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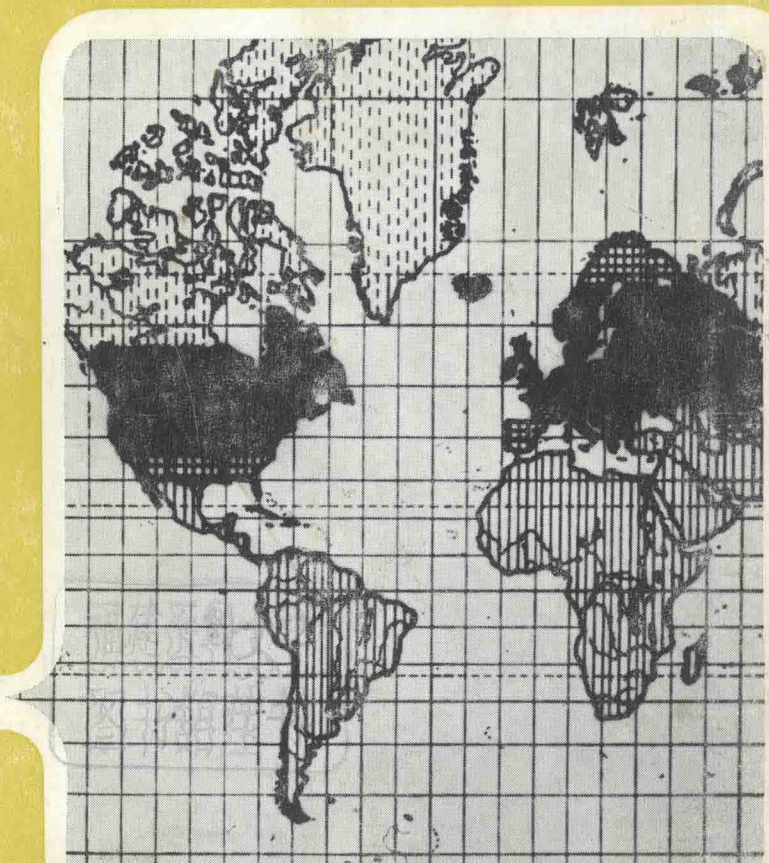
a. g. bearn, d. a. k. black,
and h. h. hiatt
editors

multiple sclerosis

progress in research

edited by
e. j. field, t. m. bell and
p. r. carnegie



MULTIPLE SCLEROSIS

Progress in Research

Edited by

E. J. FIELD, T. M. BELL and P. R. CARNEGIE

Report of a symposium held under the auspices of the

Multiple Sclerosis Research Committee,
World Federation of Neurology.

and

Medical Research Council Demyelinating
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CLINICAL STUDIES

A North-Holland Frontiers Series

VOLUME 3

Edited by

A. G. BEARN
New York

D. A. K. BLACK
Manchester

H. H. HIATT
Boston

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Editor's preface

The launching of a new series of medical books perhaps requires a word of explanation, at a time when there is no great apparent shortage of medical titles. We have, however, good reasons for doing so, which may be briefly outlined, as they also serve to indicate the scope of the series for the benefit of future authors.

We are naturally not uninfluenced by the prestige and succes of the already established series 'Frontiers of Biology', edited by Professors A. Neuberger and E. L. Tatum. This displays the advantages of a coherent publishing policy and of critical choice of individual titles. In the main, the series consists of monographs, but occasionally conference reports on clearly defined topics have been included. Our own choice of material will be similar in character, but we hope to draw contributions from another area of scientific endeavour, that which is concerned less with fundamental biology, and more with problems arising in clinical medicine. Our publishers naturally gave thought to the possibility of expanding the already well-established series in this direction; but we were able to persuade them that the clinical sciences already formed a discipline, or group of disciplines, which justified a separate enterprise.

In taking this view, we are fully aware that modern medicine, with its tantalising combination of triumphs and difficulties, is firmly based on the fundamental sciences – particularly if these are extended to include those which deal with the behaviour of animals, of man, and of society. But we are equally conscious of the intensity and depth of the scientific work which is inspired by clinical problems, and often carried out in clinical departments. Much of this work consists of careful observation of nature's own experiments; but 'observation' now means something much more

sophisticated than it did in the days of Auenbrugger and Laennec. The older scientific techniques still have a central place in studying the natural history of disease; but tools from the laboratory have greatly extended the range of what can be observed. Partly because of this, and also because the fascination of clinical studies has always attracted keen minds, we believe that in the new series our problems will be those of selection rather than of any need to instigate contributions, once the series is well under way.

In this belief, we approach our task as editors with some trepidation, but also with a good deal of confidence in the future of the series.

FOREWORD

The Research Committee of the World Federation of Neurology meets annually to discuss problems in demyelinating disease and to report on changing outlooks and "growing points" in our knowledge. It is to be expected when workers with an active interest in a field come together, that many of the "facts" which appear well established to those outside the domain are "soft" when considered critically and it is the recognition of this and subsequent attempts to harden our data which can be the most important function of small workshop-type meetings. To this end it is important to record the opinions expressed in free discussion of presented work, the latter often constituting little more than a provocative formulation as seen through the eyes of a particular worker. All care was, therefore, taken at the present meeting to record the exact comments and criticisms (and even aspersions!) made and these have been reproduced with a minimum of syntactical editing so that the doubts and uncertainties, the optimism and the confusions which pervade the topic may be appreciated. Not only may such a confessio medici clear our own minds but also it is hoped it will encourage younger workers - with their special advantage of freshness of outlook and freedom from the burden of preconceived notions - to pick out a true path in the tangle of facts and quasi-facts which have accumulated over the last century.

This recording and editing - performed to a strict time-table - has only been possible through the outstanding co-operation of all our participants, through the unstinting helpfulness of our secretary, Miss Margaret Herron, who prepared the final manuscript drafts for printing, and the unflagging efforts of our recording engineers and members of the department of photography, and Miss Joyce Davison. To all these we would express our deep thanks. Last and not least we wish to thank also Miss Greta Joyce and Dr. D. H. Adams who did so much to provide enjoyable and interesting relaxation from a concentrated two day program.

E. J. FIELD

T. M. BELL

P. R. CARNEGIE

Newcastle, England.
September, 1971.

EDITORS' NOTES

a) The meeting and production of this report were supported by contributions from the following:-

The Vice-Chancellor, Professor H. G. Miller, and the University of Newcastle upon Tyne.

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Multiple Sclerosis Research Fund Limited.

Ward Blenkinsop & Company Limited.

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b) Unfortunately due to the limited time available for the printing of this report it was not possible to include any of the photographs and electron micrographs which were shown at the meeting. Most illustrations and diagrams were photocopied directly from slides presented, consequently some of the lettering became almost illegible after photo-offset printing. However, these illustrations have been retained because of the importance of the graphical information.

c) Manuscripts of papers marked † were not received. The editors prepared a summary from a transcript of the talk.

d) Discussion of the papers by Drs. Eylar, Roboz-Einstein and Riekkinen and Rinne were incorporated in the "General Discussion of Biochemical Aspects". The five papers on epidemiology were discussed as a group.

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First Session

VIROLOGY

Chairman:
Professor J. N. WALTON

VIRUS ANTIBODIES IN SERA OF PATIENTS WITH MULTIPLE SCLEROSIS, IN CONTROLS MATCHED FOR AGE, SEX AND PLACE OF RESIDENCE, AND IN SIBLINGS

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The strongest evidence for an infectious factor in the pathogenesis of multiple sclerosis (MS) is provided by serologic studies (Adams & Imagawa, 1962; Panelius et al., 1971). In the majority of studies, increased levels of measles antibody have been found. This is of special interest after the success in confirming a relation between subacute sclerosing panencephalitis (SSPE) and measles. The difference between antibody levels to measles in these two diseases is, however, marked. Moreover, there are no reports of increasing antibody titre to measles during progression of MS as there are in SSPE. Nevertheless, the viral serology of the character and function of antibodies to measles in MS should have a high priority.

The selection of control material is of importance. Every MS patient should have a matched counterpart of the same sex, age and living area. The specimens of both groups should be tested simultaneously with a double blind technique. In addition to the matched controls, the siblings of patients with MS are of interest because of the reported increased rate of high measles antibody titres (Henson et al., 1970).

Measles antibody titres are dependent on the serological techniques used. In addition to neutralisation (NT), complement fixation (CF) and haemagglutination inhibition (HI) methods several others have been introduced during the last year in MS serology (Panelius et al., 1971).

In this preliminary report we are presenting computer analyzed results of a serological and epidemiological survey of a project including material from an MS group, a sibling group and a control group. Three levels of risk areas of different incidence of MS in Finland were chosen on the basis of earlier studies (Rinne et al., 1968).

The serum material consisted of 220 specimens from patients with multiple sclerosis, 215 matched controls and 158 siblings of the MS patients. Of the total 593 study subjects, 344 were from a high risk area, 144 from a low risk area and 105 from a medium risk area.

The MS patients were screened by two neurologists on information from the records of the hospitals and the National Pensions Institute. The Health Insurance Register was used for selecting for each MS patient a matched partner of the same sex and year of birth and the same living area. A sibling was accepted from the sibling control group whose age matched within five years, and preference was given to the same sex. Each selected study subject was interviewed by a trained nurse who also filled in a questionnaire. A blood specimen was taken at the same time.

When the geometric means (GM) of serum CF antibody titres of all the MS, sibling and control groups were compared with one another, no significant differ-

ences were found in antibody titres to para-influenza 1, herpes simplex, Eaton, varicella zoster, mumps or measles.

However, measles HI and SDI (salt dependent haemagglutination inhibition) antibody levels of MS patients were very significantly higher ($p < 0.001$) than in the control group.

Almost all of the specimens produced one or two measles-specific precipitation lines in the gel precipitation (GP) test. Only 4.8 per cent of MS patients and 14.0 per cent of the controls had a negative GP test. When specimens producing 2 or more lines were grouped together we found that they formed 53.4 per cent of the MS specimens, 33.5 per cent of the siblings and 29.0 per cent of the control specimens.

The statistical differences were highly significant ($p < 0.001$) both between patients and controls and between the patients and siblings. Similar results were noted if males and females were grouped separately.

The strength of the GP reaction was determined both by counting the number of precipitating lines and by approximating the intensity of the individual reactions. The most intensive (grade 3) reaction was seen more often in the specimens of MS patients (43.3 per cent) than in the siblings (21.9 per cent) or controls (19.6 per cent).

The differences between the MS group and siblings or control groups are highly significant ($p < 0.001$). The differences are similar if males and females in these groups are compared separately.

When the measles antibody levels were analyzed with HI and SDI tests in various risk areas, statistical differences could be demonstrated only in high risk and medium risk areas. The difference in GM between MS-patients and controls by HI test in the high risk area was significant ($p < 0.01$), by SDI test between MS patients and controls in the high risk area highly significant ($p < 0.001$) and between siblings and controls almost significant ($p < 0.05$). In the medium risk area there was an almost significant difference ($p < 0.05$) between the MS patients and controls with the SDI test (table I).

Table I

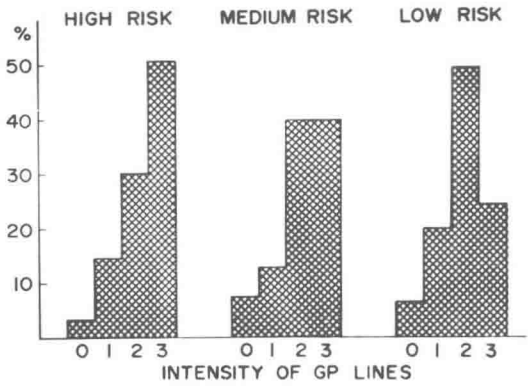
GM of antibody titres to measles virus antigen measured with HI and SDI tests by various risk areas: N = number of cases

Study group	HI - test			SDI - test		
	High risk	Low risk	Medium risk	High risk	Low risk	Medium risk
MS-patients	$33.8^{++)}$	30.6	31.2	$170.8^{+++)}$	93.2	$127.0^{+)}$
	N. 128	N. 50	N. 42	N. 127	N. 50	N. 42
Siblings	30.5	26.1	27.9	$128.9^{+)}$	46.9	97.1
	N. 94	N. 39	N. 25	N. 93	N. 39	N. 25
Controls	$25.3^{++)}$	23.6	22.1	$73.8^{++++)}$	5.34	44.6
	N. 122	N. 55	N. 38	N. 121	N. 55	N. 38

Specimens taken from the high risk area had a greater number of GP lines than those from the other areas. Similarly the intensity of the reaction was of higher degree in that area than in the medium and low risk areas. This difference in the MS group can be seen in Fig. 1.

When the measles antibody results were analyzed according to the onset of disease of the MS patients it was found that the CF antibody level was the highest

Fig. 1



in the patient group which had the onset of clinical symptoms in 1960-1969 but the HI and SDI titres were the highest among the patient groups with the onset of the disease 10-20 years earlier.

Table II
GM of antibody titres to measles virus antigen measured with various techniques by disability grade. N = number of cases.

Disability Grade	TEST			
	PA	CF	HI	SDI
1	6.2 N. 33	9.9 N. 36	37.1 N. 37	160.0 N. 36
2	4.0 N. 41	6.5 N. 45	30.7 N. 47	193.8 N. 47
3	5.2 N. 48	7.1 N. 49	34.9 N. 49	189.6 N. 49
4	3.9 N. 23	3.9 N. 21	30.5 N. 23	95.9 N. 23
5	5.8 N. 29	4.8 N. 31	31.3 N. 34	94.2 N. 34
6	2.0 N. 26	4.0 N. 24	32.3 N. 29	109.2 N. 29

When MS patients were divided into groups according to the clinical

course of the disease, no differences could be found between these groups by any of the serological tests used. When, however, antibody titres to measles virus in different disability groups were compared, there was a tendency for lower CF and SDI titres to occur with higher disability (after Hyllested, 1 for no disability, 6 for total helplessness) (Table II). Eight per cent of MS patients reported that they contracted clinical measles at 15 years of age or older compared with 2.5% of the sibling and control groups, but these differences are not significant. There were no differences between the groups in regard to the frequency of reported infections of whooping cough, diphtheria, varicella, herpes zoster, rubella, scarlatina and tuberculosis. However, individuals in the control group reported almost significantly ($p < 0.05$) higher frequencies of rheumatic fever than MS patients. A negative measles history was presented slightly more often by the subjects of the control and sibling group than the MS patients.

The presented results confirm again that the antibody level to measles virus in serum from patients with multiple sclerosis is significantly higher than in a control group. The difference between the antibody levels was however, highly significant only by HI, SDI and GP tests. The inter-relationship of these tests is interesting, because the different tests are probably measuring antibodies against quite different antigenic components (Panelius et al., 1971).

The original finding of Brody and his collaborators (Henson et al., 1970) indicating a higher antibody level to measles in the sibling group is also confirmed in the present study. Other tested virus antigens did not show any differences between the MS patients and the controls.

The antibody levels of MS patients in various risk areas have not previously been studied. The present results indicate that antibody level to measles is higher in high risk areas than in low risk areas. These findings support the hypothesis that measles virus could have something to do with the pathogenesis of multiple sclerosis. Whether the cause of the higher level of antibodies in high risk areas is a more virulent form of measles infection or whether the differences are connected with different age incidence and/or hereditary factors, cannot be concluded from the data presented up to now. The females in all of the study groups had a tendency to react more strongly in the different measles tests.

SUMMARY:

Preliminary results from a field study consisting of 220 patients with MS, 158 siblings of MS patients and 215 controls matched as to age, sex and living area are reported. In serological studies further confirmation of the selectively higher level of antibodies to measles virus antigens with haemagglutination inhibition, inhibition of salt dependent haemagglutination and gel precipitation tests was provided. The earlier observations on the increased antibody level to measles in siblings of MS patients was also confirmed. The population in high incidence areas of MS disease had a higher level of antibodies to measles than the population in low incidence areas.

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