than on the placebo. The weekly question, "Did the tablets upset you?" was usually answered "no." It was answered "yes" by two participants during treatment with the drug and by one participant during the placebo treatment.

Participants' Other Comments

General comments were not invariably made by the participants. Where clear statements of improvement or no improvement on either drug were made they are summarized in Table V. The results clearly support those in Table II.

TABLE V.—*Summary of Participants' Comments Other than Those Concerning Adverse Effects*

Group	Improvement on			
	Both Drug and Placebo	Drug Only	Placebo Only	Neither Drug nor Placebo
Placebo followed by drug	0	6	0	6
Drug followed by placebo	3	2	2	3

Conclusion

This trial showed that emepronium bromide given in dosage of 150 mg. on going to bed effectively diminished nocturnal frequency of micturition in aged women. On the basis of a double-blind cross-over trial an important difference emerged between those participants given the placebo before the drug and those given the drug first. In the first case there is little effect with the placebo but a moderate effect with the drug. In the latter case there is a more marked effect with the drug, and this is carried over into the placebo period.

The difference between control period and active drug when compared with the difference between the control period and the placebo is statistically significant ($P<0.02$). This effect is borne out by participants' own observations of the drug.

As we have found with other drugs used on the neurogenic bladder of old age (Brocklehurst and Dillane, 1967), not every person is benefited. There are some in whom no effect is observed. In such a case the drug should be withdrawn after three to four weeks.

No side-effect of importance was observed. Such side-effects as were recorded were distributed evenly between the drug and the placebo.

It may be concluded, therefore, that emepronium bromide is worthy of trial in any elderly woman whose sleep is disturbed by nocturnal frequency. Some will show no effect, most will show a moderate diminution or complete disappearance of the frequency. It is probable that 150 mg. on retiring is a low dose and that a further 100 mg. may be taken during the night if the participant awakens. Extra dosage should be introduced gradually.

We have not investigated the drug with males. We believe that nocturnal frequency in men as in women is commonly due to the uninhibited neurogenic bladder of old age, and will respond equally well to emepronium bromide. The enlarged prostate, however, is an additional hazard in the elderly male and caution is required in using any anticholinergic drug in males with prostatic enlargement because of the danger of precipitating acute urinary retention.

Our thanks are due especially to Mrs. H. Billing, S.R.N., who carried out the field work on which this trial is based; also to Mr. A. N. Nicholls and Kabi Pharmaceuticals Limited for their considerable help in organizing and financing this trial; to Miss M. Chandler for statistical assistance; and to Dr. Louis Griffiths for arranging the bacteriological tests.

REFERENCES

Brocklehurst, J. C., and Dillane, J. B. (1966). *Gerontologia Clinica*, **8**, 285.
Brocklehurst, J. C., and Dillane, J. B. (1967). *Gerontologia Clinica*, **9**, 182.
Brocklehurst, J. C., Dillane, J. B., Griffiths, L., and Fry, J. (1968). *Gerontologia Clinica*, **10**, 242.
Hansson, E., and Schmiterlöw, C. G. (1961). *Acta Pharmacologica et Toxicologica*, **18**, 183.
Jönsson, G., and Zederfeldt, B. (1957). *Urologia Internationalis*, **4**, 293.

Herpes Zoster and Multiple Sclerosis*

J. A. R. LENMAN,† M.B., CH.B., F.R.C.P.ED.; T. J. PETERS,‡ M.B., M.SC., M.R.C.P.

British Medical Journal, 1969, **2**, 218–220

Summary: No significant difference was found between 50 consecutive patients with multiple sclerosis and matched controls in respect of previous infection with rubella or measles and chicken-pox, or of previous vaccination and immunizing injections. Significantly more patients had a past history of herpes zoster compared with the controls.

Introduction

In a previous paper (Ross, Lenman, and Rutter, 1965) it was shown that patients with multiple sclerosis had significantly higher antibody titres to varicella-zoster virus as compared with matched controls. Antibody to a number of viruses was found in a greater number of cases than controls, but the difference was significant only in respect of varicella-zoster. In the present study a series of cases of multiple sclerosis, many of whom were included in the previous study, and carefully matched controls were questioned concerning a past history of chicken-pox (varicella) and shingles (zoster), and also about previous illnesses suggestive of infection with rubella, measles, poliomyelitis, and glandular fever, and about previous vaccination and immunization injections.

* Based on a paper presented to the Association of British Neurologists on 6 April 1968.

† Senior Lecturer in Neurology, Department of Medicine, University of Dundee.
‡ Lecturer, Department of Medicine, University of Dundee. Present address: The Royal Postgraduate Medical School, London W.12.

Methods

A total of 50 consecutive cases of multiple sclerosis, who had been examined by one of us (J. A. R. L.), were interviewed when seen either at a neurological outpatient clinic or when admitted to hospital. The cases of multiple sclerosis were unselected and comprised those cases who attended as neurological outpatients or who were admitted to hospital during the period of study. They included 39 females and 11 males. The controls were matched independently by T. J. P., and so far as possible were comparable in respect of sex, race, and age to within five years (Table I). It was not possible to match them closely for place of birth. Though it was not possible in every case to obtain matching between pairs in respect of social class according to the Registrar General's classification, the distribution according to social class was similar in the two groups (Table II). Multiple sclerosis patients seen as outpatients were matched with controls seen at a non-neurological clinic at the same hospital, and inpatients with controls admitted to the same general ward.

TABLE I.—*Age Distribution of Patients and Controls*

	Age (Years)					
	10–19	20–29	30–39	40–49	50–59	60–69
Percentage of patients	2	12	24	42	14	6
Percentage of controls	0	10	24	42	20	4

TABLE II.—*Distribution of Patients and Controls According to Registrar General's Classification of Social Classes*

	Social Class				
	I	II	III	IV	V
Percentage of patients ..	8	20	60	12	0
Percentage of controls ..	0	28	48	20	4

The patients and controls were asked whether they had had shingles and at what site the rash had occurred, and whether they had suffered post-herpetic neuralgia. Any relation between the zoster and the multiple sclerosis was also looked for. The patients were also questioned about a past history of facial palsy, rubella or measles, glandular fever, and poliomyelitis. Because of the reports of apparent provocation of the disease by protective inoculations, both patients and controls were asked whether they had been vaccinated and whether they had received any immunizing inoculations and if so at what site.

Results

The results are presented in Table III. In both groups the number of patients with a past history of paralytic poliomyelitis or glandular fever was too small to be included in the Table. It can be seen that the only statistically significant difference ($P<0.05$) between patients and controls is in respect of zoster:

TABLE III.—*Prevalence of Antecedent Conditions in Multiple Sclerotic Patients and Controls*

		Multiple Sclerosis	Controls	Significance
Varicella	Yes	29	27	Not significant
	No	17	20	
	Doubtful ..	4	3	
Zoster	Yes	10	2	$\chi^2=4.64$ $P<0.05$
	No	40	48	
	Doubtful ..	0	0	
Measles/ rubella	Yes	38	40	Not significant
	No	9	8	
	Doubtful ..	3	2	
Facial palsy	Yes	4	0	
	No	45	50	
	Doubtful ..	1	0	
Vaccination	Yes	40	37	Not significant
	No	10	13	
	Doubtful ..	0	0	
Immunizing injection	Yes	34	31	Not significant
	No	15	19	
	Doubtful ..	1	0	

with facial palsy the numbers were too small for statistical analysis.

On reviewing the case histories of the 10 cases of multiple sclerosis with a history of zoster no atypical features of either condition were noted. There was no relation between the site of zoster and the multiple sclerosis symptomatology. It was noted, however, that all the cases of multiple sclerosis except one suffered zoster before the onset of the multiple sclerosis.

Discussion

Zoster generally occurs in adult life and has a characteristic distribution and natural history, and therefore its ascertainment is likely to be more reliable than in the case of the exanthemata. In the case of these conditions the results should perhaps be accepted with greater caution. The finding that there is no significant difference in the incidence of past infection with rubella/measles and varicella supplements the clinical findings in the earlier study, in which no significant difference between patients and controls in the incidence of mumps and herpes simplex was obtained. The failure to find a significant difference in the past history of vaccination and immunizing inoculations in the patients and controls is in agreement with other workers (Westlund and Kurland, 1953 ; Sibley and Foley, 1965). It may throw doubt on the significance of immunizing injections as provocative triggers of multiple sclerosis (McAlpine, Lumsden, and Acheson, 1965 ; Miller, Cendrowski, and Schapira, 1967).

There are several isolated reports of zoster followed by multiple sclerosis in the literature (Alajouanine and Griffith, 1931 ; Gordon and Tucker, 1945 ; Whitty and Cooke, 1949 ; McAlpine, Kuroiwa, Toyokura, and Araki, 1959 ; Barnard and Jellinek, 1967). It has been suggested that the zoster was symptomatic, associated with a sclerotic plaque in the spinal cord (Alajouanine and Griffith, 1931), but this is unlikely, as the zoster generally precedes the multiple sclerosis and there is no consistent relation between the site of zoster and the site of the lesions of the multiple sclerosis.

It does not of course follow from an association between zoster and multiple sclerosis that the varicella-zoster virus has an aetiological role in multiple sclerosis. There is evidence suggesting that the immune mechanism in multiple sclerosis is abnormal (Alexander, Loman, Lesses, and Green, 1950 ; Smith, Espir, Whitty, and Russell, 1957 ; Field, Green, and Miller, 1961 ; Fowler, Morris, and Whitley, 1966). It may be that this impaired immune mechanism allows the varicella-zoster virus to emerge from its latent phase at an unusually early age in the same way that immunosuppressive therapy is not uncommonly complicated by zoster (Bacon, Oliver, and Shapiro, 1965), and it is conceivable that these immunologically inefficient persons would respond abnormally to "slow" viruses, which have recently been implicated as aetiological agents in multiple sclerosis (Field, 1966 ; Webb, 1967).

We are grateful to Professor Sir Ian Hill for his interest, to Dr. Constance A. C. Ross for her useful comments, and to Mr. J. C. Pearson for statistical advice.

REFERENCES

Alajouanine, T., and Griffith, B. (1931). *Revue Neurologique*, **1**, 84.
Alexander, L., Loman, J., Lesses, M. F., and Green, I. (1950). *Research Publications, Association for Research in Nervous and Mental Disease*, **28**, 178
Bacon, G. E., Oliver, W. J., and Shapiro, B. A. (1965). *Journal of Pediatrics*, **67**, 768.
Barnard, R. O., and Jellinek, E. H. (1967). *Journal of the Neurological Sciences*, **5**, 441.
Field, E. J. (1966). *British Medical Journal*, **2**, 564.
Field, E. J., Green, C. A., and Miller, H. (1961). *Journal of Neurology, Neurosurgery, and Psychiatry*, **24**, 78.
Fowler, I., Morris, C. E., and Whitley, T. (1966). *New England Journal of Medicine*, **275**, 1041.

Gordon, I. R. S., and Tucker, J. F. (1945). *Journal of Neurology, Neurosurgery, and Psychiatry*, **8**, 40.
McAlpine, D., Kuroiwa, Y., Toyokura, Y., and Araki, S. (1959). *Journal of Neurology, Neurosurgery, and Psychiatry*, **22**, 120.
McAlpine, D., Lumsden, C. E., and Acheson, E. D. (1965). *Multiple Sclerosis*. Edinburgh, Livingstone.
Miller, H., Cendrowski, W., and Schapira, K. (1967). *British Medical Journal*, **2**, 210.
Ross, C. A. C., Lenman, J. A. R., and Rutter, C. (1965). *British Medical Journal*, **1**, 226.
Sibley, W. A., and Foley, J. M. (1965). *Annals of the New York Academy of Science*, **122**, 457.
Smith, H. V., Espir, M. L. E., Whitty, C. W. M., and Russell, W. R. (1957). *Journal of Neurology, Neurosurgery, and Psychiatry*, **20**, 1.
Webb, H. E. (1967). *Proceedings of the Royal Society of Medicine*, **60**, 698.
Westlund, K. B., and Kurland, L. T. (1953). *American Journal of Hygiene*, **57**, 397.
Whitty, C. W. M., and Cooke, A. M. (1949). *Journal of Neurology, Neurosurgery, and Psychiatry*, **12**, 152.

Disodium Cromoglycate in the Prevention of Induced Asthma

H. HERXHEIMER,* M.D., L.R.C.P.S.ED.&GLASG.; HELGA BEWERSDORFF,† M.T.A.

British Medical Journal, 1969, **2**, 220–222

Summary: In 13 patients with allergic asthma disodium cromoglycate protected fully only two from an allergen-induced asthmatic attack.

Inhalation of disodium cromoglycate did not improve lung function in five patients with long-standing chronic asthma.

Previous clinical trials do not show convincing evidence that this drug improves bronchial asthma in a high percentage of cases, but it seems to help a small minority of patients.

Introduction

Recently disodium cromoglycate has been recommended for the treatment of bronchial asthma. Opinion about its usefulness in this disease is divided. The main interest in the substance is based on the report that, if given beforehand, it can protect a patient from an asthmatic attack provoked by the inhalation of antigen aerosol. For this reason it has been recommended mainly for allergic (extrinsic) asthma. Most reports about its effect, however, concern its clinical efficiency in both extrinsic and intrinsic asthma, and experimental work on its preventive action in induced asthma has so far been limited. In the experiments reported here we have attempted to suppress induced (provoked) asthma in 13 patients.

Material and Methods

Of the 13 patients investigated, five had grass pollen asthma, two house dust asthma, and six had flour asthma. The diagnosis was proved by the history, by skin testing, and by bronchial testing. The investigations took place during a period in which the asthmatic complaint was latent or at a minimum.

The asthmatic attack was provoked by the method of Herxheimer (1949), while the patient was breathing from a closed-circuit recording spirometer. His basal values for the vital capacity (non-forced, starting from the expiratory level of the tidal air) and peak flow were taken beforehand. Then a measured amount of antigen aerosol was released into the circuit. This dose had previously been determined as being sufficient to induce a mild attack, lowering the vital capacity by 10 to 20% and the peak flow by 30 to 40%. Breathing was recorded continuously and the vital capacity after 1, 2, 5, and 10 minutes and, if necessary, later. An induced attack became apparent usually within 10 minutes, both subjectively and in the lung function values. When this was the case 2% isoprenaline sulphate aerosol was released into the circuit and this aborted the attack within a few minutes.

The allergens used were a 5% grass pollen extract and 5% mixed pollen extract (Bencard), diluted 1:10, house dust extract 5% (freeze dried, Center Laboratories, Port Washington, N.Y.), and wheat flour. The flour was not given in solution, as were the other allergens, but was inhaled through the nose by means of a powder blower. The amount varied from 10 to 120 mg. In the patients we tested we had previously found that such inhalation of flour produced symptoms not only of rhinitis but also of asthma. All patients had been given placebo inhalations on a previous occasion.

Disodium cromoglycate was given as the aerosol of a 5%, later 10%, watery solution in the closed-circuit system. The pure substance, without the admixture of isoprenaline, had been made available to us by the kindness of the makers (Fisons Ltd.). This aerosol had no irritant effect on the subjects. It was inhaled for four to eight minutes—that is, the patient inhaled between 8 and 34 mg. and therefore retained (Herxheimer and Stresemann, 1961) between about 6·4 and 28 mg. Originally it had been intended to use the Spinhaler for the application of the substance, but on microscopical examination the powdered contents of the cromoglycate capsules to be inhaled by the patients proved to consist mainly of large, partially crystalline clumps with a diameter of 30–50 μ and could therefore not be expected to reach the finer bronchioli.

The inhalation of the provoking allergen was begun 20 to 30 minutes after the cromoglycate inhalation had ended. Apart from preliminary trials each patient took part in three experiments: firstly, an induced attack without cromoglycate; secondly, after three to seven days an induced attack with the same amount of allergen but cromoglycate given beforehand; and thirdly, after a similar interval another induced attack with an equal amount of allergen but without cromoglycate, as a control.

In five other patients with chronic bronchial asthma of the extrinsic or intrinsic type and a reduced but stable lung function cromoglycate aerosol was given in amounts from 8 to 17 mg. by the same method. A saline aerosol had been given on a previous occasion and baseline measurements of lung function recorded.

The subjects were informed about the purpose of the investigations and had consented.

* Director, Asthma Policlinic, Free University, West Berlin.
† Assistant, Asthma Policlinic, Free University, West Berlin.