MANAGEMENT OF E.C.T. AND ANAESTHESIA

The method used in this unit is to give atropine 1.2 mg. intravenously followed immediately by methohexitone sodium—the four patients in this report receiving 70 to 80 mg. Suxethonium bromide 90–120 mg. is then injected. When the muscular twitching has stopped the patients are ventilated gently with oxygen, the shock is administered, and the patients are ventilated again until spontaneous respirations are resumed.

DISCUSSION

Eastham (1967) reviewed the conditions associated with low serum pseudocholinesterase levels but did not mention anti-depressant drugs. Among states associated with a low serum pseudocholinesterase he included severe liver disease, chronic debilitating disease, severe anaemias, cardiac infarction, poisoning with organophosphorus compounds, and familial cholinesterase abnormalities. Low enzyme levels have recently been reported in patients with eczema (Trotter and Fairburn, 1966). None of the three patients studied suffered any of the above disorders.

It is unlikely that any of these patients were among the small group of people, 1 in 3,000 of the population, with inherited low serum pseudocholinesterase levels, as all four patients had previously recovered uneventfully from modified E.C.T. Also, in the three cases where follow-up study was possible low serum pseudocholinesterase levels returned to normal after withdrawal of phenelzine.

Of the three patients who were followed up, one was a diabetic, another had a mild hypochromic anaemia with a haemoglobin of 10.3 g./100 ml., while the third was six months into the puerperium. All three patients were having other drugs—trifluoperazine in Case 1 and diazepam in Cases 2 and 3—but these drugs were continued after phenelzine was stopped, and the pseudocholinesterase level in each case still returned to normal. Regrettably, no pseudocholinesterase levels were estimated before treatment, but there is no suggestion that the pre-treatment enzyme levels were other than normal.

Further work is planned to extend these observations. It is premature yet to conclude that phenelzine does depress pseudocholinesterase levels. Equally it cannot be said that other monoamine oxidase inhibitors do not have this effect.

CONCLUSIONS

Low serum pseudocholinesterase levels, possibly due to a hepatotoxic effect, have been observed in four patients under treatment with phenelzine. After withdrawal of phenelzine the enzyme level returned to normal in the three cases where investigation was possible. For the great majority of patients on phenelzine and other monoamine oxidase inhibitor anti-depressant drugs, modified E.C.T. is a safe procedure. At the same time, in view of these findings and their implications, when patients who require relaxation with a short-acting muscle relaxant have been on phenelzine either in high dosage or for prolonged periods it would seem a reasonable precaution to estimate first the serum pseudocholinesterase, so that if necessary anaesthetic techniques may be modified to avoid untoward complications.

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Medical Memoranda

Virus Antibody Levels in Multiple Sclerosis

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In a previous study (Ross *et al.*, 1965a) single sera from 96 cases of multiple sclerosis and from 96 matched controls were examined for complement-fixing antibodies to herpes, mumps, psittacosis-lymphogranuloma venereum group, Q fever, measles, varicella-zoster, poliovirus type 1 and type 2, and *Mycoplasma pneumoniae*. Complement-fixing antibody for each of the agents was consistently present in a greater number of patients than controls, though a statistically significant difference was obtained only with varicella-zoster. Several possible explanations were suggested for these findings—namely, that patients with multiple sclerosis might show a difference in immunological response to infective agents, that patients with

multiple sclerosis might be particularly susceptible to infection with varicella-zoster, and that infection with varicella-zoster or an antigenically related virus such as herpes simplex (Ross *et al.*, 1965b) might be associated with the aetiology of multiple sclerosis. Other workers have shown significantly higher measles antibody titres in single sera from multiple sclerosis patients than from controls (Sibley and Foley, 1965; Pette and Kuwert, 1965; Adams, 1967) and have suggested that infection with measles virus may have an aetiological relationship with the disease.

PRESENT STUDY

Following these studies on single sera it seemed relevant to investigate antibody levels in serial sera from patients with multiple sclerosis, since it seemed that if a virus such as measles, varicella-zoster, or herpes simplex were directly associated with the aetiology of multiple sclerosis that virus might remain latent in the central nervous system and its reactivation might be

associated with clinical relapse and a rise in antibody titre. For this purpose two or more samples of sera were obtained from 13 patients with established multiple sclerosis (mean age 37 years) in relation to clinical relapses, the first specimen being collected at the beginning of the relapse and subsequent sera at variable intervals from seven days to three months. Also, since retrobulbar neuritis is often the first acute manifestation of multiple sclerosis, sera were obtained from 17 patients with this manifestation (mean age 28 years) who had no previous history of neurological disease. The first specimen was collected when the patient was first examined, a second specimen two weeks later, and a third specimen generally four weeks after the second. The sera from each patient were tested in parallel for complement-fixing antibodies to measles, varicella-zoster, and herpes simplex by the methods previously described (Ross *et al.*, 1965a).

A fourfold or greater rise in complement-fixation titre to measles, varicella-zoster, or herpes was not obtained in any patient in either of the two groups. It was found, however, that the range of the serum complement-fixation titres for measles, herpes, and varicella-zoster was higher in the multiple sclerosis patients than in those with retrobulbar neuritis (Table I). Thus high titres (≥ 64) for measles, herpes simplex, and varicella-zoster were obtained respectively in 4, 10, and 6 of the 13 multiple sclerosis patients compared with 1, 2, and 0 of the 17 with retrobulbar neuritis. The difference in these results is statistically significant for herpes simplex and varicella-zoster (for both χ^2 , $0.01 > P > 0.001$) for measles the difference is not significant (χ^2 , $0.20 > P > 0.10$). In two of the multiple sclerosis patients who were observed over several years (Table II) there was persistence of high complement-fixing titres for all three viruses and also high measles haemagglutination-inhibition titres. In these two cases no complement-fixing antibodies, or low titres only, were detected for influenza A, influenza B,

TABLE I.—Complement-fixing Serum Titres in Multiple Sclerosis (M.S.) and Retrobulbar Neuritis (R.N.) Patients

C.F. Titres (Reciprocals)	No. of Patients with C.F. Titres					
	Measles		Herpes		Varicella-Zoster	
	M.S.	R.N.	M.S.	R.N.	M.S.	R.N.
<8	2	11	2	5	1	10
8-32	7	5	1	10	6	7
64-256	3	1	10	2	5	0
≥ 512	1	0	0	0	1	0
Total	13	17	13	17	13	17

TABLE II.—Serial Antibody Titres in Two Cases

Case No.	Age and Sex	Dates of Sera	Titres (Reciprocals)			
			Measles C.F.	Measles H.I.	Herpes Simplex C.F.	Varicella-Zoster C.F.
1	38 F	9/12/63	256	512	128	128
		2/4/64	256	1,024	64	128
		16/1/65	512	512	64	256
		17/4/65	512	1,024	128	256
		1/9/67	512	2,048	128	256
		8/4/68	256	N.D.	128	256
2	18 F	31/5/65	256	512	64	512
		14/6/65	256	N.D.	128	512
		28/6/65	256	256	128	256
		30/10/67	128	512	64	128
		23/3/68	128	N.D.	64	256

N.D. = Not done. H.I. = Haemagglutination inhibition.

adenovirus group, mumps, psittacosis-lymphogranuloma group, Q fever, and *Myco. pneumoniae*; influenza C titres persisted at high levels (256-512) in Case 2 but were low in Case 1.

COMMENT

Our failure to detect any rise in antibody titres for measles, herpes simplex, or varicella-zoster during acute exacerbations in patients with established multiple sclerosis lends no support to the postulate that one of these viruses might be latent in the central nervous system and that reactivation might give rise to an acute exacerbation of the disease. It is possible, however,

that though periodic reactivation of one of these viruses in the central nervous system might not provide a sufficient antigenic stimulus to produce a detectable increase in antibody titre yet it might suffice to maintain a steady antibody level analogous perhaps to the antibody response generally obtained in recurrent infections with herpes simplex. Latency of certain viruses with resulting cumulative effects of periodic reactivation might explain our finding of higher antibody levels to some viruses in established cases of multiple sclerosis than in patients with retrobulbar neuritis. The demonstration of high antibody titres to several viruses may mean that several different infective agents are involved in the pathogenesis of multiple sclerosis. It must be stressed, however, that there are serological cross-reactions between herpes simplex and varicella-zoster (Kapsenberg, 1964; Ross *et al.*, 1965b), so that complement-fixing antibody findings for these viruses may be group- and not virus-specific.

Reports of high antibody levels for measles not only in multiple sclerosis (Sibley and Foley, 1965; Pette and Kuwert, 1965; Adams, 1967) but also in subacute sclerosing panencephalitis (Connolly *et al.*, 1967; Legg, 1967) suggest that there may be a similar basic anomaly in both conditions. Recently Burnet (1968) postulated that immunity to measles may be mediated by the thymus-dependent system, and that subacute sclerosing panencephalitis is a condition in which this system has developed specific tolerance to measles antigen while the antibody system remains specifically active. He suggested that "the essential anomaly in the subacute sclerosing panencephalitis patient is that the conclusion of a measles attack finds occasional measles cells, presumably lymphocytes, lodged in immunologically privileged areas in the sense that cellular reaction against them is difficult or impossible. Two of these are the central nervous system and the thymus."

It seems possible that a similar anomaly might also be present in patients with multiple sclerosis. We would suggest that not only measles virus but also other viruses which induce delayed hypersensitivity and which are potentially latent, such as herpes simplex or varicella-zoster, might invade the thymus and the central nervous system. Burnet (1968) suggested two experimental procedures to test his hypothesis for subacute sclerosing panencephalitis—namely, skin tests with measles antigen and investigation of the thymus for evidence of viral invasion by means of immunofluorescent techniques or electron microscopy. It would seem that similar studies might be rewarding in patients with multiple sclerosis.

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