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THE PROBLEM OF CIRCULATING ANTIBRAIN ANTIBODIES IN EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS

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Since it became possible to reproduce experimental allergic encephalomyelitis in many mammals (guinea pigs, monkeys, mice, rats, rabbits, dogs, cats, sheep, pigs) as well as in birds, a large number of theories have tried to explain the pathogenesis of this disease. New researches, however, confirming older ones, point out that the illness has a firm immunological basis, but meanwhile the details of the pathogenical mechanism are not yet entirely clear, despite the numerous efforts made.

Ever since the beginning of the study of experimental allergic encephalomyelitis, scientists have tried to explain the lesions observed in the central nervous system by the action exerted by some cytotoxic antibrain antibodies. The detection of these antibodies and their characteristics has been the subject of various studies.

Thus, *Hill* (9), has demonstrated in guinea pigs with experimental allergic encephalomyelitis the existence of complement-fixing antibrain antibodies. Using both the complement fixation technique and the flocculation reaction, *Thomas, Paterson & Smithwick* (26) have found antibrain antibodies in dogs previously inoculated with a homologous cerebral substance. However, these authors have not noticed the existence

of a possible correlation either between the appearance of the disease and the presence of the circulating antibrain antibodies, or between the antibodies titre and the severity of the disease. In monkeys, *Lumsden et al.* (14) find a relationship between the appearance of the disease and the circulating antibrain antibodies incidence, without, however, being able to emphasize positively their role in the pathogenesis.

Despite these first observations, many researchers continued to attach to the antibrain antibodies an important role in the pathogenesis of experimental allergic encephalomyelitis. Less encouraging results in supporting the theory have been produced, by the numerous attempts to transfer the encephalomyelitis with the aid of serum, from ill to healthy animals. All those attempts have ended with failure, though adequate amounts of serum have been perfused, containing antibrain antibodies. (See the review of *Chase* (6)). *Lipton & Freund* (13) have however succeeded in transferring encephalomyelitis in rats—in parabiosis— thus proving the existence of humoral factors able to produce the disease. Though pointed out later on by many researchers, the serous antibrain antibodies were not always detected in all animals with experimental allergic encephalomyelitis. *Kibler & Barnes* (14) using the more sensitive method of marked antigens with I^{131} , and the precipitation of the antigen-antibody complex with ammonium sulphate, often were able to detect circulating antibrain antibodies in rabbits with encephalomyelitis and also to find a link between the presence of the circulating antibrain antibodies and the appearance of the disease. A high percentage of rabbits with antibrain antibodies were also found by *Wütrich, Rieder et al.* (24, 30) (using the double diffusion method in agar-gel), that has confirmed the correlation between these antibodies and the disease.

It is interesting to point out that the serous antibodies in experimental allergic encephalomyelitis are different from those from other autoimmune experimental diseases. Thus, *Harwin & Paterson* (8) were not able to produce passive cutaneous anaphylaxis (Ovary) using serum from the rats with

experimental allergic encephalomyelitis which have high titres of complement-fixing antibrain antibodies. The authors presumed that these antibodies are of 19S type (hypothesis proved by ultracentrifugation), being therefore different from antibodies, found in serum of animals with experimental autoimmune thyroiditis, which are of 7S type and can be shown by the Ovary test.

In the sera from animals with allergic encephalomyelitis, *Bornstein & Appel* (4) discovered certain factors able to produce demyelination of cerebellum cultures of newborn rats. The cytotoxic factors for neonatal glia cell cultures have been shown in sera of guinea pigs and rats with experimental allergic encephalomyelitis by *Berg & Källen* (3). *Sherwin et al.* (24) demonstrated through immunofluorescence in sera of rabbits with experimental allergic encephalomyelitis, the existence of a factor able to bind itself specifically with myelin, having all the peculiarities of an organ-specific antibody. Antibrain antibodies specific for species have been noted by *Berg & Denker* (2) as existing in serum of rabbits previously immunized with heterologous brain, being immunoelectrophoretically localized in the beta 1 zone of the globulines. Recently, *Jancović & Išvaneski* (10) have occasionally found in chicken with experimental allergic encephalomyelitis antibrain antibodies, the antibodies titres being very low.

Therefore, since the problem of the occurrence and role of the circulating antibrain antibodies in animals with experimental allergic encephalomyelitis is not yet completely clear, we also have studied these antibodies, following them from the onset and development of experimental encephalomyelitis. We have used several species of animals in order to see if the difference in the evolution of the experimental allergic encephalomyelitis—actually known for some time—could be explained by the differences in formation and type of the serous antibrain antibodies.

METHODS AND MATERIALS

Adult guinea pigs of both sexes have been used, weighing about 5-600 g, dogs with an average weight of 12 kg—kept in separate boxes, rabbits of both sexes weighing about 1.5-2 kg, kept in pairs in separate hutches. The animals were fed with a standardized diet for every species and previously watched for three weeks in order to note any possible neurological abnormalities. No animal has shown such inborn disturbances.

Both guinea pigs and rabbits have been inoculated with rabbit spinal cord homogenate emulsified in complete Freund's adjuvant. The inoculation was with 0.10 cm³ emulsion injected in the foot pads—in guinea pigs and 0.50 cm³ emulsion in rabbits, subcutaneously and intradermally divided in several sites, in the animal's back. The dogs were subcutaneously inoculated with 1 cm³ homologous brain homogenate, emulsified in Freund's adjuvant, injected in two sites on the back, on both sides of the median line. Each cm³ emulsion contains among others 0.2 g (wet weight) spinal cord or brain and 3 mg mycobacteria H37 Valée, heat killed.

The guinea pigs had only one inoculation while rabbits and dogs had several inoculation, repeated every 14 days, until the encephalomyelitis symptoms appeared. The animals were watched daily in order to detect the early symptoms of the disease. The rabbits and guinea pigs which showed evident signs of encephalomyelitis were sacrificed in a very advanced stage of the disease (imminence of death) in order to detect the possible clinical improvements. In all cases the sacrifice has been made by bleeding "à blanc", the blood being collected, under sterile conditions, the brain and spinal cord were fixed in formalin 10 per cent, embedded in paraffin, stained with haematoxylin and eosine for microscopic examination. The histopathological study has been done on at least four level of the brain, pons, medulla and cerebellum and from several levels of the spinal cord.

Before the inoculation, blood samples have been taken from all animals in order to eliminate from the very beginning those who might have positive serological reactions. No animal having positive serological reactions previously to the inoculation has been reported, blood samples were collected every 4-7 days until the animal was sacrificed. Immediately after the blood sample was taken, the serum was separated and inactivated 30 minutes at 56° C thus being fresh in the serological reactions.

In order to detect the serous antibodies we have used the complement-fixation reaction (26) as well as the passive haemagglutination reaction with tanned red cells. In all cases, the sera used in the reaction was diluted starting from 1/10, because we considered insignificant the possible positive reactions in lower dilutions. In some animals (guinea pigs) the antibodies were studied by the double diffusion in agar-gel, according to *Ouchterlony* (16), the agar plates being watched 8 days at room temperature. The antigens used in the reaction were brain and spinal cord extracts from guinea pigs, rabbits and dogs, precipitated with ammonium sulphate and dialysed (15). Also used was a brain extract from

dogs, homogenised in saline and centrifuged. No differences have been noted between the results obtained from the two kinds of antigenic extracts. At several periods crossed serological reactions were made, using for detection of the anti-brain antibodies from one species, antigens obtained from brain substance from the other species.

Simultaneously with the animals experimented upon (the inoculated animals) controls were used also (uninoculated), the last ones used a healthy controls in the serological reactions. The experiments were formed of 30 guinea pigs, 14 rabbits and 17 dogs injected with the encephalitogenic emulsion.

RESULTS

The clinical signs of encephalomyelitis occurred in guinea pigs at about 14 days after the inoculation with the encephalitogenic emulsion. The symptoms were: sphincter paralysis with incontinence, paresis and paralysis of the limbs, weakness, convulsions. The histological examination has always shown in these cases typical lesions of allergic encephalomyelitis, with obvious perivenous infiltrates. Some animals without evident clinical signs of the disease have however shown doubtless pathological evidence of encephalomyelitis. The percentage of animals presenting clinical signs of experimental allergic encephalomyelitis was of about 80 per cent, those presenting histopathological signs being over 90 per cent.

From the 14 rabbits inoculated with encephalitogenic antigen, only 3 presented obvious symptoms of encephalomyelitis (ataxy, paralysis and convulsions), being sacrificed on the 15th, 32th, and 73th day following the first inoculation. Four animals died at various periods (the 15th, 35th, 55th, 65th day) without presenting any evident symptom of encephalomyelitis. The other animals have been watched until the 82th day from the first inoculation, then being sacrificed. Within this interval 16 blood samples have been taken from each animal. In all animals important loss of weight has been noted. The histopathological studies showed experimental allergic encephalomyelitis lesions only in animals that have also presented clinical neurological abnormalities.

In dogs, from 17 animals injected with encephalitogenic emulsion sixteen (94.1 per cent) showed clinical signs of encephalomyelitis.

phalomyelitis within 120 days from the first inoculation, namely an alternation of the general condition, loss of weight, lack of appetite, ataxy, paralysis of limbs of several degrees, as well as drowsiness up to precomatous condition. We have considered that animals are ill of encephalomyelitis only when evident neurological disturbances were present. In most cases the symptomatology was progressive, culminating in 4-5 days either toward death or toward healing. Sometimes the symptoms occurred suddenly with a fast lethal development. Three animals with a severe symptomatology (tetraplegia, deep somnolence) gradually recovered within 3-4 days, becoming clinically healthy after about one week from the onset of the illness. In nine animals, acute episodes were noted, followed by recoveries and later relapses, more severely, within 10-70 days, showing hypotonicity, equilibrium disturbances and paresis. In a large number of dogs the encephalomyelitis symptoms appeared on the 12 day following the last inoculation with encephalitogenic emulsion. The hystopathological examinations have confirmed the experimental allergic encephalomyelitis diagnosis in all cases of animals presenting neurological signs.

In guinea pigs, the serous antibrain antibodies have rarely been detected, only in very low titres (1/10) by complement-fixation and passive haemagglutination reactions. Through the diffusion in agar method, no antibrain antibodies have been noticed in the guinea pigs with experimental allergic encephalomyelitis. It might be important to mention that in the rare cases when antibodies were found, the animals did not have any symptoms of disease. Moreover, the antibrain antibodies were not detected the day when animals were sacrificed, while they usually presented at that time severe signs of disease.

In contrast with guinea pigs, we were able to detect antibrain antibodies in serum, in a large number of rabbits inoculated with the encephalitogenic emulsion. Thus, by means of the complement-fixation reaction antibrain antibodies were detected in 92.8 per cent of the animals already on the 7th day following the first inoculation. On the 15th day, the percentage of rabbits having serous antibrain antibodies dropped to 76.9

per cent. On the 20th day following the first inoculation, complement-fixing antibodies have been found in all surviving rabbits. The titre of these antibodies were rather low, $1/20$ – $1/40$, with a maximum (peak) of $1/160$. All rabbits had the highest titre of complement-fixing antibrain antibodies on the 45th day following the first inoculation. The day the rabbits were sacrificed, we were not able to detect antibodies in animals presenting obvious clinical forms of experimental allergic encephalomyelitis.

By the passive haemagglutination reaction antibrain antibodies in serum were detected only in a smaller number of rabbits, thus there does not exist a perfect superposition between the two serological reactions. Thus, on the 2th day following the first inoculation, no antibodies were detected in any rabbit while on the 11th day, 21.4 per cent of the animals showing agglutinating antibrain antibodies, and on the 15th day, 23 per cent of the animals had antibodies. The titre of the serious antibrain antibodies, detected by the passive haemagglutination reaction was low, $1/10$ – $1/20$. The highest percentage of rabbits having serous antibrain antibodies detectable by the passive haemagglutination reaction (41.6 per cent) was found in the 26th day following the first inoculation.

The titre of antibrain antibodies detected through both complement-fixation reaction and passive haemagglutination reaction has shown time variations in the same animals the antibodies in serum were present, then disappeared to reappear later again after a variable period (see Tables 1, 2).

The dogs had complement-fixing antibrain antibodies in varying percentages, from 68 per cent on the 9th day following first inoculation and 47 per cent on the 15th day, to 31 per cent on the 23th day and 11 per cent on the 44th day. The titres fluctuated between $1/10$ to $1/160$ (see Table 3). Through the passive haemagglutination reaction, the highest percentage of dogs presenting serous antibrain antibodies were found on the 9th day following the first inoculation (78 per cent). On the 15th day only 5 per cent of dogs had antibrain antibodies, and in the 42th day they were found in 42 per cent of

TABLE 1

Appearance of Antibrain Antibodies in Animals Previously Immunized with Encephalitogenic Antigen.

Group	Animals	No.	No. anim. antibodies*	
			Complement fixation reaction	Passive haemagglutination reaction
With paralysis	guinea pigs	26	2	3
	rabbits	3	3	3
	dogs	16	16	16
Without paralysis	guinea pigs	4	—	—
	rabbits	11	10	10
	dogs	1	1	1

* Number of animals with detectable antibodies at certain period, until they were sacrificed.

TABLE 2

Antibrain Antibodies Titres in Inoculated Rabbits† at Various Days after First Inoculation.*

No.	Complement fixation reaction					Passive haemagglutination reaction				
	0§	15	32	56	73	0	15	32	56	73
4	—	—	40°			—	—	—°		
6	—	20	10	160	—°	—	—	10	—	—°
7	—	—°				—	—°			
3	—	10	40	160	10	—	—	20	40	—
11	—	20	40	40	10	—	—	40	—	20
12	—	40	10	80	10	—	—	—	—	—

* Are given reciprocal figures of the highest dilution of serum in which reactions were clearly positive.

† First 3 rabbits, presenting paralysis, have been sacrificed.

§ Days since first inoculation.

° Sacrification day.

the cases. The highest titre of antibrain antibodies detected by passive haemagglutination reaction was 1/360. After 100 days following the first inoculation with encephalitogenic emulsion, we were not anymore able to detect circulating antibrain antibodies, either by the complement-fixation reaction or by the

TABLE 3
Antibrain Antibodies Titres in Dogs, at Various Days
 after First Inoculation.*

No.	Complément fixation reaction								Passive haemagglutination reaction							
	0	15	33	52	86	92	100	109	0	15	33	52	86	92	100	109
1	-	10	-	-	-	-	80	-†	-	-	-	10	20	40	360	-†
4	-	40	-†						-	-	-†					
7	-	-	-	40	-	-†			-	10	-	20	40	-†		
8	-	-	-	10	-	-	160	-†	-	-	-	10	40	40	360	-†
10	-	40	-	-	-†				-	-	-	10	40†			
11	-	-	-	40	-	-	160†		-	-	-	40	-	-	-†	

* Titres are given in reciprocal values of maximal dilution of serum, in which reactions were clearly positive.

† Sacrificion day.

passive haemagglutination reaction. Similarly with our observations made on rabbits we also notice in dogs variable titres of antibodies, such as complete disappearance followed by a transitory reappearance (antibodygenesis waves at about 15 days interval). No superposition of the two reactions could be seen either regarding antibrain antibodies titres, or the percentage of cases where antibodies were detected. We must emphasize that from the sixteen dogs that had shown obvious symptoms of encephalomyelitis, only in two dogs antibrain antibodies were detected by the complement-fixation reaction and passive haemagglutination reaction on the very day when the disease began. Both in rabbits and dogs similar results have been obtained using in serological reactions either the homologous brain antigen, or the heterologous one.

DISCUSSION

The presence of the antibrain antibodies in the serum of the animals with experimental allergic encephalomyelitis, although demonstrated in several species of animals, has not yet been unanimously accepted. The antibodies detected, depend on the sensitivity and the specificity of the serological reaction used

for that purpose. Thus *Kibler & Barnes* (11) do not find in rabbits with experimental allergic encephalomyelitis antibodies by complement-fixation reaction and diffusion in, agar-gel while using the more sensitive method of marked antigens, the antibodies were detected in the same rabbits in a high percentage. In studies on the circulating antibrain antibodies in experimental allergic encephalomyelitis the serological reactions were performed using different brain extracts (alcoholic, saline, tripsinized, et al.) and the induction of encephalomyelitis was done with the homogenised all nervous tissue, facts which might explain the different results obtained by various authors (11).

Many authors who have studied the serous antibrain antibodies during experimental allergic encephalomyelitis have noticed obvious clinical signs of the disease, without circulating antibrain antibodies, as well as animals in which these antibrain antibodies were present even in high titres, but which have not shown either clinical signs, or histopathological evidence of encephalomyelitis (14, 24). No correlation could be found between the antibody titre and the severity of the disease even in animals that had encephalomyelitis and had circulating antibrain antibodies. At the same time, no link could be found between cytotoxic activity of the serum in the glial cell cultures and the clinical condition of the animals (2).

The results we obtained studying rabbits and guinea pigs also do not show any relationship between the presence of the antibrain antibodies and the occurrence of encephalomyelitis. However in all dogs such antibodies have often been found and almost all of them showed, sooner or later, obvious signs of the disease, we cannot establish any sure correlation between the antibodies and encephalomyelitis, because even in the same animal the antibodies were not present in the serum consistently, almost always missing on the day of sacrifice, when the animals had very marked signs of disease. *Thomas, Paterson & Smitwick* (26) found variation of the antibodies titre in dogs, going as far as complete disappearance, followed by later reappearance.

If one could explain the existence of the animals with obvious signs of experimental allergic encephalomyelitis, but without circulating antibrain antibodies, through the low level of the last ones and the rather low sensitivity of the serological detecting methods, the significance which should be attached to animals with serous antibrain antibodies but without any clinical or histopathological signs of experimental allergic encephalomyelitis, is a totally different one. It might be possible nevertheless that such animals could fall ill later, as we have found in our experiments on dogs (where it is necessary to watch the animals inoculated with encephalitogenic emulsions⁴ for a longer period, even if they do not soon fall ill).

One might nevertheless consider that the serous antibrain antibodies play no role in the pathogenesis of the disease. There is no doubt that with the complex antigenic stimuli, represented by homogenised all brain or spinal cord—with which the disease is usually induced—that several kinds of antibodies should appear in response. Only certain antibodies might have a role in producing the disease, and these would quickly and continuously fix themselves on the nervous matter, their detection in serum would not be possible, while the other antibodies—usually found in serum—would have no pathogenic role, but be the evidence of the immunization of the animal. From these last antibodies, some would have an organ specificity and others would not. *Lipton* (13) has found in serum of monkeys with experimental allergic encephalomyelitis antibodies fixing complement with both brain from various animal species and placental tissue. The existence had been shown of antibodies specific for species and organs, in the sera of animals previously immunized with heterologous spinal cord (2). *Harwin, Paterson & Didakow* (7) have pointed out that serum of rats with experimental allergic encephalomyelitis contains complement-fixing antibodies, which react with the autologous brain. In our experiments, the role played by serous antibrain antibodies in the pathogenesis of experimental allergic encephalomyelitis is also doubtful because of the difficulty the antibodies have to pass the haematoencephalic barrier.

More recently, *Appel & Bornstein* (1) reported that in presence of a complement source, the β_2 (7S) globulin fraction from rabbit serum with experimental allergic encephalomyelitis produced a total demyelination of cerebellum cultures, in rats. It has been emphasized that this fraction represents antibodies with organ specificity.

Supposing that in animals with experimental allergic encephalomyelitis the serum might contain cytotoxic antibodies which might react "*in vivo*" with their own central nervous system, probably these antibodies are not detected by the complement-fixation reaction, largely used in most researches on experimental allergic encephalomyelitis (1). Complement-fixing antibrain antibodies were also found in mammals following inoculation with cerebral tissues from fishes, reptiles or amphibians, tissue which was not encephalitogenic. In rats—after inducing an artificial tolerance for cerebral tissue, subsequently experimental allergic encephalomyelitis cannot be produced yet, circulating antibrain antibodies are detected, in high titres (18).

All these observations prove that circulating antibrain antibodies play no role in the pathogenesis of experimental allergic encephalomyelitis. Recently, *Paterson & Harwin* showed that the complement-fixing antibrain antibodies have a protective role in experimental allergic encephalomyelitis, which explains why in guinea pigs with severe, often mortal forms of disease, there are very seldom serous antibrain antibodies (21) while in rats, which usually have a less severe form of the disease, with recovery, the complement-fixing antibrain antibodies are always present in the serum, even after clinical healing.

Our data obtained on guinea pigs do support this standpoint, although certain authors constantly find complement-fixing antibrain antibodies in the sera of guinea pigs with experimental allergic encephalomyelitis (25). Only in two dogs from the lot of sixteen which presented encephalomyelitis symptoms, we were able to find serous antibrain antibodies on the sacrifice day.

The existence of circulating antibrain antibodies might also

depend on the way of inoculation. It is well known that rabbits that are inoculated subcutaneously with the cerebral antigen fall ill very seldom, but frequently have complement-fixing antibrain antibodies, while rabbits that are inoculated intradermally more often present encephalomyelitis but do not have complement-fixing antibrain antibodies (17). It seems that the different results in guinea pigs as compared with dogs and rabbits could be explained in this way.

Based on the relative ease with which encephalomyelitis could be induced in various animals using intradermal inoculations, in contrast with a rather more difficult way to induce it, using other ways (more shots, longer incubation period), as well as the failures in transmitting the disease from an ill to a healthy animal by serum, and so on, *Waksman* asserted that in experimental allergic encephalomyelitis pathogenesis is involved a hypersensitivity reaction of a delayed type (27, 28, 29). Among the most conclusive arguments in support of this hypothesis, is the possibility of transferring the disease to healthy animals, using lymphocytes from ill ones (18, 19, 20). However, lymphocytes can also transfer small amounts of antibodies, which might also be responsible for the onset of the disease. It has been pointed out that cells from the perivenous foci in the brain with experimental allergic encephalomyelitis have originated from blood lymphocytes (12).

These data show only the immunological mechanism of experimental allergic encephalomyelitis, which, more correctly, might therefore be named "immunologic" experimental encephalomyelitis, without showing, meanwhile, which is the immunologic factor which leads to the occurrence of the disease. It is known that X-rays reduce the formation of antibodies, and irradiation with X-rays exerts a suppressive effect on the appearance of experimental allergic encephalomyelitis in animals previously inoculated with encephalitogenic emulsion (quoted after 22). As a matter of fact, the protective role of the complement-fixing antibodies in producing experimental allergic encephalomyelitis might also be explained through the prevention of formation of some cytotoxic antibrain anti-

bodies (22). Consequently, the circulating antibrain antibodies might—at least theoretically—play a role in the pathogenesis of experimental allergic encephalomyelitis.

In the present study we were not able to find a clear relationship between the serous antibrain antibodies and encephalomyelitis, nor are we able to specify their role (protective or pathogenic). However, there is obviously differences existing between the results obtained by means of the two serological methods used by us, a fact which points out the existence of various types of antibodies in the sera of animals with experimental allergic encephalomyelitis. Between the three species of animals used in our experiments, differences can be noted between the immunological response to the antigenic encephalitogenic stimuli, a fact which has also been emphasized by *Berg & Dencker* (2), who do not find either gliotoxic factors in rat's serum. The rare cases of guinea pigs having serous antibrain antibodies in contrast with the great number of dogs and rabbits in which we have detected these antibodies—though they fell ill, much later makes us think of the possible existence of a protecting role of the antibrain antibodies, both complement-fixing and agglutinating. This seems even more probable if we consider the fact that in the moment of the occurrence of the disease, in the largest majority of the animals with experimental allergic encephalomyelitis, no serous antibrain antibodies have been detected.

Perhaps the attempts made to transfer the disease using concentrated and purified antibodies, as well as the study of lymphocytic antibodies, will show if the antibrain antibodies have a role in the pathogenesis of experimental allergic encephalomyelitis, also whether there are more than one factor, independent from each other, one against the vascular endothelium, others against the nervous matter.

Thus the role played by the serous antibodies is still to be defined more accurately. The explanation of circulating antibrain antibodies detected in some cases of multiple sclerosis, could be taken as an argument favouring the "autoimmune" pathogenesis of this disease.

SUMMARY

Experimental allergic encephalomyelitis has been produced in guinea pigs, dogs and rabbits, and the onset and evolution of the serous antibrain antibodies have been followed. Antibrain antibodies have been evinced in all the rabbits inoculated with encephalitogenic emulsion, even when they did not show clinical signs of disease. Antibrain antibodies have always been shown in dogs, while in guinea pigs these antibodies have very seldom been found.

Our researches, together with those of other workers, suggest a possible part played by circulating antibrain antibodies in the pathogenesis of experimental allergic encephalomyelitis.

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