era in treatment. From the clinical point of view bretylium tosylate itself has proved disappointing.

In a series of 43 patients tolerance has been experienced in two-thirds, bringing attendant failure, disappointment, and even death as the patient passes out of control. We have found exceptional sensitivity in some, which indicates that treatment must be begun with a very small dose at first, and exceptional resistance in others, which results in the waste of weeks or months in hospital while stabilization is sought with a steadily increasing dose. We have found many side-effects which might be bearable were the treatment more effective, but which, combined with tolerance, sensitivity, and variable absorption must convince the most optimistic that in bretylium there is no new hope for hypertensive patients. In particular, recurrent dizziness and syncope are effects which no clinician can be willing to impose upon his patient.

While bretylium will produce a fall in blood-pressure in almost all patients the pressure can be safely and comfortably maintained at reasonable levels in only a very few, and certainly not in those with severe or malignant hypertension. We certainly agree with the Hammersmith workers that bretylium is not the drug of choice for patients with severe hypertension. Since none of the more potent drugs yet produced is sufficiently safe or free from side-effects to justify treating patients with mild hypertension, the only ones for whom it might be considered are those with hypertensive disease of moderate severity or in whom only a moderate lowering of blood-pressure is desirable. However, tolerance develops so frequently that treatment should not be persisted in for long. Thus, although the research workers can be congratulated for their breakthrough into a new field of autonomic blockade, bretylium tosylate is not a practical and effective therapeutic agent, and may, in fact, jeopardize the patient's life. In our opinion it should not be used for the treatment of hypertension. Initial experience with guanethidine has been more encouraging.

Summary

Forty-three patients with hypertension of a severity sufficient to cause secondary changes in the retinae or heart have been treated with bretylium tosylate for an average period of six months.

A short-lived fall in blood-pressure was usually found, but in two-thirds of these patients tolerance developed and the blood-pressure rose again despite steady increases in dose.

Side-effects were frequent, including dizziness, parotid pain, dyspnoea, and syncope, the last being a potentially dangerous end-result.

Some patients showed sensitivity to doses of 100 mg. t.d.s., and a few were resistant to doses rising to 6,000 mg. daily.

It is concluded that bretylium tosylate should not be used for the treatment of hypertensive patients.

Our thanks are due to Miss Norma Millar, our technician, who recorded with painstaking accuracy and good humour the very large numbers of blood-pressures upon which this study is based.

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CEREBROSPINAL FLUID GAMMA-GLOBULIN IN MULTIPLE SCLEROSIS

OBSERVATIONS ON ITS NATURE

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It has been known for some time that the gamma-globulin level in the cerebrospinal fluid of cases of multiple sclerosis is commonly raised (Kabat, Moore, and Landow, 1942; Yahr, Goldensohn, and Kabat, 1954; Volk, Saifer, and Rabiner, 1954). It has been suggested that the rise may in part result from antibody formation within the central nervous system (Kabat, Moore, and Landow, 1942; Kabat, Freedman, Murray, and Knaub, 1950), though direct evidence of this is not available. The antiglobulin consumption test introduced by Steffen (1954) is capable of demonstrating increased globulin in the spinal fluid in multiple sclerosis, and in the present paper the ability of this excess globulin to fix to brain substrate has been examined.

Material and Methods

Spinal fluids of eight cases of acute exacerbation of multiple sclerosis and of 24 chronic cases have been tested.

A suitable specimen (clear of all blood) was diluted 1 in 16 times. Dilutions of a Coombs serum (final titre 1 in 2,048) from 1:16 to 1:512 were prepared and single drops plated out on to a clean glass plate. To each, one drop of the diluted spinal fluid was added. Interaction, aided by occasional gentle agitation, was allowed to take place for five minutes at room temperature. One drop of sensitized Group O Rh+ cells was then added to each mixture and any agglutination recorded at five and again at ten minutes. The globulins of the spinal fluid reacted with some of the Coombs reagent so that its original titre was reduced.

A suspension of normal human white matter was prepared by cutting frozen sections of the fresh tissue at 30 μ, and disrupting these in saline in a blender. The finely dispersed material was washed eight times to

remove all blood—so that the supernatant washing no longer reduced the titre of a Coombs serum with which it was mixed. The brain suspension was then made up to 20% v/v. Three drops of this suspension (from a standard-sized pipette) were put into a small tube, 20 drops of 1:16 C.S.F. added, and incubation was carried out in a water-bath at 38° C. for half an hour with occasional gentle agitation. This gave an opportunity for any antibody to brain present in the spinal fluid to become fixed upon the brain substrate. The spinal fluid was then spun off and its power to reduce the titre of Coombs serum re-estimated as described above—that is, its remaining content of globulin after exhibition to brain was assessed. Any reduction would be attributable to globulin antibody having become sessile.

Similar experiments were also carried out with lyophilized normal brain (from same subject), 2 mg. of this material being substituted for the three drops of 20% brain suspension in such cases. In this way the slight dilution of spinal fluid by water content of the brain suspension was obviated. Results were identical in both cases.

The whole series of experiments was repeated with wet acute multiple sclerosis brain, since it was thought that this might provide a better substrate than the normal organ.

Results

None of the spinal fluids from the eight different patients with an acute exacerbation gave a positive result—that is, in no case could antibody capable of fixing to either normal or multiple sclerosis brain be demonstrated. The fluids from 24 chronic cases of multiple sclerosis in various stages of the disease were also tested, with negative results.

Experiments were carried out on batches of six sera, chronic and acute cases being included, together with a healthy normal control. The accompanying table is the protocol of one such experiment, in which, as it happens, one normal control (B.V.) was examined at the same time as one acute case (P.T.) and four chronic cases. The failure of demonstrable absorption of any antibody upon the brain substrate, as shown by the absence of any significant difference between Coombs serum titre before and after exposure to it, is typical of all the results.

Typical Protocol of an Experiment Involving Six C.S.F. Specimens Showing Coombs Serum Titre Before and After Exposure to Brain Which had Been Incubated with the C.S.F. Under Examination. Eight Times Washed Normal Brain Used as Substrate

Patient		C.S.F. Dilutions					
		16	32	64	128	256	512
B.V. (normal control)	Before	+	+	+	+	+	±
	After	+	+	+	+	+	±
R.F.	Before	+	+	+	±	0	0
	After	+	+	+	±	0	0
P.T. (acute)	Before	+	+	+	±	0	0
	After	+	+	+	±	0	0
S.F.	Before	+	+	+	+	0	0
	After	+	+	+	+	±	0
E.C.	Before	+	+	+	+	0	0
	After	+	+	+	+	0	0
E.M.	Before	+	+	+	±	0	0
	After	+	+	+	±	0	0

Patient S.F. showed a half-step decrease in titre. This is regarded as being within the limits of experimental error.

Readings of the completed agglutination at 10 minutes only are shown.

Discussion

These results suggest that the considerable increase in gamma-globulin known to occur in many cases of multiple sclerosis is not due in any large measure to antibody capable of becoming sessile upon normal brain substance under the conditions of the experiment. It is of course possible that only a small proportion of the gamma-globulin is in fact antibody, and an attempt was therefore made to set some limit to the sensitivity of the method in detecting globulin concentration changes.

1:16 dilutions of spinal fluids of known globulin concentration were titrated out as above. The lowest difference in concentration which could be detected (by difference in Coombs serum consumed) was estimated at 0.225 mg./100 ml., corresponding to 3.6 mg./100 ml., in the undiluted spinal fluid. Applying this figure to patient E.M., whose spinal fluid contained 50.5 mg. of gamma-globulin per 100 ml., but showed no antibodies capable of fixation to brain, it would seem that not more than 7% of his spinal-fluid globulin was antibody (as judged by the experimental criterion employed). It may, of course, have been a good deal less, or even nil.

The idea that a rise in the level of gamma-globulins in the spinal fluid is associated with the presence of antibody has an attractiveness which may be beguiling and deserves close examination, since it may colour thinking in respect to pathogenesis. Its immediate appeal derives from the presumed parallelism between the mechanism of multiple sclerosis and experimental allergic encephalitis in which some fraction or fractions of normal brain are known to be antigenic. On this basis the disease might be regarded as an autoimmune condition with the expectation of antibodies to brain in blood and cerebrospinal fluid—the situation being analogous to that in Hashimoto's disease. With the use of thyroid as a substrate there is no difficulty in demonstrating antibodies capable of becoming fixed in the serum of a high proportion of cases of Hashimoto's disease (Field and Ridley, 1960). While Steffen (1955) has successfully shown antibodies in the serum of multiple sclerosis cases, the titres he has found are far weaker than in Hashimoto's disease. Moreover, we have not so far been able to confirm Steffen's finding, and it seems reasonable to suppose that any antibodies present are of weak concentration and far less readily demonstrable than in a well-authenticated autoimmune condition such as Hashimoto's disease.

In interpreting the rise in gamma-globulin in the cerebrospinal fluid in multiple sclerosis, semantic equivalence between "gamma-globulin" and "antibody" must be avoided. "Whether all gamma-globulins are actually antibodies cannot be resolved at the moment," for "the amount of gamma-globulin readily accounted for by the more easily measured antibodies represents only a small fraction of the total gamma-globulin in adult human plasma" (Gitlin, Gross, and Janeway, 1959). The same caution in interpretation should apply to cerebrospinal fluid gamma-globulin. The present experiments suggest that there is no great local formation of antibody to brain tissue. The excessive gamma-globulin which is commonly (though not always) present might be (*a*) antibody to some other antigen—for example, virus or other infective agent such as a spirochaete—or (*b*) not of the nature of antibody at all.

As to the former possibility we have no evidence save that of Roach, Rosenberg, and Ichelson (1959), who

claimed to have found antibody to spirochaete antigen in the spinal fluid in multiple sclerosis. This claim has not been substantiated so far.

If the globulin (including gamma) rise in spinal fluid is not predominantly antibody, it may come from the disintegration of nervous tissue. This possibility was examined in the careful study by Yahr *et al.* (1954), who found that 35 cases of advanced amyotrophic lateral sclerosis, Friedreich's ataxia, poliomyelitis, syringomyelia, olivo-ponto-cerebellar degeneration, and combined system disease, all had gamma-globulin percentages within the normal range. From this they concluded that "destruction of neuronal tissue alone does not necessarily cause alteration in cerebrospinal fluid gamma-globulin content" (p. 662). However, the concentration in spinal fluid of any product of nervous-tissue disintegration must depend upon several factors, by no means all of which can be assessed. The degree of tissue destruction, the time over which it takes place, and the balance between liberation and resorption into the blood are perhaps the most obvious. It may be also that the clearance from the spinal subarachnoid space is less efficient in older and/or diseased subjects. Histological examination of active cases of multiple sclerosis will often show widespread disintegration of nervous tissue the total bulk of which appears much greater than in many advanced cases of the other diseases cited above. However, in the absence of quantitative data, the relative amounts of tissue destruction in these different conditions must remain an open question.

Direct evidence of the electrokinetic character of the protein material liberated when normal brain undergoes disintegration has become available (Hofmann and Schinko, 1956). This shows that about 19% alpha globulin, 54% beta-globulin, and 23% gamma-globulin are liberated from white matter. From cortex the percentages are 12, 67, and 19 respectively. It can be seen, therefore, that brain disintegration will make available for eventual passage into the spinal fluid considerable amounts of globulins, especially that characterized electrokinetically as beta. Whether breakdown along the lines which takes place in multiple sclerosis would result in a different spectrum of liberated protein is not known, but it does seem possible that under certain conditions the electrokinetically slower gamma fraction might be liberated in larger proportion. Concentration of different fractions (if indeed they exist as entities *in vivo*) must depend also upon the relative ease with which they are able to leave the subarachnoid space. The position is still further complicated by the fact that specimens of spinal fluid are nearly always taken from the lumbar cul-de-sac—a region far from the periventricular zone where lesions of multiple sclerosis tend to be greatest—so that opportunity exists for chemical modification of the fluid to be brought about before it is sampled.

In view of the multiplicity of uncontrolled factors it seems not unreasonable to entertain the hypothesis that the protein changes in spinal fluid may be secondary to nervous-tissue disintegration taking place under the spatial and temporal conditions peculiar to multiple sclerosis. There is general agreement that the greatest and most consistent elevations of gamma-globulins are found in long-standing cases of multiple sclerosis. It is difficult to reconcile an active pathogenetic significance of this with the burned-out picture which such cases present. On the other hand, it is consistent with derivation from destroyed nervous tissue with differential alteration in electrokinetic protein spectrum.

The presence or otherwise of antibodies to brain in spinal fluid has obvious significance for the formulation of a heuristic approach to the disease. So long as it is tacitly assumed that the frequent presence of gamma-globulin excess in spinal fluid indicates local brain antibody formation, the disease is likely to be regarded primarily as of an immune character. Liberation from such a shackling notion might stimulate effort in other directions.

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TRICHOPHYTON SULPHUREUM IN A RESIDENTIAL SCHOOL

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Trichophyton sulphureum has been recovered from humans in many parts of the world, but is an important cause of ringworm in only a small number of geographically limited areas. In Northern Ireland it is the most common cause of scalp ringworm among children (Beare, 1958), in contrast to other parts of Britain and Western Europe, where species of *Microsporum* tend to predominate. The lesions produced by *T. sulphureum* range from a mild, scarcely perceptible scaling or erythema to a relatively severe inflammatory and suppurative reaction (kerion) which may result in atrophy or scarring. Infection may persist for years, and the difficulty of clinical detection and the absence of Wood's light fluorescence of infected hairs make eradication of an outbreak in an institution "practically impossible" (Meenan, 1955).

In May and June, 1959, seven children from a Belfast residential school were found to be infected with *T. sulphureum*—three had infections of the glabrous skin and four had scalp infections. At this stage it seemed probable that the number of infected children in the school was higher than the seven known to be infected, and an attempt was accordingly made to determine the total number of infected children in the school, and to