, while the inner part, which is predominantly desoxyribose nucleic acid (DNA), enters the bacterium and there undergoes multiplication (*2*). Very little is known about the mechanism of the penetration process. It is the purpose of this article (*3*) to show that quite ordinary physical processes offer the possibility of explaining the phenomenon of entry, and that, although no one clear explanation is presented here, there is certainly no reason to feel that this process offers anything extraordinary.

The processes we call attention to are, first, the linear Brownian movement of a long thin object through a tube containing a viscous medium and, second, the centrifugal pull exerted by oscillatory thermal movement of the part of the genetic thread that has already entered. The analysis we give of the two processes indicates that they can offer a plausible explanation for the entry of the viral DNA into the host, but that, under some circumstances, entry by these methods may be severely restricted. It is also suggested that hydration changes in the viral DNA might play a certain role.

The dimensions of the nucleic acid thread that enters the host are not accurately known. If we take the figures for phosphorus atoms per virus particle as given by, for example, Stent and Fuerst

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