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Immunological Reactions in the Central Nervous System

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Allergic reactions in the brain are basically the same as those in other tissues. It is instructive, however, to consider the extent to which they may be modified by factors peculiar to the central nervous system. The most striking difference stems from the fact that oedema in the brain and cord is a far more serious matter than oedema elsewhere. A degree of inflammatory swelling giving rise to only minor transitory effects in the liver or skin might well result in serious functional disturbance and irreversible neural damage in the brain stem. Less obvious differences may derive from the unique location and composition of the extravascular fluid, and from the inability of the serum proteins, including antibody, to diffuse freely into the brain and cord.

In muscle the interstitial fluid constitutes about 14 per cent of the organ by weight, and the concentration of gammaglobulin in this space is about one-third of that in the serum (Gitlin and Janeway, 1954). Approximately 50 per cent of the total gammaglobulin of the body is held extravascularly in this way (Cohen, 1963). In brain, on the other hand, the ratio of antibody in the tissues to that in the serum is considerably lower than it is in the other organs (Freund, 1930). This is now considered to be due to the small volume of the extracellular space, rather than to any special impermeability of the cerebral vessels to protein. Water and electrolytes are contained within the glial cells, and the volume of the extracellular fluid is less than 5 per cent (*see* Dobbing, 1961). Penetration of the brain parenchyma by substances of large molecular weight, presumably by diffusion within this space, is restricted both *in vitro* and *in vivo* (Klatzo *et al.*, 1965; Pappius, 1965) although the final concentration attained is unknown.

A large area of brain surface is exposed to the cerebrospinal fluid. In this fluid, too, the concentration of gammaglobulin is low, being reduced by a factor of about 350 compared with serum (Lumsden, 1965). IgG and IgA are present in normal human cerebrospinal fluid (Chodirker and Tomasi, 1963), but the large molecular weight IgM cannot be detected (Dencker and Swahn, 1961). The central nervous system, therefore, is characterised by a very low

level of extravascular antibody, and by the limited access of both antigen and antibody from the blood stream.

Although the pathological picture may be infinitely varied, there are basically only four ways in which immune reactions in the body can cause tissue damage (Coombs and Gell, 1963). These are:

(*a*) Immediate-type hypersensitivity (anaphylaxis);
(*b*) The Arthus reaction (serum sickness);
(*c*) Direct cytotoxic effects due to antibody;
(*d*) Delayed-type hypersensitivity.

Lesions of the central nervous system can be experimentally induced by each of these methods, with the exception of the first.

IMMEDIATE-TYPE HYPERSENSITIVITY

The essential feature of this form of hypersensitivity is antibody with a high affinity for tissue cells. On exposure to antigen the reaction takes place at the cell surface causing an explosive release of pharmacologically active agents, including histamine. Since the cerebral vessels are sensitive to histamine it must be assumed that they are involved, to some extent, in systemic anaphylactic shock, although the effect is not perceptible against the general background of respiratory and circulatory failure. Local cerebral anaphylaxis has, apparently, never been demonstrated; and brain does not figure in the long list of tissues that have been tested for the *in vitro* release of histamine on exposure to antigen.

In most mammalian species mast cells can be found in the meninges, the vessels of the choroid plexus, and the pituitary stalk (Riley, 1959), and anaphylactic effects due to local histamine release in these areas must be regarded as feasible. In the deeper regions of the brain, however, and away from the larger vessels, immediate-type hypersensitivity responses are unlikely. Although histamine is present in many areas, it is not contained within mast cells (Michaelson and Dowe, 1963); and the low concentration of antibody and impaired diffusion of antigen within the extravascular space are likely to be seriously limiting factors.

VASCULAR NECROSIS OF THE 'SERUM SICKNESS' TYPE

Antibody-antigen complexes formed in the zone of antigen excess are highly damaging to blood vessels. They cause a fibrinoid necrosis that is the basis of the Arthus reaction (Fig. 1) and of serum sickness (Weigle, 1961). In the Arthus reaction the lesion is brought about by repeated local injections of antigen, and successive intracerebral inoculations have been shown to repro-

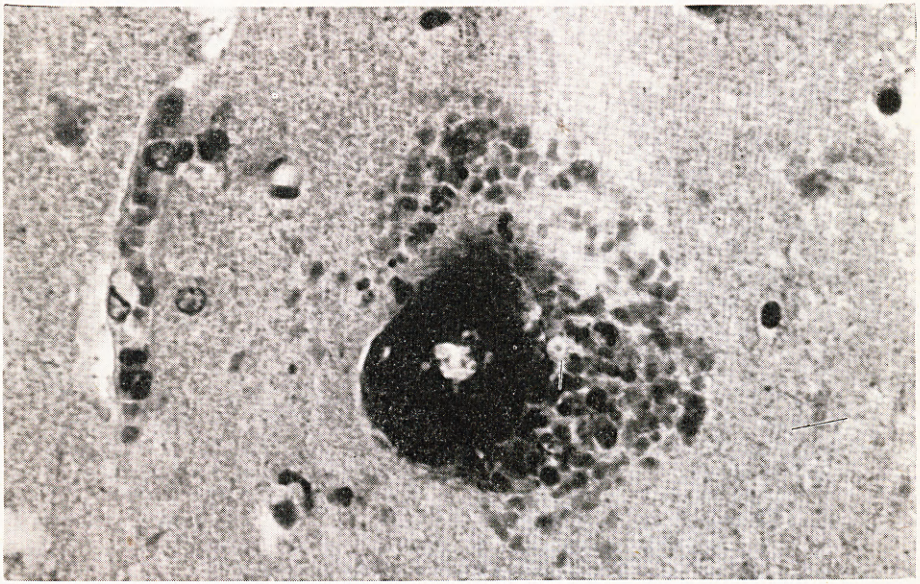

Fig. 1. Arthus-type lesion. Fibrinoid necrosis in a cortical vessel. Case of cerebral polyarteriolitis. Phosphotungstic acid haematoxylin. (× 500) (Section by courtesy of Dr G. A. K. Missen.)

duce this phenomenon in the brain of monkeys (Davidoff *et al.*, 1932). In serum sickness, the complexes are formed intravascularly, and the effects are widely distributed in the vascular tree. Lesions of this type are primarily dependent upon the concentrations of antibody and antigen in the serum, and the low extravascular antibody level in the brain is irrelevant. Cerebral lesions would, therefore, not be expected to differ from those elsewhere. In polyarteritis nodosa, which morphologically, at any rate, is a disease of the 'serum sickness' type, vascular damage may be found in the central as well as the peripheral nervous system (Foster and Malamud, 1941). It is interesting to note, however, that these lesions are far commoner in the peripheral nerves than they are in the brain.

DIRECT CYTOTOXIC EFFECTS DUE TO ANTIBODY

Circulating serum antibody against antigenic components of a cell surface may, in the presence of complement, cause cell damage and lysis. The classical example of this is immune haemolysis. In the brain a very striking phenomenon of this type is the Forssman heterophil reaction. The Forssman antigen is a lipopolysaccharide widely distributed in both plants and animals. In the guinea-pig it is found in many tissues, including the vascular endothelium,

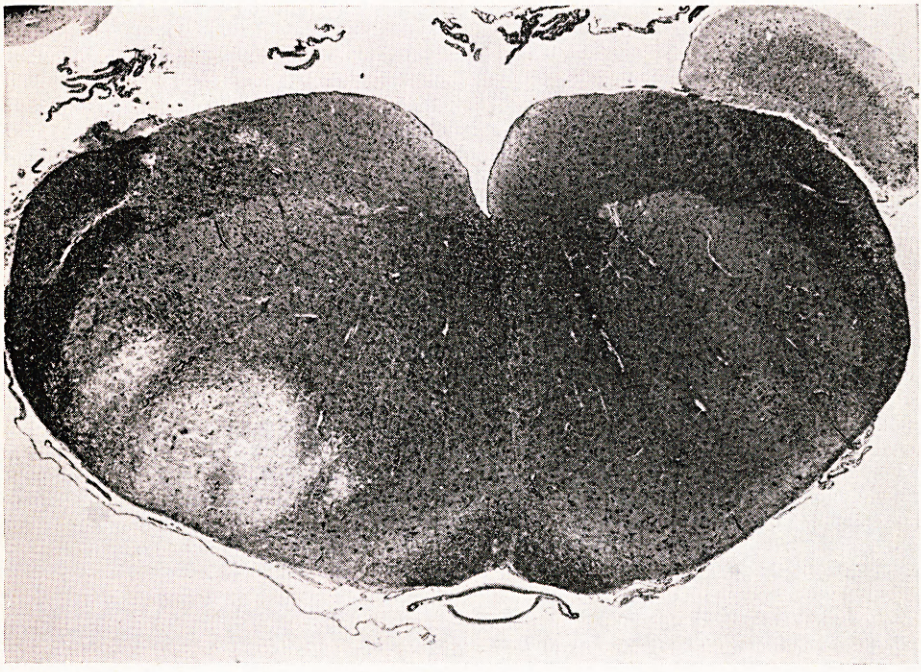

Fig. 2. Cytotoxic serum effect. Unilateral oedema and tissue destruction in the hindbrain of a guinea-pig. Effect of anti-Forssman serum (Rt. vertebral artery). (H. and E. × 20)

and the intravenous administration of an antiserum causes generalised vascular damage and shock. If the injection is so administered as to cause the serum to flow directly up one vertebral artery, destruction of the endothelium of the cerebral vessels results in death, due to massive unilateral oedema and tissue destruction, mainly in the mid- and hind-brain (Forssman, 1920; Leibowitz *et al.*, 1961) (Fig. 2).

There is, as far as is known, no naturally occurring lesion of this type. The phenomenon is of great interest as an example of cerebral damage caused by a circulating antibody directed against an antigenic component of the central nervous system. The antigen in this case is in the vascular endothelium, and no effect has yet been shown with antibody to purely extravascular components. A similar problem is posed by antibody action in other organs. Cytotoxic and cytolytic effects can readily be demonstrated against elements in the circulating blood, leucocytes, red cells and platelets, but not, convincingly, against cells in solid tissues; although in the case of graft rejection and in the various autoimmune diseases, this is still a matter for dispute.

It is probable that the difference in effectiveness of antibody against intra-

vascular and extravascular components is a purely quantitative phenomenon, and due to the low concentration of antibody in the interstitial fluid. If this is so, then brain is likely to be the least susceptible of all tissues to such damage, having the lowest level of extravascular antibody. To be effective under such circumstances the antibody would have to gain access to the parenchymal cells by some initial lesion of the vascular endothelium, or be produced locally in the tissues by a cellular infiltrate containing plasma cells.

DELAYED-TYPE HYPERSENSITIVITY

Unlike the three previous examples this form of hypersensitivity is not due to circulating antibody, but to the development of specifically sensitised mononuclear cells. Experimental allergic encephalomyelitis, the most extensively studied of the immune reactions in the brain, is thought to be a lesion of this type. The intradermal inoculation of an emulsion of homologous or heterologous brain tissue and Freund adjuvant in the guinea-pig is followed, after an interval of about ten days, by the development of an acute encephalomyelitis accompanied by severe neurological signs, including paralysis.

The disease is due to the production of mononuclear cells of the lymphoid series specifically sensitised against a small molecular weight basic protein component of myelin (Laatsch *et al.*, 1962). These cells enter the brain from the blood stream giving rise to an acute meningo-encephalitis. The cellular

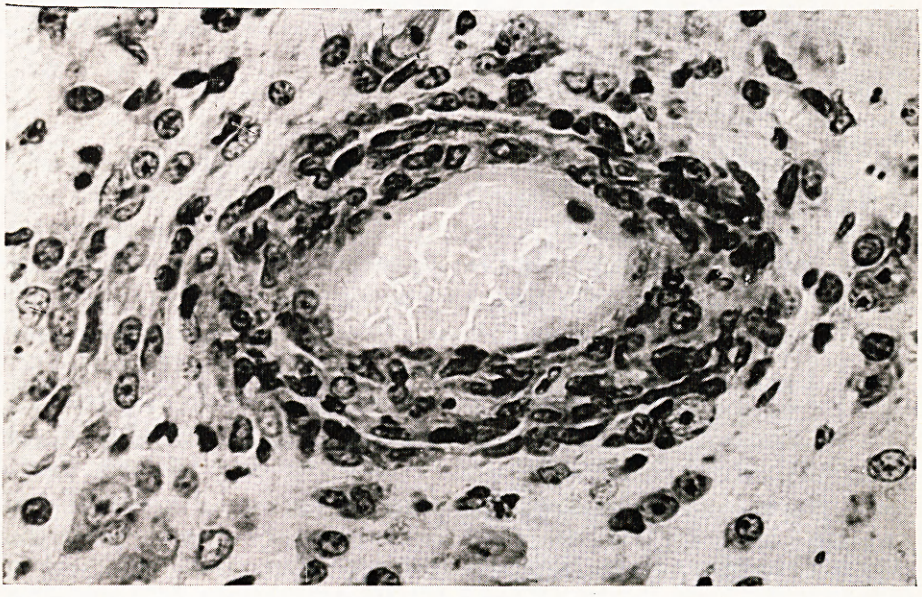

Fig. 3. Delayed-type hypersensitivity. Experimental allergic encephalomyelitis in the guinea-pig. Perivascular infiltration by mononuclear cells. Cresyl fast violet. (× 500)

infiltrate is mainly perivascular (Fig. 3) but may extend further out into the parenchyma. Demyelination may be present, but, in the guinea-pig at least, is minimal.

The cellular infiltration is accompanied by a striking increase in vascular permeability and cerebral oedema is an important element in the development of the neurological signs. The permeability changes in the forebrains of a large series of guinea-pigs developing allergic encephalomyelitis are shown in Fig. 4. They were measured by a double radioisotope technique (^{131}I and ^{125}I labelled albumin) which allows cerebral oedema to be estimated independently of changes in blood volume. There is a sharp increase in vascular permeability between the tenth and eleventh day after sensitisation, and Fig. 5 shows the very close correspondence between the onset of these changes and the development of the clinical signs, including paralysis.

Allergic encephalomyelitis can be passively transferred, in guinea-pigs of an inbred strain, by means of lymph-node cells (Stone, 1961). The transfer of serum has no such effect. This forms the basis of the generally accepted view that the lesion is due to the production of sensitised mononuclear cells rather than to circulating antibody. The serum of affected animals, however, has been shown to cause demyelination and damage to glial cells in tissue culture

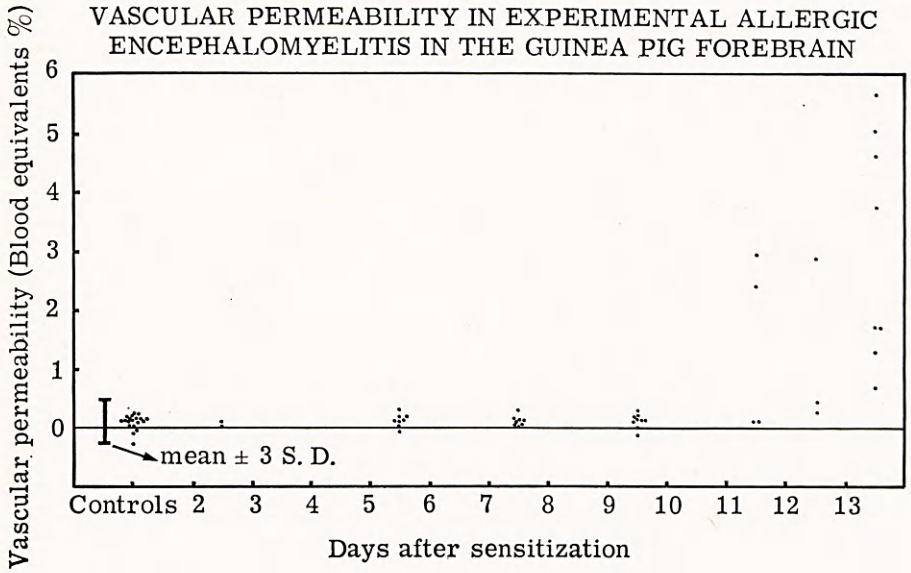

Fig. 4. Permeability measured by the accumulation of ^{131}I serum albumin in the brain over a period of twenty-four hours after i.v. injection. Results expressed as a ratio of the concentration in the blood. Allowance was made for changes in the cerebral blood volume, which was measured independently (^{125}I serum albumin).

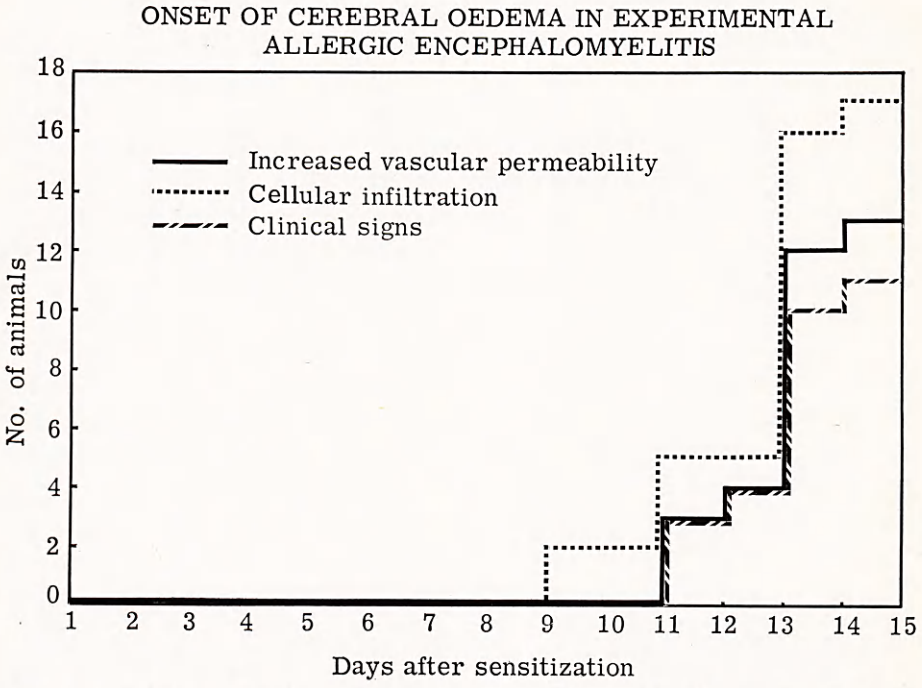

Fig. 5. Cumulative graph showing onset of oedema, cellular infiltration and clinical signs in allergic encephalomyelitis in the guinea-pig. Groups of animals were killed at fixed intervals after sensitisation.

(Bornstein and Appel, 1965), and the question arises as to whether this cytotoxic antibody plays any part in the development of the lesion *in vivo*. The fact that the disease can be passively transferred by means of cells does not entirely dispose of the matter, because the gliotoxic factor has been shown to appear in the serum of the recipient animals (Paterson, 1963). Similar cytotoxic antibody has been reported in experimental autoimmune disease in the thyroid and the testis, and the problem is of general theoretical interest.

It has been claimed that changes in vascular permeability may precede cellular infiltration in allergic encephalomyelitis (Vulpé *et al.*, 1960), which would certainly imply the action of some circulatory serum factor in this disease. From Fig. 5, however, it appears that histological lesions are present well before there is any evidence of increased permeability of the vessels—at least as measured by this method. Similarly, when animals with allergic encephalomyelitis are injected intravenously with indian ink, a leak of carbon particles is found only in vessels showing inflammatory cell infiltration (*see* method of

Majno *et al.*, 1961). These findings suggest that the permeability changes follow, and do not precede, the cellular infiltration.

Penetration of cytotoxic antibody is certainly much restricted in brain with an intact vascular endothelium. Oedema accompanying the cellular infiltration, however, would allow access of antibody to parenchymal cells in the later phases of the development of the lesion. It is also possible that immune tissue damage may be brought about by antibody produced locally at the sites of cellular infiltration in the brain. On present evidence, however, there is little reason to implicate the cytotoxic serum factor in the pathogenesis of the disease.

CONCLUSION

Allergic lesions in the central nervous system follow the same basic pattern as those in other tissues, despite the very low level of antibody and complement in the extravascular fluid, and the restricted passage of large molecular weight substances into the brain and cord. In delayed-type hypersensitivity in which the lesion is due to specifically sensitised mononuclear cells, and in serum sickness where the antibody–antigen reaction is intravascular, these considerations are largely irrelevant. In those types of hypersensitivity that are dependent upon the entry of antibody or antigen (or both) from the circulation, the brunt of the reaction—in all tissues—is borne in the region of the blood vessels. In the central nervous system this tendency for lesions to be vascular or perivascular would merely be accentuated.

Damage to cells by cytotoxic antibody directed against extravascular tissue components has never been demonstrated unequivocally in any organ of the body. This is probably due to the difference between the concentration of antibody (and complement) in the serum and in the tissues. In the brain, where this gradient is most marked, such cytotoxic serum effects are even less likely to occur than elsewhere.

Finally, cerebral oedema is an important element in the development of allergic lesions in the brain, and in experimental allergic encephalomyelitis the permeability changes can be shown to correlate well with the clinical manifestations of the disease.

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Scrapie: an experimentally transmissible degenerative disease of the central nervous system in sheep

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INTRODUCTION

In 1755 Parliament was petitioned by a group of Lincolnshire farmers for legislation to make it illegal for 'distempered' sheep affected with 'rickets' or 'shaking' to be mixed with healthy sheep. The clinical signs described by a committee appointed at that time to investigate the disease leave little doubt that the 'distemper' in question was scrapie. This name is descriptive of compulsive rubbing and scraping against fixed objects, which is the most obvious abnormality in one form of the disease. In addition, there is progressive ataxia, especially of the hind-legs, until the animal finally collapses. Characteristically the disease occurs in sheep about four years of age, and is fatal after a few