EDITORIAL

Viruses as Causes of Psychiatric Disease

If, as seems likely, the neural disturbance is not generalized but affects certain specific chemical systems within the brain it must be assumed that the pathogenic agent itself has chemical selectivity. The two classes of causative factor which might have this characteristic are antibodies and viruses. In both cases there is a replicative process and this could allow the pathological process to be widespread. Both types of agent attack cell surface components. Although autoimmune and virus-induced diseases have commonly been considered as distinct categories, evidence from animal models of diseases considered to be autoimmune suggests that these are often initiated by a viral infection (Lewis, 1974).

Evidence has been presented (Tyrrell **et al.**, 1979; Crow **et al.**, 1979) that a virus-like agent can be detected in CSF in some patients with schizophrenic illnesses and also in some suffering from Huntington's chorea. The agent responsible for the cytopathic effects seen in cell culture is of the size of a small virus (50 to 100 nm), is relatively heat stable, and apparently does not have a lipid coat. At the present time it is not possible to say that this agent is a virus since serial transmission in cell culture has not been achieved. Still less is it possible to say that the agent has a causal relationship to the diseases with which it has been associated. Nevertheless the possibility that schizophrenia is a virus disease introduces the question of treatments which are radically different from those which are in current use.

Perhaps the most interesting possibility is that it might be feasible to devise agents which are both chemically specific in their distribution in the brain and have antiviral activity. Amantadine is one such agent since it is known to have a selective affinity for catecholaminergic pro-

cesses, and has antiviral activity, at least against some influenza viruses (Bauer, 1977). Unfortunately in so far as evidence is available from studies of its use as an antiparkinsonian agent no therapeutic affects in schizophrenic patients have been observed (Mindham et al., 1972), and no activity against the virus-like agent has been seen in cell culture studies (unpublished data).

However, other agents with activity against slow virus diseases may become available. Very little work is in progress on the therapy of slow virus diseases of the central nervous system in man, and there are few leads. However, some recent work on scrapie, a slow degeneration of the nervous system in sheep which is transmissible both to sheep and to mice, may be relevant. It has recently been reported (Kimberlin & Walker, 1979) that the initiation of scrapie following inoculation in the mouse can be delayed and in certain circumstances prevented by administration of the agent HPA 23 (ammonium-5-tungsto-antimoniate). This is perhaps the first instance in which the course of a slow viral disease has been clearly shown to be influenced by a pharmacological agent. It is generally assumed that the relevance of scrapie for human disease is as a model for the Creuzfeldt-Jakob syndrome. However, there is a case that the disease may have wider implications, for example for Alzheimer's disease. The neuropathological lesions of scrapie may resemble those of the spongioform encephalopathies but they may also resemble those of Alzheimer's disease in presenting with plaques and neurofibrillary tangles, the type of change depending upon the strain of mouse and strain of scrapie agent (Wisniewski, Bruce & Fraser, 1975). The interest of these findings for Alzheimer's disease is enhanced by the demonstration that in scrapie in the mouse there is a loss of choline acetyl transferase activity in the brain (McDermott, Fraser & Dickinson, 1978) closely similar to that which has been observed in Alzheimer's dementia (Davies & Maloney, 1976; Perry et al., 1977; Spillane et al., 1977). Thus although transmission of Alzheimer's disease has been achieved only in one or two atypical and doubtful cases (Traub et al., 1977) the possibility that this disease like Creuzfeldt-Jakob disease is associated with an unconventional virus should be given serious consideration.

Research on slow viral diseases is in its infancy and little of it is yet related to psychiatric disease. It is perhaps worth considering how much of current research on schizophrenia (and other functional psychoses) has the potential for discovering a primary cause, whether or not this be viral. The various disciplines of psychiatric research can be placed into categories according to whether it seems likely that the phenomena they study are related to predisposing factors, manifestations of disease, therapeutic effects or disease processes.

Some disciplines (e.g. genetics) seem likely to be concerned mainly with predisposition, and others (e.g. electroencephalography) with manifestations, while several (e.g. sociology, psychology and epidemiology) are concerned with both these aspects. These fields are mostly well supported. So also are therapeutic studies (particularly drug research) which may tell us something about the disease process, but only indirectly. Those disciplines which have the potential for revealing the disease process directly are those which study the affected tissue, the brain itself, or those fluids which are in direct contact with it. These disciplines include neurochemistry, immunology, and neuropathology. Only the first of these is at all well supported in relation to the functional psychoses, and even then this has only recently been the case. Thus there is a case that we are avoiding working on the disease process, and those fields of research which could help us are undersubscribed. Proposals for developing research in these areas should be given very serious consideration.

In addition there appears to be three areas where a substantial investment at the present time could facilitate research which might not otherwise take place. These areas are (i) facilities for obtaining post-mortem brain material. Much work in the above fields is dependent upon a supply of such tissue, and these facilities must be located in proximity to mental hospitals and psychiatric departments. (ii) the development of position emission tomography and related techniques for studying receptor function in vivo in psychiatric patients. (iii) the continued support of a nucleus of workers with experience of multicentre trials to ensure that important questions concerning long-term efficacy and interactions bet-

ween therapies will be examined in sufficiently large populations of patients.

CONCLUSIONS

The drug treatment of the functional psychoses that we have are empirical. They help us to understand the disease process, but this is not necessarily so, and they may actually distract attention from the search for a causal agent. Recent work has focussed on the receptor as the site of the disturbance in schizophrenia, and possibly also in manic-depressive psychosis, and this in turn directs attention toward pathogenic agents (e.g. viruses or auto-antibodies) from outside the cell which may be acting at the cell surface. It is suggested that these possibilities are likely to be elucidated only by studies of brain tissue and cerebrospinal fluid aimed at determining the nature of the disease process and its causation. Relatively little current research has the potential of achieving these objectives.

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