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The Role of Hyperergy in Measles Encephalitis

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According to our belief the disease of measles comes into being in the following manner: the microorganisms are taken in in a small quantity (in all probability through the respiratory tract); they multiply in the organism and simultaneously produce an irritation leading to the development of a specific antibody which to a certain degree destroys the microorganisms. The development of the antibody takes place only after 8 to 12 days. As soon as the antibody is present in greater quantities, the interaction between the microorganisms and antibody leads to the formation of the toxic by-products ('apotoxine') which cause a febrile response and an inflammatory reaction on the part of the cells of the organism. In the case of measles and vaccinia the causative microorganisms are killed and totally destroyed. Therefore, the illness terminates quickly . . . .

The fever is explained by the effect of the toxic by-products ('apotoxine') on the central organs. The petechiae result from the action of the 'apotoxine' on the skin and mucous membranes.

—von Pirquet.

This concept of hyperergy in measles was presented by von Pirquet almost half a century ago.[1] This great clinician, who coined the term "allergy," was audacious enough to formulate as an explanation of the signs and symptoms of measles a theory which remains very much *au courant* today. Direct experimental evidence supporting this hypothesis is still as scarce at present as it was in the time of von Pirquet, but indirect evidence accumulated during the past 20 years suggests that a "nonspecific" reaction of the host to a virus infection is perhaps one of the few factors which among many others [2] of less importance may decide the ultimate outcome of the infection.

Although we have little knowledge of the mechanisms operative in a virus disease of mammalian species, a hypersensitive reaction of the host to the multiplying virus, or to the products of damage inflicted by the virus on the tissue, is a better, though more complicated, explanation of the disease syndrome than is an inflammatory reaction of tissues associated with the spread of the virus. However, in order to postulate such a course of events in measles encephalitis

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it may be advisable to search for somewhat more tangible experimental data associated with clinical observation of the disease.

Although the first instance in which neurological complications accompanied measles infection had already been described in 1790,[3] and dealt, interestingly enough, with a 23-year-old woman who had previously suffered from the same type of complications while recovering from an attack of variola, numerous papers published since than have dealt almost exclusively with the clinical and statistical aspects of measles encephalitis (cited in Reference 4), but not with laboratory investigations related to the etiology of the disease.

Schaffer et al.[5] presented in 1942 the first—and, as far as is known, the only—paper on the isolation of measles virus from the brain tissue of a child who died after an attack of encephalitis accompanying measles. It is rather surprising that in this modern era of research, when many tissue culture systems could have been used in attempts to isolate virus from cases of measles encephalitis, almost no papers can be cited which deal with this problem, and the single reference found in the literature [6] describes, curiously enough, the isolation of measles virus from all organs except the brain.

And yet, if signs of illness and occasionally the death of the subject would have to be ascribed to the direct effect of the multiplying virus upon the brain, the postulated massive invasion by the virus of the central nervous system cells would lead to many successful attempts at virus isolation in the laboratory. If the paucity of the published reports reflects a preponderance of negative findings rather than any lack of attempts to isolate the virus, then this, per se, should incline one towards von Pirquet's hypothesis [1] that an antigenic material which provokes a hypersensitive reaction in spite of the existence of a blood-brain barrier is released by brain tissue of the infected host in the course of the infection, and this barrier, theoretically, at least, should prevent the escape of antigen from brain tissue.

Does the Blood-Brain Barrier Prevent Communications?

Perhaps the best way to visualize the role of a hematoencephalic barrier in the separation of the potentially antigenic myelin of the central nervous system from the immunologically reactive system of the host is to draw a parallel between the blood-brain barrier and the cheek pouch of the hamster. It has been shown by Billingham, Ferrigan, and Silvers [7,8] that homografts of cheek-pouch skin may not be rejected by the recipient animal, even though it would uniformly and regularly reject skin homografts from the same donor. However, rejection of the skin grafts does not take place when they are transplanted, instead of grafted directly, onto the areolar connective tissue of the cheek pouch. Apparently, some obstacle has been created which prevents the escape of donor antigens from the grafts into the recipient animal and the stimulation of a response by the latter's antibody-forming organs. That the grafts remain vulnerable, however, to an immunological reaction is proved by experiments in which hamsters bearing established cheek-pouch homografts are injected with suspensions of leukocytes or other cells from the original donor strain. This results in a fairly prompt rejection of hitherto accepted pouch-skin grafts, presumably as a consequence of sensitization effected by proxy.

The hematoencephalic barrier, acting somewhat in a similar way to cheek-pouch grafts, may block the escape of brain tissue antigens and prevent their contact with the immunologically reactive system of the host.

Bypassing of the blood-brain barrier through parenteral inoculation of the animal with a preparation of central nervous system tissue will elicit in most instances a prompt and often violent reaction on the part of the host to its own brain tissue, resulting in clinically or histologically discernible encephalitis. In the course of the

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TABLE 1.—*Effect of Storage of Spinal Cord Tissue upon Its Encephalitogenic Properties*

Days Storage at −20 C	Ratio of Allergic Encephalitis in Lewis Strain of Rats	
	Male	Female
None (fresh)	8/43	
Less than 21		9/16
More than 21		23/29

past 1½ decades, many species of animals were found to be susceptible to the so-called allergic encephalitis when inoculated with hetero-, homo-, or isografts of nervous tissue, either in crude or in purified form (cited in Reference 9). Perhaps the classical experiment in this series is that of Kabat, Wolf, and Bezer,[10] who caused encephalitis in monkeys injected parenterally with their own lobotomized brain tissue.

Methods of handling nervous tissue prior to its injection into the recipient animal may influence the release of the antigen, since, as shown in Table 1, the incidence of allergic encephalitis in the Lewis strain of rats seemed to be higher in animals inoculated with guinea pig spinal cord tissue stored at −20 C for 3 weeks or longer.[11]

Passive Transfer of Encephalitis

Even though normal brain tissue in situ does not seem to release enough antigen to cause a reaction of the host, the central nervous system, like pouch-skin homografts, remains vulnerable to an immunological attack through exposure to immunologically reactive cells. Observation of the passive transfer of allergic encephalitis was first made by Lipton and Freund[12] in a rat kept in parabiosis with an animal sensitized against brain tissue. Transfer of allergic encephalitis through inoculation of lymphoid cells has been accomplished by Paterson,[13] who caused paralysis in Wistar rats made tolerant to the donor tissue prior to injection of its cells. The donors were splenectomized rats of the same random-bred strain, sensitized with guinea pig spinal cord tissue.

Work conducted with an inbred strain of Lewis rats[14] resulted in successful transfer of allergic encephalomyelitis. Lymphoid cells from sensitized splenectomized donors were injected intravenously into recipients previously irradiated with x-ray. As shown in Table 2, splenectomy of the donor seemed to play a role in the successful outcome of the transfer of allergic encephalomyelitis. However, even then, only about one-half of the recipients developed encephalitis, and, as indicated in the summary of 5 transfer experiments (Table 3),[14] it is difficult to single out only one factor contributing to the successful outcome of the experiment. The donor:recipient ratio may have been of greater importance than appeared, since Stone[15] was able to achieve positive results in the passive transfer of allergic encephalomyelitis in inbred guinea pigs when the donor:recipient ratio was 2½:1.

Histological lesions observed in the recipient animals in the above experiments were not unlike those described in human subjects who died after measles encephalitis. Passive transfer of encephalitis with serum

TABLE 2.—*Attempts at Passive Transfer of Allergic Encephalitis in Lewis Rats*

	Donors		No. Cells †	Recipients	
				Ratio	
Splenectomy	No. Rats	Day * Killed	Transferred × 10^6	Paralyzed	Histologic ‡ Lesions
No	40	7-12	165-500	0/58	4/58
Yes	79	3-15	150-515	19/68	32/68

* After inoculation of antigen.
† From jugular, axillary, inguinal, and mesenteric lymph nodes.
‡ Suggestive of allergic encephalitis.

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TABLE 3.—*Successful Transfer of Allergic Encephalitis*

Experiment	Donors: Day Killed	Donors: No. Cells Transferred × 10^6	Donor/Recipient Ratio	Recipients: Paralysis—Day After Transfer	Recipients: Ratio	Recipients: Histological Lesions
J	9	515	4/5	6	5/5	5/5
M	9	57-500	4/4	12-16	4/4	4/4
U	3	112-119	3/3	15	1/3	1/3
	10	230	1/2	8	1/2	2/2
Y	10	500	5/4	8	4/4	4/4
X	10	500	15/8	7	3/8	?

from the sensitized donors always gave negative results [11,13,14] (cited in Reference 9).

Although these data establish beyond any doubt the ability of sensitized lymphoid cells to attack brain tissue of the host, the actual mechanism of such type of sensitization in the case of measles encephalitis must remain within the realm of speculation.

Possible Mechanism of Hyperergic Reaction

Invasion of the central nervous system by the measles virus, which may occur much more frequently than originally suspected,[16] may take place quite early in the course of infection. Indirect evidence supporting this contention may be found in data showing the lack of effect of γ-globulin administered during the early stages of the incubation period of measles upon the subsequent development of encephalitis (cited in Reference 17). After damage to the brain tissue by the virus, an antigenic material is released which may come into contact with immunologically active host cells circulating through, for example, brain capillaries. These sensitized cells may then circulate freely throughout the body of the host and be removed from the circulation by such blood-clearing organs as the liver, spleen, bone marrow, etc. Instead of perishing, one or another sensitized cell may start dividing and give rise to a "clone" which will attack the brain tissue of the host. Since there is virtually nothing known about the changes in the antigenic make-up of virus-infected cells, it is impossible even to speculate whether the antigen which possibly provoked an immunological reaction of the host against "self" is closely associated with the virus or not. If the former is correct, then the sensitized lymphoid cells will attack only virus-infected cells of the central nervous system.

In view of the lack of data on the presence of virus in the central nervous system of encephalitic cases, it is difficult to postulate how large a proportion of nervous tissue cells would be subject to this "immunological" attack. Conversely, if the virus invasion had caused only an initial release of antigen (through damage of brain tissue?) by the central nervous system and from then on the antigen were essentially unrelated to the virus itself, the number of central nervous system cells destroyed by the sensitized cells of the host would be quite large.

An argument against the latter hypothesis is based on the fact that if virus participation were not essential for the continuous release of antigen, there would be no reason why the production of sensitized cells should cease at one time or another, permitting the host to recover instead of leading to a chronic and possibly incurable autoallergic state. However, results of experiments in rats indicate that animals paralyzed after exposure to brain tissue rarely die and usually recover.[11,18] Moreover, the animals which recover are completely resistant to subsequent challenge with brain tissue and adjuvants.[11,18] Since no virus is involved in the etiology of allergic encephalitis of the rat, there has to be a mechanism able to inhibit continuous production of autoantibodies against brain

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tissue. The nature of this mechanism is unknown, but the presence of a "repressor" substance in the serum of the recovered animal is suggested by a report, as yet unconfirmed, by Paterson and Marvin.[18] A similar mechanism may be operative in the recovery from measles encephalitis, even though an autoallergy against brain tissue itself, and not hypersensitization against the virus-infected portion of the brain only, has to be postulated. It is interesting at this point to note that the incubation period of the encephalitis often corresponds to that of the rash or other manifestations of measles which may also be explained by hyperergy.[19]

Treatment and Recovery

Experimental results summarized in the preceding section point directly to a mechanism of recovery in measles encephalitis, even if it is a true autoallergy and not hypersensitization to the virus and the products of its metabolism. Regardless of the source of sensitizing antigen, treatment with steroids should hasten the recovery of the patient, since corticotropin and cortisone have been found to inhibit partially or completely allergic encephalitis[20] (and cited in Reference 9). However, therapy of man with adrenocorticotropin and adrenal corticosteroids gave equivocal results at best, and therapeutic successes[21,22] were balanced or even outweighed by a statistically more significant number of failures.[23] Although this may be cited as an argument against the hyperergy theory of measles encephalitis, it should be remembered that in the experimental sensitization of animals against their brain tissue, the effect of steroids was related directly to the time the therapy began in relation to the sensitization period. Best results were obtained if the steroids were administered early in the sensitization process (cited in Reference 9), and often signs of encephalitis reappeared when the drug was discontinued. Late administration of the drugs resulted only in partial suppression of the experimental disease, and yet, in human therapy mentioned above, steroid treatment was started only after onset of the encephalitis, when the sensitization process had been in operation for a long period of time. Thus, it would be perhaps too late for the therapy to affect the course of the disease. In contrast, in antirabies treatment of man with nervous-tissue vaccines, the success of steroid therapy seems to be more pronounced,[24-26] since the antigen is administered by the parenteral route and the process of autosensitization may not be as advanced as in the case of measles at the time treatment starts.

Liselotte and the Treatment of Measles

Although the results of the therapy of the neurological complications of measles are equivocal, a very clear statement was made in the year 1712 of how *not* to treat the disease itself. In a letter addressed to the Duchess Sophie, mother of the future George I of England, Princess Elizabeth Charlotte (Liselotte) von Pfalz, Duchess of Orleans and widow of the younger brother of Louis XIV, writes as follows[27]:

> Our misfortune continues. The doctors have made the same mistake treating the little Dauphin as they did ministering to his mother, the Dauphiness. When the child was quite red from the rash and perspired profusely, they [the doctors] performed phlebotomy and administered strong emetics; the child died during these operations. Everybody knows that the doctors caused the death of the Dauphin, since his little brother who had the same sickness was hidden away from the 9 physicians who were busy with his older brother, by the young maids, who have given him a little wine with biscuits. Yesterday, while the child had high fever, they wanted also to perform phlebotomy but his 2 governesses were firmly opposed to the idea and instead, kept the child warm. This one also would have certainly died if the doctors had had their way. I do not understand why they don't learn by experience. Had they no heart, when they saw the Dauphiness died after phlebotomy and emetics, not to dispose of her child.

They also did not realize, which they could not, that in all probability they were changing the course of the history of France, since the child who survived measles remained after the death of his brother,

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mother, and father (all within 3 weeks, and all after measles) the heir to the French crown, and who, later, as Louis XV, was not the best occupant of the throne. Otherwise, Liselotte's opinion about the treatment of measles can be summarized in one motto: "Avoid physicians and thou wilt be cured."

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