Schizophrenia as a Genetic Morphism

Huxley, Mayr, Osmond, and Hoffer[1] have discussed the theory that schizophrenia is dependent on a selectively controlled genetic polymorphism. Although the evidence for this is strong there is no certainty about its mode of inheritance, which must be determined from observed correlations between relatives. Although a number of attempts to fit simple models to such data have been made they are far from convincing since, contrary to the statement of the above authors, there is abundant evidence that the incidence of schizophrenia varies greatly in different social classes. Since this variability is almost certainly due, in part at least, to variations in gene frequency, the calculation of expected correlations between relatives on the assumption of a random mating population must lead to misleading results.

There is also considerable evidence that schizophrenics leave fewer children than those not developing the disease. Although fertility is not necessarily the only component of genetic fitness it seems very probable that this lowered fertility results in a decrease in fitness. Using plausible figures for such fitness and the simplest of the proposed models, we are forced to conclude that if heterozygote advantage, in some sense, is the explanation of the observed stability of the polymorphism, this advantage must be at least 5–10 per cent (Moran[2]).

As Huxley *et al.* suggest, such a selective advantage might be due to the heterozygotes being resistant to some types of infection in early childhood. However, it seems more likely that the selective advantage occurs earlier. It has recently been shown (for example by Levene and Rosenfield[3]) that large variations exist in the probabilities of fertilized eggs resulting in a pregnancy, and that such variations are dependent, in part at least, on blood group incompatibilities. It is also known that such incompatibilities can interfere with each other, and in particular that the effect of Rh incompatibility is greatly reduced in the presence of ABO incompatibility.

I therefore suggest that the presence of a gene for schizophrenia has a protective effect for one or more of the genetic factors which cause the loss of fertilized ova. It would therefore seem valuable if a study could be made of such incompatibilities in the families of schizophrenics.

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MORPHOLOGICAL EVIDENCE OF IMMUNOLOGICAL RELATIONSHIPS IN THE LYMPHOID TISSUE OF RABBIT APPENDIX

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INVESTIGATIONS of the ontogenesis of lymphoid tissue have revealed that mammals and birds possess central organs of lymphopoiesis—the thymus gland and the bursa of Fabricius. Their removal in the early postnatal period results in the lymphoid tissue not developing properly and a general decrease in the immunological competence of the animal[1,2]. It has been assumed[3,4] that uncommitted lymphocytes are formed in these organs, and also that these lymphocytes later re-populate the lymph nodes and the spleen. The exceptional positioning of the central lymphoid tissue organs may possibly be associated with the presence of epithelium in them, as well as with their isolation from any foreign antigens which may penetrate into the body.

According to Archer[5] the appendix of the rabbit is also a central organ of lymphoid tissue. Results which we present here confirm that a peculiar immunological situation is created in the lymphoid tissue of this organ, the importance of which is at present obscure. This tissue is subject to a constant, intensive antigenic stimulation unaccompanied by any of the usual morphological features of immunological activity.

Investigations were carried out on the wall of the appendix of healthy adult rabbits (weighing 2·0–3·0 kg), which were kept in ordinary vivary conditions for 1–90 days after birth. After fixing the material with alcohol-formol, formalin, alcohol, and Bouin's fixing fluid, a series of sections was stained with Gram-Weigert stain, periodic acid–Schiff (PAS)–polysaccharide stain, sudan black and methyl green pyronin.

The appendicial wall of adult rabbits is built up of lymphoid follicles lying directly beneath the epithelium lining the lumen. The epithelium forms pelvi-form crypts connected with the appendicial lumen by pores. The cryptic epithelium covering the lymphoid follicles contains a large number of lymphocytes, and the layer is in many places incomplete. The lymphoid follicles are found to consist of an upper part lying directly beneath the epithelium, a massive basal part, and a connecting isthmus. The basal part of the follicles possesses large germinal centres surrounded by a mantle zone.

A peculiarity of the rabbit appendix is that the lymphoid tissue of its wall is densely packed with bacteria (Fig. 1*A* and *B*). Numerous large Gram-positive bacteria showing a markedly PAS-positive reaction and a green auto-luminescence can be seen in sections, lying between the lymphocytes and in the reticular cells. A great number of similar bacteria are also present in the appendicial lumen. Their penetration from the lumen through the lymphocyte-infiltrated epithelium of the crypts into the lymphoid tissue of the follicles is frequently observed. The bacteria are phagocytosed by the reticular cells. In the macrophages of the upper parts of the follicles the bacteria retain their form; the macrophages situated in the lower parts of the follicles contain, in addition to unaltered bacteria, fragmentary remains of bacteria and bacterial cells which have lost their staining properties (Fig. 1*C*).

Aggregations of large reticular cells occur in the peripheral zones of the germinal centres; unstained slides show the cytoplasm of these cells to be full of a yellowish granular pigment. This granular substance displays a sharply positive PAS-reaction. It consists partly of fragments of bacteria and partly of the products of intracellular digestion (Fig. 1*D*). Some of this stains with sudan black. A histochemical study of the macrophages has shown that their cytoplasm contains substances which are apparently polysaccharide or lipoid in nature[6]. Most probably these are the products of digestion of the bacteria by the macrophages, or an association of these products with substances released during the destruction of the lymphocytes[6].

The cellular composition of the appendicial lymphoid tissue distinguishes it from ordinary lymph nodes. The germinal centres which occupy the major part of the basal half of the secondary follicles of the appendix consist