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VIRUS OF ACUTE ENCEPHALOMYELITIS OF MAN AND MULTIPLE SCLEROSIS

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In the spring of 1957 our colleague Dr. R. S. Allison received a request to obtain for patients with multiple sclerosis a vaccine which has been studied in Russia and for which some success had been claimed (Choubladze and Gaidamovitch, 1956a). This vaccine consists of a formalized suspension of the brains of rats or mice which have been infected with the SV strain of a virus of acute encephalomyelitis of man—encephalomyélite humaine aigue (E.H.A.) (Specification of the State Medical Testing Laboratory, Moscow*). It is manufactured and distributed by the Metchnikoff Institute in Kharkov, where it is called the "vaccine of Margoulis and Choubladze." Before this vaccine was tried in Northern Ireland it seemed desirable to know more about the virus from which it was made and the reasons for using it.

SV Strain of E.H.A. Virus

The E.H.A. virus was recovered in 1942 by Margoulis, Soloviev, and Choubladze in the course of research on the

*"Specification for the preparation and testing of vaccine for the treatment of patients suffering from acute disseminated encephalomyelitis, from disseminated sclerosis, or from a condition brought about by an antigen for intracutaneous diagnostics." State Medical Testing Laboratory, Moscow.

aetiology of multiple sclerosis (Choubladze, Gaidamovitch, and Ivanowski, 1956); five strains of this virus, including the SV strain, were isolated from cases of sporadic encephalitis. The properties and host range of the SV strain have been described by Choubladze *et al.* (1956) and Choubladze and Gaidamovitch (1956b), who showed that E.H.A. virus was immunologically closely related to rabies but that it differed from rabies virus in certain respects. In particular, Negri bodies were never found in the nerve cells of vertebrates infected with the SV strain of E.H.A. There were also other important differences from rabies, such as the symptomatology of infections with E.H.A. virus and its epidemiology. The association of infections with E.H.A. virus and multiple sclerosis was deduced by Choubladze *et al.* (1956) from their observations that "a large percentage" of individuals convalescent from infections with E.H.A. or with multiple sclerosis neutralized the virus of E.H.A., while sera from individuals suffering from other diseases of the C.N.S. failed to do so. Furthermore, Dr. Wolancski claimed that 50% of patients suffering from multiple sclerosis had antibody to E.H.A. virus (personal communication to Dr. R. S. Allison).

Neutralization Tests

Sera from 50 individuals suffering from multiple sclerosis and from 10 individuals with neurological diseases other than multiple sclerosis were tested for their ability to neutralize the SV strain of E.H.A. virus.

The virus was received from Dr. C. H. Andrewes (National Institute for Medical Research, London) in the form of a lyophilized preparation in an ampoule labelled (in Russian) "Acute virus encephalomyelitis of man—strain 'SV' dried May, 1956." The virus was infective for VSBS mice by the intracerebral route, and mice of this strain (weighing 16–18 g.) were used in all experiments. The incubation period and titres obtained in mice were similar to those described by Choubladze and Gaidamovitch (1956b).

A large pool of infected mouse brain was prepared and aliquots were stored at -70°C . For the neutralization tests 0.2 ml. of undiluted whole serum was mixed with equal quantities of dilutions of infected mouse brain containing 200 and 20 LD₅₀ of virus to give a final concentration of 100 and 10 LD₅₀ in the test. The virus-serum mixtures were incubated for one hour at 37°C . and for a further hour at $+5^{\circ}\text{C}$. and were then intracerebrally inoculated in 0.03-ml. amounts into groups each of six mice. Normal control sera from normal rabbits and healthy human beings were used. Immune serum controls consisted of sera from rabbits immunized with the SV strain of virus by the intraperitoneal inoculation of 5 ml. of 10% infected mouse-brain suspension at 0, 3, and 15 days and bled on the 20th day.

In preliminary tests it was found that a few fresh non-inactivated sera from normal healthy human beings and from normal rabbits were capable of protecting a proportion of mice inoculated with virus-serum mixtures containing 10 LD₅₀ of virus. In order to detect minimal quantities of any neutralizing antibody which might be present 39 of the 50 sera from patients with multiple sclerosis were tested fresh (or after storage at -70°C .) and after inactivation at 56°C . for 30 minutes against 10 LD₅₀ of virus, with the results shown in the accompanying Table. The 50 sera (except one of which there was insufficient quantity to test

inactivated serum), both fresh and inactivated, were also tested against 100 LD₅₀ of virus.

It will be seen from the Table that none of the sera tested showed any significant neutralization of 100 LD₅₀ of virus. Occasionally a few mice survived which were inoculated with some of the serum-virus mixtures containing 10 LD₅₀ of virus (see Table). The amount of inactivation of virus by these sera cannot be accepted as evidence of specific neutralizing antibody, for, as has been noted, we have found occasional sera from normal rabbits and human beings that will similarly inactivate small quantities of this virus.

We also tested sera from 10 individuals suffering from neurological conditions other than multiple sclerosis. The results of these tests with both fresh and inactivated sera were no different from those with sera from patients with multiple sclerosis or from healthy individuals.

Histology

A group of 16 mice were inoculated intracerebrally with 3,000 mouse i.c. LD₅₀ of the S.V. strain of H.E.A. virus and two mice were killed daily for histological examination of the brain, cord, and visceral organs.

In those animals killed one to two days after inoculation the brain and cord showed marked hyperaemia but only a very early inflammatory reaction. By the third day the lesions were well established and the picture was that of a widespread meningoencephalitis. The meninges were infiltrated with lymphocytes; perivascular cuffing was a marked feature in both grey and white matter, and particularly in the region of Ammon's horn (Fig. 1). Nerve-cell degeneration, with shrinkage, hyperchromasia, and loss of Nissl substance, was found in the cerebral cortex and other sites, and there was frank necrosis of cells, especially in Sommer's sector. The Purkinje cells were also affected, but the inflammatory infiltration was less intense in the cerebellum. Microglial proliferation with the formation of Babes's nodes was a notable feature in all areas of damage. With Mann's methyl-blue eosin stain and Lendrum's phloxine tartrazine method, acidophilic inclusions of Negri-body type were readily demonstrated in the cytoplasm of the nerve cells, and were best seen at a distance from the most intense inflammatory foci (Fig. 2). Changes in the spinal cord were much less marked than those seen in the hemispheres but were of the same nature. The only visceral lesions noted were hyperplasia of the lymphoid follicles in the spleen,

FIG. 1.—Cerebral cortex, with lymphocytic infiltration of meninges and perivascular cuffing. ($\times 100$.)

FIG. 2.—Nerve cells with intracytoplasmic inclusions. (Mann's stain. $\times 1,333$.)

Results of Tests of Fresh and Inactivated Sera from Patients with Multiple Sclerosis Against 10 and 100 LD₅₀ of the SV Strain of E.H.A. Virus

Protection Ratios No. of Survivors No. Inoculated	10 LD ₅₀		100 LD ₅₀	
	Fresh Sera	Inactivated Sera	Fresh Sera	Inactivated Sera
0/6 or 0/5	23	29	43	44
1/6 or 1/5	8	5	7	4
2/6	6	2	0	1
3/6	1	3	0	0
4/6	1	0	0	0
5/6 or 6/6	0	0	0	0
Total	39	39	50	49

and capillary congestion and endothelial swelling in the glomeruli of the kidney.

Discussion

Choubladze *et al.* (1956) have observed that a "large percentage" of patients with multiple sclerosis had antibody to E.H.A. virus. This, in conjunction with other virological studies of E.H.A. virus, led them to believe that there was infection with this virus in some cases of multiple sclerosis. They accordingly used a formalized preparation of E.H.A. virus called the "vaccine of Margoulis and Choubladze" for the treatment of acute encephalomyelitis and multiple sclerosis. This vaccine, which is produced and used in the Soviet Union, is given in two courses, each of divided subcutaneous injections of 24 ml. of the vaccine, or three courses of intracutaneous injections of a total of 5.2 ml. These courses of treatment may be repeated (Instruction*).

We have been unable to find that sera from patients in Northern Ireland with multiple sclerosis show any significant neutralization of the SV strain of E.H.A. virus. The results presented by Choubladze *et al.* (1956) showed that 9 out of 10 patients with multiple sclerosis had neutralization titres ranging from 269 to 2,564. We were unable to obtain information on the exact method of neutralization which was employed by Professor Choubladze and her associates, but the method we employed is the one commonly used to demonstrate antibody to rabies virus and similar to the techniques commonly used to demonstrate antibody to encephalitis viruses.

The results of the studies of Choubladze *et al.* (1956) indicated that E.H.A. virus was immunologically related to rabies virus. They considered that the virus was different from rabies, and they failed to find any Negri bodies in histological material (Choubladze and Gaidamovitch, 1956b). Our demonstration of Negri bodies in mice inoculated with the SV strain of E.H.A. virus and the immunological studies of Choubladze and Gaidamovitch (1956b) seem to indicate that E.H.A. virus cannot be differentiated from rabies virus. (It should be noted that no rabies virus had been handled in our laboratory prior to this investigation.)

Since we cannot find any relationship between the virus of E.H.A. and multiple sclerosis in Northern Ireland, and since this virus cannot be differentiated from that of rabies, there seems to be no rationale for using the "vaccine of Choubladze and Margoulis" in preference to any other rabies vaccine in the treatment of multiple sclerosis.

Choubladze and Gaidamovitch (1956a) claimed that "the vaccine of Margoulis and Choubladze" has produced amelioration in 30% of cases of multiple sclerosis, but Choubladze (personal communication from Dr. R. S. Allison) notes that while their vaccine helps one-third of treated patients it does not help those who have been ill for a long time. Numerous claims have been made for successful treatments for multiple sclerosis. In the assessment of any treatment it must always be remembered that spontaneous remission characterizes early cases. From Brickner's (1936) compilation of recorded results of various treatments of multiple sclerosis, Putman (1939) concluded that 665 out of 1,407 cases (47.5%) profited from the treatments. He also showed that 44% of fresh lesions in untreated patients are capable of a complete functional recovery. If it is assumed that patients usually seek a new form of treatment when a new lesion occurs it is perhaps not surprising that 47.5% of patients given any kind of treatment have been reported to show improvement in view of the 44% of spontaneous remissions (Putman, 1939). On this basis there is thus no evidence for the success of the "vaccine of Choubladze and Margoulis." Indeed, the use of this vaccine (formalized rabies-virus-infected rodent brain), which is given in multiple inoculations, might do harm.

*Instruction for the administration of the vaccine against acute encephalomyelitis and sclerosis multiplex. Souischimeaport, Moscow.

Summary

The SV strain of E.H.A. virus which has been used to prepare the vaccine of Choubladze and Margoulis for the treatment of multiple sclerosis appears to be rabies virus.

We were unable to demonstrate any specific neutralization of the SV strain of E.H.A. virus with sera from patients with multiple sclerosis.

Choubladze and Gaidamovitch's (1956a) claim for amelioration of 30% of patients with multiple sclerosis treated with this vaccine is of the same order as that of spontaneous remissions (44%) of fresh lesions in untreated patients.

The possible danger associated with the use of any rabies vaccine may make the use of the "vaccine of Choubladze and Margoulis" dangerous in the treatment of multiple sclerosis.

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AMISOMETRADINE, A NEW ORAL DIURETIC

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Much importance is attached to the search for an orally active diuretic to support or replace parenteral mercurial preparations in the management of cases of heart failure. To date, all such drugs have had in common the disadvantage of poor gastro-intestinal tolerance when given in effective doses.

Of the active diuretics in the amino-uracil series of drugs, aminometradine ("mictine") has been most widely investigated (Kattus *et al.*, 1952; Platts and Hanley, 1956). In effective doses it has at least half the diuretic strength of mersalyl, but such doses produce epigastric discomfort, nausea, vomiting, or diarrhoea in almost 50% of patients; headache, tinnitus, and albuminuria are less common side-effects. Several chemically similar drugs have been studied, and amisometradine ("rolicton"*) is the most promising of them at present. In animals it has an equal or a better diuretic action than aminometradine, but causes far less vomiting; in both long and short trials it has been found relatively

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