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GUEST EDITORIAL

Multiple Sclerosis

A COMPENDIUM OF PRESENT KNOWLEDGE

Basil Grogono, MB, BS, FRCS

Guest Editor

Multiple Sclerosis (MS) is one of the most distressing and common disorders. It affects young healthy adults between the ages of 20 to 40 in unpredictable and highly variable ways. A young woman may suddenly notice defective eyesight, a young man notes tingling and weakness or incoordination of his limbs. Alterations and difficulties in control of micturition or transient paralysis herald further distressing symptoms such as slurred speech or unexpected changes in mood.

Often the diagnosis is delayed and prognosis doubtful. Sometimes the initial symptoms clear up and there are no more developments for years. In other instances, there is a rapid progress of neurological symptoms leading to extensive paresis or complete paralysis.

Most authorities agree that the disease is common in northern climates, and a data base on incidence in Canada has now been established. Despite many years of research, the disease remains an enigma. Unlike tuberculosis, poliomyelitis and smallpox, where specific therapy or immunization has had a dramatic impact, there is no such remedy or prevention for sufferers of MS. Fortunately in Canada and the United States, the Multiple Sclerosis Society is very active in combatting the impact of the disease and in establishing active research programs.

This issue endeavors to present some examples of the excellent research in progress, gives some idea of the significance and future application of the recent findings from different centers.

Incidence and Diagnosis

Professor D.W. Paty, from the University of British Columbia, has become a leading authority on Magnetic Resonance Imaging (MRI) of the nervous system in multiple sclerosis. Somewhat surprising is his finding that there are significant changes detectable in the patients with the disease, which vary in size and distribution. Some lesions are asymptomatic, others variable. Using MRI in patients with multiple sclerosis and in their relatives, may be a tremendous help in the understanding of the disease process and in monitoring the response to treatment.

Professor B. Ziola, from the University of Saskatchewan, presents an excellent paper on T-cell response in multiple sclerosis. To the uninitiated, the numerous abbreviations of medical terms seem almost difficult to comprehend. However, with the assistance of the diagrams it is hoped that family practitioners, specialists and patients will be able to comprehend the significance of his excellent paper.

Professor George Ebers, for the Multiple Sclerosis Clinic at the University Hospital, London, Ontario, is a recognized authority on genetic factors in multiple sclerosis. His paper discusses the influence of environmental factors, geographic distribution and the influence of genetic factors in the incidence of the disease, paying particular attention to the study of twins. The topic is complex, being that the studies seem to show that there is a polygenetic background on which environmental factors play.

Dr. T.J. Murray has an international reputation. As Dean of Dalhousie Medical School, not only does he direct the Nova Scotia Multiple Sclerosis Research Unit but he has been chairman of the Medical Advisory Board of the Federation of Multiple Sclerosis. This Federation publishes numerous articles and coordinates a wide variety of research. Dr. Murray's beautifully graphic description of a young man's struggle with multiple sclerosis highlights the progressive process of the disease and his brave attempts to deal with his ever changing situation.

Dr. R.L. Kirby has extensive experience in many aspects of rehabilitation. His contribution to wheelchair patients with multiple sclerosis shows real understanding of the problems of ensuring that the wheelchair or device is what the disabled person really needs.

Paul Gouett has been a victim of multiple sclerosis for many years. As a young biochemist, he became suddenly paralyzed. At first he could continue to use his upper limbs but gradually he lost their use and retained function only of his neck and cranial muscles. His brain and indomitable spirit remain. His contribution, typed on his home computer, is a superb example of concise, informative and impressive writing.

The Multiple Sclerosis Society of Nova Scotia is an active and enthusiastic organization. It is hoped that some of the dreams of those with multiple sclerosis will be answered by the assiduous work so many people are devoting to the study of this disease. □

The Editorial Board Members wish to express our thanks to our Guest Editor, Dr. Basil Grogono for his efforts in making this issue on Multiple Sclerosis possible.

Multiple Sclerosis Society of Canada

ATLANTIC DIVISION

Established in 1974, the Atlantic Division of the Multiple Sclerosis Society of Canada serves the four provinces of Atlantic Canada. A non-profit health organization, the Atlantic Division is managed by a volunteer Board of Directors from across the Atlantic region. The mandate of the Society is to fund research into the cause and cure of MS, to provide services to individuals with MS and their families, and to promote public awareness of MS.

The Atlantic Division is involved in the provision of many programs and services such as:

- Education and information dissemination through library and video loan, pamphlets, *MS Atlantic* newsletter, presentations, and an annual Conference;
- Support services for individuals with MS and their families through self-help, spousal support, and one to one support groups;
- Equipment and Special Assistance Programs providing equipment and funding for individuals with MS who are unable to get support from other community resources;

The Society has 23 chapters and units throughout New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland. These individual chapters and units sustain heir own recreational and support programs and meet on a regular basis throughout the year.

Each chapter and unit is actively involved in the fundraising and public awareness activities of the Atlantic Division. fundraising campaigns include the Carnation and Residential Campaigns, which fall under the umbrella awareness campaign entitled "May is Multiple Sclerosis Awareness Month".

The Society has a budget of $700,000 and besides providing service for individuals and families of Multiple Sclerosis, they donated $233,000 to Research Fund.

There are approximately 50,000 Canadians with Multiple Sclerosis, a ratio of 1.8:1 for women aged 20 to 40. Canada has the highest prevalence in the world. □

In treating their anxiety...

are benzodiazepines always appropriate...?

Correspondence

To the Editor:

ON BEING WRITTEN OFF

In 1992, for the first time in 30 years, my name will not appear in a medical register. My thoughts on this change follows.

I glanced at the letter from the Medical Board of Nova Scotia and hastily tucked it back in the envelope. It was too depressing to face now. I would read it when I was alone and could let the tears flow without having to explain them.

Two weeks passed before I found the courage to re-read the letter. The Board was eliminating the "Retired List" from the N.S. Medical Register. To practise, one had to pay a licensing fee. That sounded reasonable enough. I would never practise again, and needn 't pay the fee. Why was I so upset about being written off? What were the implications of not being listed in the Medical Register?

How would colleagues get hold of me if I weren't listed in the directory? (Be logical now; how many doctors need to get hold of me?) What if I wanted to prove my credentials? I tried to think why this might be necessary. The bit of teaching I do for Dalhousie Family Medicine could continue without registration, but what if a medical journal accepted an article and wanted to confirm my professional status?

Would my membership in the N.S. Medical Society continue or would they be retiring me? Would I be knocked off the mailing lists? Would I still get the N.S. Medical and CMA Journals? The Board's Newsletter and directory? "Junk" journals? The newsletters and free journals that are a nuisance in an office can keep a housebound physician in touch with her profession.

I was manufacturing arguments for being listed, and I knew it. I called the Medical Board to clarify the ruling and put my mind at ease. Dr. Steele answered my questions kindly, with the understanding of a wise doctor reassuring an overly anxious patient. Others had reacted similarly to the notice. "Will I still be a doctor?" someone had asked. I chuckled, not at his misgivings, but at my own. I could adjust to this as I had to the other stages of surrendering my practice.

The process had started in Montreal 10 years ago. "I'm going home. Cancel my appointments for two days," I said to my secretary, reluctantly admitting that I was sick. I had not been ill for years.

I never returned to practice. Later, in hospital, I fought the spectre of long-term disability. Another doctor moved into my office. I phoned the McGill personnel officer. "I hate to retire," I said, "it's bad enough to be sick without being unemployed as well." "But you're not retiring," she comforted, "you're resigning." When co-workers brought me a farewell gift, the card said "On Your Retirement." I was so choked up I could hardly thank them. I wasn't ready to retire at 53.

When I moved to Halifax, my doctor was still holding out some hope of recovery, so I registered with the Medical Board of N.S. Recovery never came. I moved to the retired list, studying it to find other retirees my age. They had all graduated much earlier. Wasn't there a better word than "retired"? I hadn't quit early because I was lazy; I was disabled.

As my armchair activities increased, I wrote, facetiously, "retired but retreading." Retreading didn't get me back on the road. After several of my articles were published, I became inured to seeing "retired" after my name. I accepted my state until the Medical Board decided to retire the retirees.

Sick, resigned, unemployed, disabled, retired, and now retired from retirement – written off, forgotten. Forgotten? So that was the fear that was causing all my anxiety. Fear, once identified, can be faced. The solution is up to me. I have a telephone, a voice, a pen, a computer, and an on-going interest in medicine.

Dear colleagues, you won't find my name in the register, but don't write me off. Keep in touch, for you'll continue to hear from me.

Yours truly,

Anna Mary Burditt, M.D., CCFP, FCFP, Retired
1200 Tower Rd., Apt. 606
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Magnetic Resonance Imaging in the Evaluation of Patients with Multiple Sclerosis

Donald W. Paty,* MD, FRCPC

Vancouver, B.C.

Diagnostically abnormal magnetic resonance imaging (MRI) head scans can be seen in about 90% of patients with clinically definite MS (CDMS).[1] (See Figure 1). In addition, serial imaging of individual patients often shows the asymptomatic accumulation of new lesions, lesion enlargement, and striking changes in the blood brain barrier (BBB) with time. This MRI detected disease activity provides an objective measure of disease that is partially independent of changes in clinical neurological function.[2] Serial and quantitative MRI studies thus provide objective supportive data for clinically documented stabilization or improvement of function.

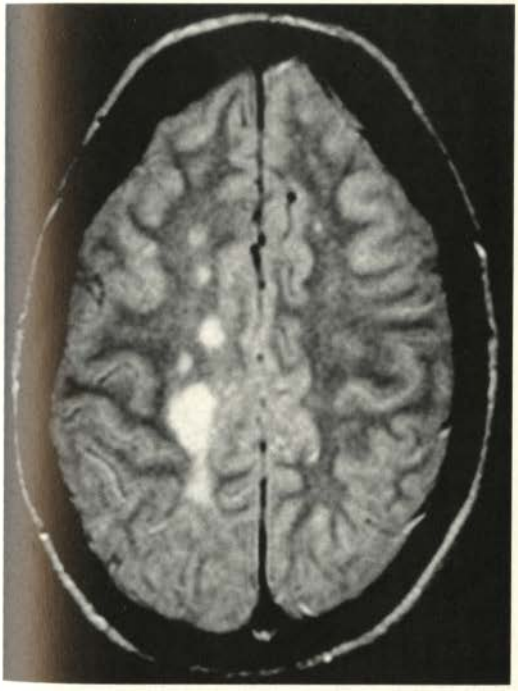

Figure 1

This Figure illustrates multiple lesions on a T2 weighted scan above the level of the ventricles. The MS lesions are the white areas. *Note* that any of these lesions could be temporary, so one single scan does not allow the determination of exactly which lesions are chronic and which lesions are acute. Gadolinium enhancement many times will distinguish between acute lesions and chronic ones by showing a leaky blood brain barrier.

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However at this time, MRI cannot determine the pathology of individual lesions reliably. The appearance of MRI lesions seen on coronal MRI slices in patients with MS is very reminiscent of the classical appearance of periventricular demyelination seen at autopsy. Stewart and her colleagues[3] and Ormerod *et al*[4] have carried out correlation studies between pathology and the MRI image on formalin fixed MS brains. Their analysis showed good concordance between the areas of abnormality on the MR images and the histopathology. They concluded that the abnormalities seen on the MRI scan originated from chronic plaques of MS. Stewart found also that the MRI scan underestimated the degree of abnormality. Newcombe and colleagues have completed an MRI correlation study on 17 MS cases using unfixed brain material.[5] In contrast to Stewart's findings, Newcombe found the MRI abnormalities to be more extensive than the actual plaque areas, suggesting, to them, that edema in otherwise normal appearing white matter contributed significantly to the MRI findings.

MRI AS AN AID IN DIAGNOSIS

The mainstay of the diagnosis of MS is the clinical evaluation. No single clinical or laboratory finding is diagnostic. A number of diseases (both old and newly recognized) can have features that suggest MS, and the clinician must be very wary of making the diagnosis unless these disorders can be clearly excluded. The diagnosis of MS depends upon the ability of the physician to determine that white matter lesions are disseminated in both time and space and cannot be explained on another basis. Schumacher and his colleagues gave an excellent explanation of this principle which has served for many years as the standard diagnostic guide for MS.[6] In addition to showing dissemination of white matter lesions in time and space, the physician must take into consideration that the risk for MS is high in young adults; in women; in those of Northern European caucasian descent; in persons who spend their childhood years in temperate latitudes; and in first degree relatives of patients who are known to have MS.

The last 15 years have seen considerable improvement in making the diagnosis of MS both earlier and more accurately. A number of procedures have been developed which detect either immunological evidence for CNS inflammation, such as CSF electrophoresis for oligoclonal banding (OB), or help in the detection of clinically asymptomatic lesions disseminated in space such as evoked potentials (EP), computed tomography (CT) and MRI. At UBC, we did a prospective study of 200 patients with clinically suspected MS.[7] The patient sam-

ple included 52 patients with chronic progressive myelopathy (CPM), and 38 patients with optic neuritis (ON). All patients were entered into a prospective evaluation protocol using EP, MRI, CT, and CSF evaluation for OB.

Using conservative criteria for interpreting the MRI, it was determined that MRI was the best procedure for demonstrating asymptomatic dissemination in space. Follow-up studies on the same cohort have shown that abnormalities on the MRI or the presence of OB were very strong predictors for the development of CDMS.[8] It is interesting to note that abnormal EP, suggesting asymptomatic dissemination in space, could be helpful in making a diagnosis of laboratory supported definite MS (LSDMS).[9] However, the EP usually did not contribute anything diagnostically if an MRI was available. MRI was twice as sensitive for detecting asymptomatic dissemination in space as were the EP.

A tendency has developed for overenthusiastic interpretation of MRI findings for the diagnosis of MS.[10] MRI abnormalities must be considered in an appropriate clinical perspective. For example, it is difficult to use MRI when evaluating patients over the age of 50, because of the frequency of non-specific findings that occur with increasing age. In addition, MRI cannot distinguish between various tissue characteristics such as edema, infarction, inflammation, or demyelination. In the future, various MR techniques, including MR spectroscopy will help in the identification of specific tissue abnormalities. Now however, in spite of these problems, MRI evidence for dissemination in space, when interpreted conservatively, taking into consideration the clinical presentation and results from other studies, can be used as strong evidence for the diagnosis of MS, particularly in patients under the age of 50.

MRI IN THE EVALUATION OF DISEASE ACTIVITY

Clinical severity, as measured by the EDSS is determined to a great extent by the location of lesions.[11] Spinal cord lesions are much more important than others in determining motor disability. However, most MRI studies in MS have imaged the head and not the spinal cord. However in head scans, MRI gives a reasonably accurate measure of the extent of the disease process .

MRI is being used more and more in the assessment of therapeutic trials. In a prospective evaluation of 100 patients, during a placebo controlled therapeutic trial of alpha lymphoblastoid interferon, 80 of the subjects had quantitative MRI evaluations at entry, at 6 months, and at 2 years.[12] An MRI quantitation technique was used to analyze the MRI changes that occurred over time. The changes in the "burden of MS" ranged from -70% to +221% over 2 years. (The mean change in extent was +21%). The results were disappointing in that no significant difference was seen between the treated and placebo groups of patients, in either the clinical or MRI measurements. However, this experience has shown that a quantitative measure of disease burden by MRI can contribute important information to the assessment of outcome in MS clinical trials.

Early experience with intermittent MRI scans showed that chronic lesions could be seen to increase in size and asymptomatic lesions could be seen to come and go.[13,14] It quickly became apparent that disease activity, as measured by MRI, could be quite dynamic and was often subclinical. Therefore, systematic serial studies combining frequent neurological and MRI examinations were done.

Three MRI natural history studies have been completed at UBC. Frequent (biweekly or monthly) carefully repositioned MRI scans were performed over 5 to 6 months duration. MRI activity events were defined as follows:

a) *new lesions* were those that had never been seen before and developed in previously normal areas of white matter.

b) *reappearing lesions* were those which reappeared at the same site from which an earlier lesion had disappeared.

c) *increasing size (enlarging) lesions* were those that increased in size from a previously seen stable appearance. *Significant enlargement* was measured as approximately a change of more than 70% in small (< 1cm) lesions or a change as little as 10%, which was usually obvious, in larger lesions.

Any of the above changes was considered to be signs of increasing disease activity. However, if a lesion enlarged continuously in repeated scans, for the purpose of these studies, it was counted as only one disease activity event.

In the 3 studies done a total of 24 patients were assessed.[15,16,17] (See Table I). Most of the MRI changes seen were asymptomatic. The rate of appearance of new MRI lesions was 5 to 10 times the rate of clinical evidence of activity.

TABLE I

THREE SERIAL STUDIES DONE AT UBC

Study No.	Ref No.	No. Pts	Relapse Category	Rate* Of Clinical Relapses	Rate Of New MRI Lesions	Rate Of Active MRI Lesions	Rate Of Active Scans**
1	21	7	RR	1.4	4.9	7.7	4.9
2	22	9	RR	0.4	2.0	3.1	2.6
3	23	8	RP	0.0	6.25	21.5	12.5

* No./patient/year

RR Relapsing Remitting

RP Relapsing Progressive (chronic progressive after a relapsing start)

** An active scan is any scan in which there is a new or enlarging lesion. A continuously enlarging lesion (new or otherwise) is only counted as one activity event. For example, if a new lesion continues to enlarge over 3 or 4 scans before it begins to fade, it is only counted as one activity event on the scan in which it was first seen.

This table is based on Table 1 in the chapter Outcome Measures by DW Paty, E Willoughby and J Whitaker in *Treatment of Multiple Sclerosis* by RA Rudick and DE Goodkin. Berlin: Springer-Verlag, 1992.

Other MRI serial studies have been reported, some using gadolinium (Gd).[18,19,20,21,22,23] (See Table II) Up to 90% of new MRI lesions enhanced with Gd, and occasionally an enhancing area was seen before the standard MRI lesion was seen.[19] Spinal cord imaging added about 20% to the activity rate seen using head scans alone.[21]

TABLE II

OTHER SERIAL MRI STUDIES

Senior Author	Ref No.	Year	Type Of Patient	Activity Rate Comments Clin+ MRI*
Miller	24	1988	RR	MRI activity higher than clinical. All new MRI lesions enhanced
Kermode	25	1990	RR	Gd enhancement can precede standard MRI lesion
Bastianello	26	1990	Mixed	All new lesions enhanced
Wiebe	27	1990	Mixed	Spinal MRI of limited value since it increased the yield of activity by only 10%
Tanton	19	1990	RR	6-weekly MRI's used to monitor a treatment trial with Beta Interferon. MRI activity rate twice the clinical rate
Harris	28	1990	RR	MRI activity greater than clinical
Thompson	29	1991	I°CP	Pattern differs from RR and RP. These primary CP patients have a low number of small non-enhancing new lesions
Smith	30	1991	RR	Continuation of Harris study. Lesion activity comes in "bursts"

RR Relapsing and remitting
RP Relapsing progressive (chronic progressive after a relapsing start)
\+ Relapses per patient per year
* Active scans per patient per year
I°CP Primary chronic progressive (progressive from outset without relapses)

This table is based on Table 4, Outcome Measures, by DW Paty, E Willoughby and J Whitaker, in *Treatment of Multiple Sclerosis* by RA Rudick and DE Goodkin, Berlin: Springer-Verlag, 1992

Thompson and his colleagues found that primary chronic progressive (I°CP) MS patients had the lowest rate of development of new lesions, very few of which were enhancing, suggesting a fundamental difference between relapsing MS and I°CPMS.[24]

Unfortunately the rate of MRI activity varies considerably over time even in the same patient. A given patient can be active over a 3-month period of time and then be totally inactive over the next 2 or 3 months. Unfortunately, such variability means that a "run in" period of scanning prior to the start of a clinical study does not predict the subsequent MRI activity that will be seen in that individual patient.

At UBC we are currently using MRI assessment of disease activity in a therapeutic trial by scanning patients once every 6 weeks. We have seen an MRI activity rate of 3.0 active MRI scans per patient per year that is twice the clinical activity rate (1.5 relapses per patient per year).[25]

Follow-up on the 24 patients evaluated by the first serial studies performed 5 years ago at UBC, has shown that the patients who remained clinically stable during that time had a lower initial rate of MRI activity than did the patients who subsequently deteriorated clinically (See Table III). However, there was considerable overlap in activity rates between the groups and the differences seen were not statistically significant. Therefore we do not have clear-cut evidence that a high MRI activity rate is predictive of a bad clinical outcome.

TABLE III

THREE UBC SERIAL STUDIES

CLINICAL FOLLOW-UP ON 24 PATIENTS IN THE ORIGINAL UBC SERIAL STUDIES (ABOUT 2 YEARS FOLLOW-UP)

	Clinically Worse	Clinically Stable
Number of patients	7	17
Average No. active lesions during study	9.9 (2-26)	3.4 (0-13)
Average No. new lesions	3.1 (1-6)	1.7 (0-5)
Average No. reactive lesions	6.8 (0-20)	1.6 (0-9)

CONCLUSIONS

The most immediate impact of MRI has been to aid in the diagnosis of MS. In addition, experience has shown that both quantitative and serial MRI studies can reveal a new aspect of measurable activity of the pathological process. In the long run, assessment of disease activity may turn out to be the most important contribution of MRI to the understanding of MS. The degree of activity, revealed by serial MRI studies, is considerably greater than the degree of activity determined by history and physical examination. In addition, the extent of the abnormality, as seen on MRI, can be measured by outlining the lesions and summing the areas of abnormality slice by slice. A markedly dynamic yet asymptomatic nature of the MS pathological process has been revealed by frequent systematic serial MRI studies. However, careful clinical follow-up studies must be done in order to determine the prognostic implications of these MRI data. In the meantime, frequent MRI scanning is considered to be a necessary method of assessment of disease activity in major therapeutic trials. A quantitative approach to the MRI scan is complementary to the clinical evaluation and it is an important measurement of outcome for clinical research studies.

Common sense would suggest that if one could reduce the rate of MRI or clinical activity events with a new therapy, then the ultimate outcome of the disease would

also be improved by that therapy. This is the strategy that has been used for the treatment or suppression of relapses in previous therapeutic trials. We are faced with exactly the same problem in using MRI studies. It is not yet proven conclusively that activity, as detected either by relapses or by MRI scan changes, is a clear-cut predictor of the ultimate clinical outcome in our patients. Even today clinical relapse rates are not firmly established as accurate prognostic markers. So, until clear-cut indications are provided for the use of multiple MRIs in patient management, other than use for diagnosis, the technique of disease activity assessment by serial and quantitative MRIs scans must remain a research tool. □

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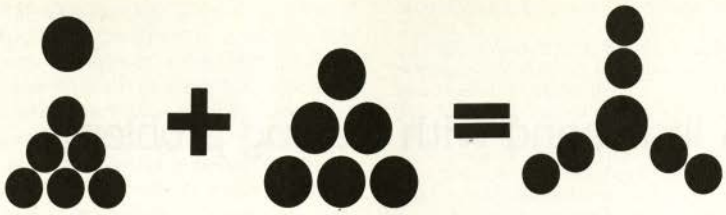

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Evolving Aspects of T Cell Immunity in Relation to Multiple Sclerosis

Barry Ziola,* PhD

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In a two-part review published in 1982, McFarlin and McFarland state that the cause and pathogenesis of multiple sclerosis (MS)* remain unknown and that no preventive measures or definitive therapies for MS exist.[1] The situation in 1992 unfortunately remains essentially unchanged. Nonetheless, the intervening decade has seen considerable effort devoted to delineating immunological events occurring in MS patients. This research focus is not surprising, since MS is generally considered to be an autoimmune disease due to the localized inflammatory response involving lymphocytes and macrophages consistently seen in the central nervous system (CNS) of patients. In this article, I discuss what I believe are important recent findings related to T cell immunity and MS.

BBB – blood-brain-barrier;
CNS – central nervous system;
EAE – experimental allergic encephalomyelitis;
IFN – interferon;
IL – interleukin;
MBP – myelin basic protein;
MS – multiple sclerosis;
TCR – T cell receptor

T CELL SUBSETS

While many aspects of T cell immunity in MS patients remain controversial, it has been confirmed that MS patients show fluctuations in the level of T cells thought to be associated with immunoregulatory function. Antel and colleagues were the first to report that lymphocytes from MS patients have altered ability to mount immunosuppressive responses in vitro.[2] This effect was initially suspected to be due to altered function in CD8+ T cells. This view changed based upon work with monoclonal antibodies identifying the common leukocyte antigen CD45 which showed that MS patients have changes in the CD4+ T cells regulating ability of CD8+ T cells to cause suppression of immunoglobulin synthesis in vitro.[3-5] Because decreases in CD45+ CD4+ lymphocyte levels are frequently associated with MS disease exacerbations, it was suggested that altered immune regulatory mechanisms are allowing autoimmune effector T cells to function.[5] However, it is possible the CD45+ CD4+ T cells disappearing from the peripheral blood of MS patients are playing direct role in pathogenic events occurring in the CNS of MS patients.

Human CD45 is now known to exist in a number of isoforms.[6] By analogy with murine lymphocytes, human CD45+ CD4+ T cells with high levels of isoform B are likely associated with memory cells having characteristics of a type 1 helper T cell.[6] Such T cells upon activation preferentially produce interleukin (IL) 2 and interferon (IFN)-gamma, which distinguishes them from type 2 helper T cells producing mainly IL4 and IL5.[7] Until recently, it was believed that the equivalent of mouse or rat type 1 and 2 helper T cells did not exist in humans, since alloreactive or mitogen-stimulated human CD4+ T cell clones generally did not neatly fit into either expected pattern of lymphokine production. However, determined work by Romagnani and colleagues has now shown that human type 1 and type 2 helper T cells with stable and expected patterns of lymphokine production are found in humans.[8] Accumulation of one or other CD4+ cell type occurs in patients with different diseases and, if T cells specific for a given antigen are analyzed, it is clear that helper T cells of predominantly a type 1 or type 2 phenotype are involved.[8] If this information is put together with recent work looking at ability of CD4+ T cells with high and low levels of defined CD45 isoforms to effect or prevent autoimmunity in rats, the suggestion that a subset of CD45+ CD4+ T cells could play a direct role in MS lesion formation becomes worth considering.[6] In particular, recruitment to the CNS of activated type 1 CD4+ T cells secreting IL2 and IFN-gamma could in large part explain the inflammatory nature of demyelinating lesions.

IS MYELIN BASIC PROTEIN (MBP) THE ELUSIVE T CELL TARGET ANTIGEN IN MS?

If MS is a T cell-mediated autoimmune disease, then specific immunotherapy of MS potentially is attainable, if the antigenic specificity of the T cells causing disease could be determined. Experimental allergic encephalomyelitis (EAE) is regarded by many as an appropriate model of MS. Because EAE is inducible in many different animals by immunizing with MBP emulsified in an appropriate immune adjuvant, it is evident why MS patient T cell responses to MBP have been extensively studied.

Many laboratories have now documented three basic findings concerning MBP-specific T cell responses in humans; for example.[9] First, both MS patients and healthy controls contain T cells with specificity for MBP. Second, T cell lines reacting with MBP can readily be established from both MS patients and controls. Third, the T cells responding to MBP in MS patients and controls are predominantly CD4+ CD8-. If these findings are put together with the study showing that none of the 57 and 235 cloned T cell lines respectively derived from MS CNS

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lesions and cerebrospinal fluid were specific for MBP, the question that immediately arises is whether MBP-specific T cells alone are sufficient to cause MS.[10] Because MBP-specific T cells make up only a few percent of the T cells in the CNS of animals with EAE, and because MBP-specific T cells either activated in tissue culture or derived from animals with active EAE are required to serial transfer EAE, these suggest that, even in EAE, MBP-specific T cells on their own are not sufficient to cause disease and lesion formation requires recruitment of augmenting non-specific immune cells.[11,12] As already discussed, a type 1 CD4+ T cell able to produce IL2 and IFN-gamma upon activation likely will prove to be the T cell found to fulfill this role.

One additional line of T cell research linking EAE and MS needs mentioning. When EAE is studied in inbred strains or laboratory animals, T cell receptors (TCRs) of MBP-specific T cells show restricted usage of alpha and beta gene variable regions; for example.[13,14] This has meant that immunotherapeutic approaches designed to delete T cells carrying these restricted TCR chain variable regions have proven effective in preventing and in treating EAE.[13,14] If the EAE model is applicable to MS, then restricted TCR alpha and beta chain variable region usage might also be expected and, if found, form the basis for treatment of MS. While reports tending to show common restricted TCR variable chain usage in MBP-specific T cells from MS patients have appeared[15-17], information to the contrary has also been published.[18] If MBP does prove to be the (or one of the) target antigen(s) for the autoimmune process in MS patients, it appears that there will be no universal TCR chain variable region upon which to design an immunotherapy applicable to all patients. Likely, the best that would be possible is that any such immunotherapy could be based upon the restricted TCR chain variable region usage for MBP-specific T cells in each patient.[19] As humans represent an outbred population, a similar scenario is highly probable for immunotherapy based upon the TCR of T cells responding to any autoantigen found to be important in the pathogenesis of MS.

IMMUNOLOGICAL EVENTS LOCALIZED AT THE BLOOD-BRAIN-BARRIER (BBB)

Due to being constructed by endothelial cells with tight junctions, the BBB has long been considered to be impermeable to immune cells and large molecules. This thinking largely was responsible for the dogma that the CNS is a privileged immunological compartment. From magnetic resonance imaging of MS patients, however, it is known that formation of new lesions is dependent upon a localized breakdown in the BBB, with soluble and cellular blood components then infusing CNS tissue surrounding the breached vasculature.[20] Determining how the periodic localized breakdown in the BBB comes about in MS patients clearly is important for understanding the pathogenesis of this disease.

Contrary to the earlier belief that immune cells do not cross the BBB, it is now apparent that small numbers of activated T cells routinely do find their way into the CNS.[21,22] This process probably is mediated by adhesion molecules on endothelial cells in the CNS and by adhesion molecule receptors that are upregulated on activated T cells.[23] Lymphokines, particularly IFN-gamma, secreted locally by activated T cells may actually enhance the expression of adhesion molecules on endothelial cells, such that even unactivated T cells now readily bind.[24]

Once T cells bind to brain endothelial cells, it appears that the integrity of the BBB is locally compromised such that the T cells gain passage into the CNS. This idea has been directly supported by in vitro work with rat brain vascular endothelial cells and rat T cell lines.[25] In this study, brain endothelial cells were damaged either by bound CD4+ T cells that were activated following class II-restricted recognition of specific antigen presented by the endothelial cells or by bound CD4+ T cells that had been activated elsewhere and simply were added to the cultures of endothelial cells. That localized antigen presentation at the BBB can ultimately lead to autoimmune disease has been proposed recently by Cross *et al.*[12] This may be occurring in EAE, as MBP-specific T cells can initiate disease. However, whether a similar antigen-specific mechanism is operative at the BBB in MS patients remains a moot point. Pending further information, CD4+ T cells activated elsewhere in the body and then binding to brain endothelial cells could as easily be initiators of BBB damage.

IMMUNOLOGICAL EVENTS AFTER BBB BREAKDOWN

Once the BBB has been damaged, and soluble and cellular components from blood have entered the CNS, it is likely that several mechanisms can lead to demyelination. From in vitro work, it is known that mature oligodendrocytes are able to fix and activate complement in the absence of antibody, and that soluble factors (e.g., tumor necrosis factor) released by activated macrophages can damage oligodendrocytes.[26] Similarly, perforins and lymphotoxin produced by activated T cells also damage oligodendrocytes, but not astrocytes, in vitro.[27,28] It may be that initial damage to oligodendrocytes in MS patients is done by complement, with the demyelinating lesion then enlarging due to continued involvement of activated macrophages, activated T cells and selected "activated neural cells (i.e., astrocytes, glial cells).

While events leading to initiation and propagation of demyelination are still not clear, there is strong evidence that cytokines play an important role. Immunohistochemical work has shown that IFN-gamma in particular is present on astrocytes and macrophages associated with actively demyelinating lesions.[29] As well, astrocytes and glial cells are known to express class II major histocompatibility antigens upon exposure to IFN-gamma implicating these cells in presenting antigen to at least some of the invading T cells so as to keep ongoing the localized inflammatory response.[30,31] The in vitro finding

that strong class II antigen expression by glial cells occurs upon reexposure to IFN-gamma levels at 1% of the initial exposure level suggests class II antigen expression by these cells in the CNS would easily be maintained by the localized inflammatory response.[31] And in turn, conditions are established for propagation of a localized class II antigen-restricted T cell response.

WHY DOES REMYELINATION STOP?

Detailed electron microscopy studies of new lesions in the CNS of MS patients dying shortly after onset of symptoms has shown that cells with oligodendrocyte properties appear in a new lesion immediately following myelin breakdown.[32] These cells are clearly associated with the remyelination that is occurring in many lesions early in the course of MS. If early lesions show evidence of remyelination, why do chronic or old lesions show little or no remyelination, indicating the remyelination process has been stopped and even been reversed?

The answer to this question may lie in a recent publication by Selmaj *et al.* in which T cells bearing a gamma/delta chain TCR (as compared to the conventional alpha/beta chain TCR) were found in chronic MS lesions.[33] T cells bearing a gamma/delta TCR have received considerable attention lately due to their responding to inducible proteins called heat-shock proteins, likely in a non-class I or class II major histocompatibility antigen-restricted manner. That gamma/delta T cells were found co-localized in chronic MS lesions with oligodendrocytes expressing heat shock protein hsp65 suggests a role for these unusual T cells in stopping remyelination. If the study by Selmaj *et al.* is confirmed, it would mean that MS demyelinating lesions progress from an acute through a chronic/active to a chronic/silent phase, during which the population of T cells associated with the lesion changes from one with predominantly alpha/beta chain TCRs to one with predominantly gamma/delta TCRs.[33] The autoimmune process occurring in the CNS of MS patients thus would take on a new level of complexity.

FINAL REMARKS

The word pathogenesis is defined by Webster's Third New International Dictionary as "the origination and development of a disease". In this article, I have attempted to highlight those aspects of T cell immunity in MS that I believe are important for our coming to know how MS develops. While many aspects of the autoimmune process in MS clearly are still unsettled, I have attempted to convey my impression that the picture of disease-related events occurring in MS patients is slowly being assembled. While existing controversial findings in MS research reflect the difficulty in studying this disease, they should also serve to stimulate the new ideas and experimental approaches that will finally make MS an understood and hopefully treatable disease. □

AUTHOR'S EXPLANATORY NOTE

Pathogenesis of MS: overview based upon recent findings on T cell immunity in MS

- Events through childhood up to onset of MS (infections; mostly viral?) lead to induction and reactivation of autoimmune T cells in genetically predisposed individuals.
- Coincident with disease exacerbations, a particular subset of helper (CD4+) T cells decreases in the blood. These T cells may regulate or actually be the autoimmune effector cells.
- Autoimmune CD4+ T cells, activated elsewhere in the body or at the BBB (through brain vascular endothelial cells presenting specific antigen), bind to and damage the cells forming the BBB.
- Soluble and cellular components of blood infuse the CNS surrounding the BBB breach. Complement, as well as cytokines and other soluble factors released by activated macrophages and T cells lead to oligodendrocyte damage and demyelination begins.
- IFN-gamma secreted by activated CD4+ T cells induces expression of class II major histocompatibility antigen on astrocytes and microglial cells. This allows local antigen presentation and, if sufficient numbers of antigen-specific CD4+ T cells are reactivated, the localized inflammatory response in the CNS is propagated and demyelination continues.
- Once demyelination has started, cells with oligodendrocyte properties move into the lesion and remyelination is initiated. As a demyelinating lesion progresses with time, however, attempted remyelination stops.
- T cells with gamma/delta receptors are preferentially present in older lesions. This type of T cell appears able to directly recognize cells expressing (increased levels of?) heat shock proteins. Since oligodendrocytes undertaking remyelination apparently express selected heat shock proteins, these cells may be targeted for destruction by gamma/delta receptor T cells, thus stopping remyelination.

ACKNOWLEDGEMENTS

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Editor's Comments:

MECHANISMS IN MULTIPLE SCLEROSIS

Several types of cells are involved in the immune response to an antigen. For example, to get an antibody response to most antigens involves participation of four cell types (Figure1). Soluble mediators, including helper factors, suppressor factors and a variety of lymphokines are also involved in directing the T-cell and antibody response to a given antigen.

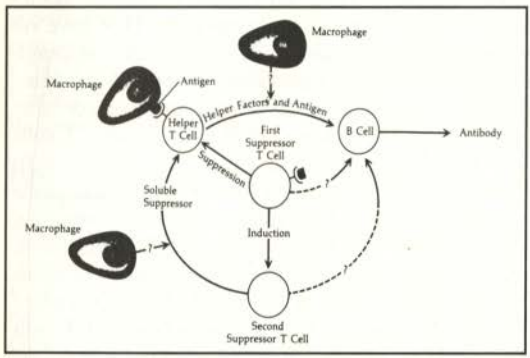

Figure 1

The mechanism of antibody production as illustrated in Scientific American. Induction of T-cells with helper, suppressor, cytotoxic or delayed-type hypersensitivity function involves similar complex networks of different cell types.

The finding of T-cells in brains of patients with multiple sclerosis (MS), but not in brains of normal patients has brought a flurry of research activity which attempts to answer two questions. The first question is how do the T-cells get into the central nervous system of MS patients? Dr. Ziola explains his thoughts on this subject. Once specific T-cells are targeted, the walls of Jericho – the blood-brain-barrier – is locally breached. Other T-cells may be recruited to the site and the inflammatory process established by T-cell recognition of specific antigen results in myelin breakdown. Dr. Ziola also explains the chronicity of the process and suggests why attempted remyelination of affected neurons does not continue.

The second question is what are the antigen(s) in the central nervous system of MS patients to which the targeted T-cells are responding? Is there a specific T-cell response to myelin basic protein (MBP)? Alternatively, are other antigens in the central nervous system stimulating the T response?

The T-cell receptor (Figure 2) is comprised of several proteins. For most T-cells, including those apparently found early on in areas of MS demyelination, antigen is recognized through a T-cell receptor having alpha and beta chains. For other T- cells, however, including those found later in areas of MS demyelination, antigen is recognized through a T-cell receptor having gamma and delta chains. Determining the repetoire of variable regions (Figure 3) of the alpha and beta chains, or gamma and delta chains, of these T-cell receptors likely will go a long way in explaining the immunological mechanisms involved in establishing and maintaining plaques of demyelination in MS patients.

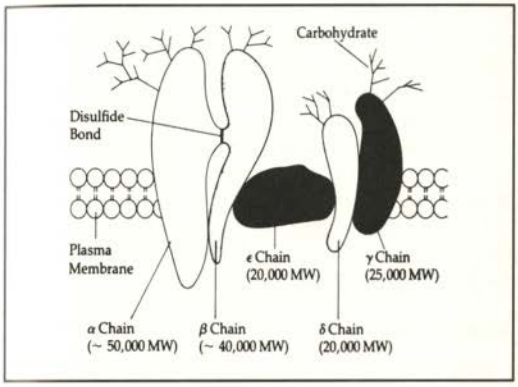

Figure 2

The T-cell receptor is a highly complex structure. This illustration from Scientific American depicts the receptor found on most T cells. For T cells with a gamma/delta T-cell receptor, the alpha and beta chains are replaced by gamma and delta chains of approximately the same size. The other proteins comprising the T-cell receptor remain the same.

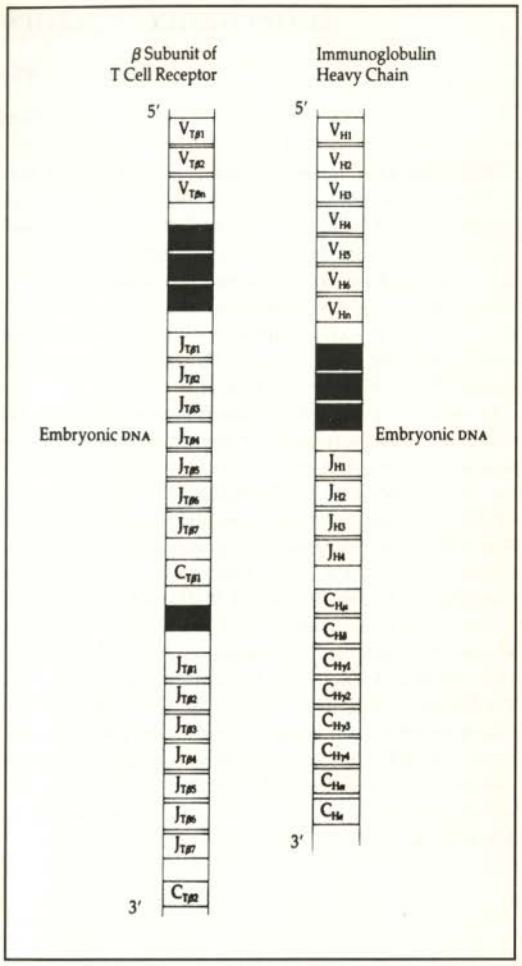

Figure 3

Like antibodies, the two large chains of the T-cell receptor (i.e., the alpha and beta, or the gamma and delta chains) on a given T cell are composed of four regions; namely, the variable, diversity, joining and constant regions. For both T cells and antibodies, the variable region primarily defines the specificity involved in antigen recognition (from Scientific American).

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THE WHEELCHAIR AS A MOBILITY AID FOR PERSON WITH MULTIPLE SCLEROSIS

Continued from page 65.

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Inheritance Factors in Multiple Sclerosis

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There has been increasing evidence that genetic factors have a role in determining susceptibility to MS. Re-examination of results from prevalence and migration surveys reveals that there remains considerable ambiguity in interpretation. Some patterns previously thought to decisively support environmental determination may still be explained, at least in part, on a genetic basis. It seems inescapable that MS is probably due to an interaction of genetic and environmental factors.

It remains undetermined whether or not genes exist which are truly necessary for the development of the disease. Existing data are consistent with the notion that the study of MS susceptibility will parallel the findings in experimental models or spontaneous autoimmunity and that at least two genes will be found to influence susceptibility and interact in as yet unknown ways. One of these loci appears to be the Class II MHC and another with considerably less certainty, the T-cell receptor complex. However, we predict that additional loci will be identified which influence both susceptibility and outcome. Furthermore, it is clear that the understanding of the contribution of individual susceptibility loci will continue to be difficult because of the constraints of human pedigree data. It is likely that further resolution of the questions posed above related to genetic susceptibility in MS will require multicentre collaboration.

The possible role of inherited factors influencing the development of Multiple Sclerosis (MS) has intrigued neurologists for almost a century. Eichhorst labelled MS an "inherited, transmissible" disease.[1] In the nineteenth century, genetic factors were implicated in MS because the disease was observed to occasionally occur in families. By 1950, 85 families were reported in the literature in which there were at least two family members with MS.[2] Genetic analysis of such families led to limited speculation about the nature of susceptibility to MS, although it was clear that the data were inconsistent with fully penetrant Mendelian patterns of inheritance. Concepts of genetic/environmental interactions have been relatively recent developments.

Davenport, studying data from the United States Armed Forces, suggested that the distribution of MS in the United States matched the geographic distribution for immigration from Scandinavia.[3] Pratt believed that susceptibility to MS arose from the presence of two or more independently segregating genes, thus suggesting the concept of "polygenic" inheritance.[4]

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THE DISTRIBUTION OF MULTIPLE SCLEROSIS

Geographic Distribution

The worldwide distribution of MS is not uniform. In general, temperate climates and economically developed countries tend to have higher prevalence rates. In the Northern Hemisphere, the prevalence of MS decreases from North to South and in the Southern Hemisphere, from South to North.[5,6] These geographic patterns have been postulated to result from environmental factors such as climate, diet, e.g. consumption of saturated or unsaturated fats, or the differential presence of an infective agent in a high risk as opposed to lower risk area, which itself could be somehow climate dependent.[7]

Two main lines of evidence support the role of environmental factors in the geographic distribution - migration studies, and geographic trends.

Migration Studies

Studies of migration are much easier in concept than in execution. In principle, studies focus on migrants who move from an area of "high risk" for MS to an area of "low risk" or vice versa. If migrants adopt the risk of their new residence, an environmental cause is believed to be operative. However, a number of undocumented assumptions are often made in migration studies, the most important being that migrants are representative of the country from which they come. It is also assumed that these migrants, when they settle in their new homeland, distribute themselves randomly. In actuality, it is doubtful if either of these assumptions is ever true. The greatest migrations in history have invariably been prompted by religious persecution, wars and other upheavals. As well, migrants are commonly selected for economic, social, religious, health-related and even personality and anthropological characteristics.

Influence of Ethnic Origin

The frequency of MS has been shown to differ among populations of the same ethnic origin, some of whom have remained in the region of origin and others who migrated to areas where MS occurs at a different rate from the region of origin. It was first shown by Geoffrey Dean in South Africa that immigrants tend to adopt the low MS frequency patterns seen in the indigenous population.[8] This trend has been reported for migration to and from both high and low risk prevalence regions.[5,8,9] Not all of these findings can be accepted unreservedly.

The Israeli studies concluded that age at migration was an important risk factor for developing MS. The assumption is made that migrating children and adults are a homogeneous population, a belief which superficially might seem likely to be correct. However, recent work

has suggested that the prevalence of MS is clearly higher among Ashkenazi (European) Jews than Sephardic (African/Asian) Jews.[10] That these two groups are genetically different is shown by differences in the incidence and prevalence of many known genetic disorders between the two populations.[11] After World War II, the period used for Israeli immigration studies, it is likely that there were relatively more Sephardics (African/Asian) among migrating children and relatively more Ashkenazi (European) among migrating adults. The holocaust tended to spare entire Sephardic (African/Asian) families living in Spain, Turkey and Bulgaria whereas a relatively high proportion of Ashkenazi (European) Jews may have migrated as single individuals or as partial family units. These considerations may conceivably account in part for the observation that those who migrated to Israel as children had a lower risk to subsequently develop MS compared to those who were older at migration.

Some difficulties arise from these studies because of the small number of migrants available and the difficulty in making comparative studies done at different time. The prevalence of MS appears to be steadily rising in most areas and may be due to improved diagnostic techniques and survival.

Geographic Gradients in Stable Populations

The role of environmental factors in the geographic distribution of MS comes from studies of the geographic gradients observed in smaller areas where MS has been surveyed serially. In continental Australia, comparative studies in 1961 and 1987 showed that there is a gradient in the frequency of MS, with it being less common in Queensland and more common in western Australia, New South Wales and Tasmania.[12] These trends hold for prevalence, incidence and mortality. Increased rates of MS were found in each area surveyed at an interval of 20 years, most probably because of differences in diagnostic criteria, clinical vigilance and the differential immigration of high risk young adults. In New Zealand, the prevalence and incidence of MS is higher in the South Island than the North Island.[13] It is not possible to conclude from these studies that environmental factors alone are responsible for the geographic distribution since no formal genetic analyses were carried out. Nevertheless, it must be concluded that environmental factors seem to be the most likely explanation for the differential gradient.

US ARMY STUDY

The study by Kurtzke and co-workers of the incidence of Multiple Sclerosis in the US Army showed that there was a special advantage because MS was considered a service-related disease and therefore compensable on this ground.[7] Case ascertainment was uniquely high because of potential financial benefits and the availability of extensive demographic data within this data set. The work showed that within the United States, a geographic gradient for a decreasing rate of MS existed from North to South and, to a lesser extent, West to East. In addition, data on migration within the United States for this population suggest that the risks for MS changed according to age at migration. However, at the time of the study, it was impossible to control for genetic factors. The possibility that some of the North-South gradient reflected the distribution of genetic susceptibility alleles was not entertained. Recently, these data were reanalyzed and it cannot now be excluded that some of the distribution may be influenced by ethnic/genetic factors.

TABLE I

EVIDENCE AGAINST A PURELY TRANSMISSIBLE ETIOLOGY IN MULTIPLE SCLEROSIS

1. Low Rate in Dizygotic Twins (Ebers *et al.*, 1986)
2. Low Rate in Conjugal Pairs (Schapira *et al.*, 1963)
3. Negative Birth Order Studies in Multiplex Sibships (Cripps *et al.*, 1982), (Gaudet *et al.*, 1992 - submitted)
4. High Rate of Multiple Sclerosis in Second and Third Degree Relatives of Patients (Sadovnick *et al.*, 1988a; 1988b)
5. Groups Resistant to Multiple Sclerosis in High Risk Areas
   - Aboriginal/Torres Islander (Australia) (Miller *et al.*, 1990)
   - Amerindians (North America) (Hader *et al.*, 1985)
   - Inuit (Northern Canada, Alaska) (Ebers, 1983)
   - Hutterites (Western Canada) (Ebers, 1983)
   - Hispanics (California) (Enstrom and Operskalski, 1978)
   - Asians, e.g. Chinese, Japanese (North America) (Kurtzke, 1979)
   - American Blacks (North America) (Kurtzke, 1979)
   - Lapps (Scandinavia) (Gronning, 1985)
   - Gypsies (Hungary) (Palffy *et al.*, 1986)
   - Maoris (New Zealand) (Skegg *et al.*, 1987; Miller *et al.*, 1990)
   - Yakutes (Far North, Russia) (Popov, 1983)

TWIN STUDIES

Twin studies allow comparison of concordance in monozygotic twins, who are genetically identical, with that for dizygotic twins, who are no more genetically alike than non-twin siblings. Dizygotic twins would be expected to share more common environment than non-twin siblings. Comparison of concordance rates between monozygotic and dizygotic pairs measures the influence of genetic factors.

Ascertainment Bias

Twins occur in approximately 1/80 births with an expected monozygotic to dizygotic ratio of 1:2. One measure of ascertainment bias is therefore to determine whether the monozygotic to dizygotic ratio in a study sample approaches 1:2. A large twin study conducted by MacKay and Myrianthopoulos comprised of substantially

more monozygotic pairs than expected.[14] This study exemplifies some of the practical problems associated with twin studies. Since there are few available patient populations with a sufficiently large number of twins in which to conduct such a study, most investigators have relied on the solicitation of volunteers by public appeal. This method tends to result in over-representation of females and of monozygotic and concordant pairs. The excess of females has been seen in many studies in which volunteers are solicited.

The excess of monozygotic pairs is probably because the "twin status" of monozygotic pairs is more likely to be known to friends and relatives. To minimize this ascertainment bias, four separate studies of identical twins from large populations either of MS patients or of twins.[15] The combined results of these studies (see Table II) demonstrate a concordance rate of about 26% for monozygotic pairs compared with only 2.5% for like-sex dizygotic pairs, a figure close to the rate derived for non-twin siblings of MS patients (not corrected for sex). In fact, the sibling concordance rate, drawn from a study in which more scrutiny was given to siblings was actually slightly higher than the dizygotic rate, as determined by actual neurological examination of unaffected twins. There appears to be an increased risk for concordance among like-sex siblings from empiric risk data. These data give the like-sex age-corrected concordance rate for MS as 4.14%±1.28% for male-male pairs and 5.65%±1.10% for female-female pairs.

Inference From Twin Studies

A number of inferences can be drawn from the data in Table II. There appears to be a substantial genetic component to susceptibility (although one must consider the possible increased environmental sharing for monozygotic compared with dizygotic twins).

Secondly, genetic susceptibility is unlikely to be accounted for by a single dominant or even a single recessive gene since the difference in concordance rates suggests the operation of at least two or more genes.

Thirdly, a modest tendency for concordant pairs to be female (data not shown), even allowing for the expected female to male excess in MS, shows that gender is an independent factor influencing susceptibility.

Twin data also have implications for the nature of the environmental effect, since most monozygotic twins are discordant even after age correction and magnetic resonance imaging (MRI) scans. These factors suggest that a substantial environmental effect is required. The similar concordance rate for dizygotic twins and siblings suggests a more global environmental effect such as climate, diet or an ubiquitous infectious agent(s). This notion is supported by the finding that sibling pairs tend more toward the same age of onset than year of onset, and that affected sibling pairs are randomly ordered in birth sequence. While these observations do not rule out the long-held speculation that there is a specific infectious agent which causes MS, it seems considerably less attractive.

TABLE II

RESULTS FROM POPULATION-BASED TWIN STUDIES

Authors	Monozygotic Concordance	Dizygotic Concordance	Sibling Concordance
Heltberg *et al.* 1982	4/19 (21.05%)	1/28 (3.57%)*	Not Available
Bobwick *et al.* 1978	2/5 (40.00%)	0/4*	Not Available
Ebers *et al.* 1986	7/27 (25.92%)	1/43 (2.32%) 0/20 (0.00%)	87/4582(1.9%)**
Kinnunen *et al.* 1988	2.7 (28.57%)	0/6*	Not Available
TOTALS	15/58 (25.9%)	2/81 (2.5%)	See Below***

* Like-sex pairs

** The crude sibling concordance rate is not corrected for age.

***Age-adjusted empiric risks for like-sexed sibling pairs are 4.14% for males and 5.65% for females.[18]

TWIN STUDIES

Monozygotic Genetically Identical	Dizygotic Not Genetically Identical	Non-Twin Siblings
Comparison	Comparison	
Concordance Rates due to Genetic Factors	Concordance Rates due to Environment Factors	

Bias - Monozygotic females tend to be over represented in studies obtained by soliciting for volunteers.

INFLUENCE OF INFECTIOUS DISEASE

For poliomyelitis, data from a twin study, methodologically very similar to the Canadian twin study, found concordance rates of 35.7% and 6.0% for monozygotic and dizygotic pairs respectively.[15] In one large study of tuberculosis, the monozygotic concordance rate was 51% compared with 26% for dizygotic pairs with a similar figure for non-twin siblings.[17] The high rate of monozygotic discordance does not necessarily imply the operation of an environmental agent. Other reasons for discordance such as translocations, deletions, somatic mutations and other random or chance processes may be responsible. MS concordance rates in twins are probably underestimated. Subclinical disease including asymptomatic co-twins of MS patients has been reported when diagnostic procedures have included cerebrospinal fluid examination, evoked potentials and MRI scans.

A recent study reported cranial MRIs on 35 clinically normal individuals from 13 MS multiplex families. Four family members under age 40 and six over age 50 also had multiple white matter lesions. It is especially difficult to interpret the findings for these older individuals since non-specific white matter abnormalities that can mimic demyelination start to appear on MRI over the age of 40,

particularly in individuals with hypertension and known arteriosclerotic disease. Thus, the appearance areas of increased signals of white matter in clinically asymptomatic individuals should be interpreted with caution. MS lesions have often been found at autopsy in a series of clinically asymptomatic individuals, making it possible that even if these MRI lesions do represent demyelination, the individual may never be clinically symptomatic. Genetic factors thus seem to be important in MS susceptibility and the number of genes involved is at least two.

SUSCEPTIBILITY TO MULTIPLE SCLEROSIS

Animal Models

Studies of animal models of autoimmunity have had a large impact on the thinking of clinical investigators researching susceptibility genes for a number of known or suspected autoimmune disorders in humans. There is no spontaneous experimental animal model for MS and it remains unclear whether the induction of the various forms of experimental allergic encephalitis (EAE) has direct relevance since the immunological stimulus given to induce disease may not be "physiological". Injection of myelin basic protein (MBP) or extract of crude white matter can, in the presence of adjuvant , lead to paralysis in a wide range of experimental animals. Nevertheless, susceptibility to EAE appears to be related to the genetic strain of animal used and further study seems necessary.[16]

There are a few general lessons to be learned from these animal models. First, in virtually all cases, the inheritance of susceptibility is polygenic. Secondly, the number of genes interacting may be large. Finally, genes conferring susceptibility appear to interact at different steps in the initiation of the autoimmune process.

Human Autoimmune Disease

It has been possible to carry out studies on the frequency of MS among family members of affected index cases. Clinic studies have been carried out at the Vancouver MS Clinic where all consecutive, unrelated index cases have detailed genetic histories taken and documented by the geneticist.[18] These family histories are updated annually. The familial rate for MS in this population approaches 20% (compared with first-, second- and third-degree relatives of index cases). The data indicate, for example, that the risk for offspring, given an otherwise negative family history with respect to MS, may be as high as 5%, compared with a background rate of 0.1%. Although this risk seems low, in absolute terms, it is not inconsistent with the predictions derived from a polygenic model.

Autosomal recessive inheritance, postulated by MacKay and Myrianthopoulos on very weak evidence is now readily rejected because the frequency of parent-child concordance is similar to that for siblings.[14] A recessive locus with a dominant modifier is less readily excluded. Autosomal dominant inheritance would require extremely low penetrance and does not explain either the altered sex ratio among affected individuals or the observed differential parent-child concordance rates.[19] X-linked recessive inheritance is completely incompatible with both the sex ratio of affected and parental concordance pattern. For male and female index cases, the proportion of affected paternal and maternal uncles does not differ significantly - χ^2=0.04 and χ^2=0.96 respectively (df=1; p>0.05). In addition, because the frequency of concordant father-daughter pairs is as expected, when adjusted for the sex ratio,vertical (mitochondrial or placental) transmission can be excluded.

Specific Susceptibility Loci

Potential sites for genetic control of autoimmunity have been focussed on the genetic components of the trimolecular complex of antigen, T-cell receptor and Class II major histocompatibility complex (MHC) which results in T-cell activation.[20]

THE GENETIC CONTRIBUTION TO MULTIPLE SCLEROSIS - IS IT RESOLVABLE?

In no polygenic disorder, including spontaneous animal models of autoimmunity, is genetic control fully or even largely, understood. Formidable obstacles could exist to understanding genetic susceptibility in disorders where polygenic control is suspected. Even for single gene disorders, a number of independent influences on phenotype such as epistatic interactions, parental imprinting and genetic heterogeneity are known. Genetic heterogeneity seems more likely to be present in a condition as complex as MS.

Individual Loci

Some loci are highly polymorphic and a more complex relationship may exist. This phenomenon may be true for the MHC complex in MS where its role is still incompletely understood. At least two levels of complexity seem plausible. The first is that more than one locus in this complex could influence susceptibility. The second is that individual Class II alleles may influence susceptibility in a hierarchical way.

Interaction of Loci

It is possible that the action or effect of individual loci may be altered or nullified by other loci. Several orders of interaction are possible. Potential interactions may need to be specifically and systematically sought. Similarly, it is not impossible that susceptibility for some disorders reflects the additive effects of a number of loci, none of which are individually necessary or sufficient.

Prognosis Genes Versus Susceptibility Genes

Since subclinical forms of MS exist and may be common, the presence of genes which serve to lower detection threshold (symptoms and disability) could be manifested by population associations for such a locus in the absence of an effect on susceptibility. This is a possibility, although an unattractive explanation for the finding of

an association at a population level with no linkage in families.

The degree of complexity of genetic control in MS may be large and not easily defined. There are plausible models in which the understanding of susceptibility would be intractable because of the complexition of interactions and heterogeneity. For the present, it seems appropriate to consider models for which a solution is feasible with present technology and patient material. A major necessary gene locus for susceptibility remains a reasonable expectation but has not yet been identified. □

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May is Multiple Sclerosis Awareness Month

Multiple sclerosis is the most common neurological disease affecting young adults in Canada today. Approximately one in every 750 Atlantic Canadians has MS. The cause and cure are unknown.

Please support the Carnation and Residential Campaigns this May.

The Journal of a Disappointed Man

A PATIENT'S PERSPECTIVE ON MULTIPLE SCLEROSIS – 1909-1919

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Dealing with a long-standing and disabling medical condition that alters one's feelings and attitudes about life, self, and the future, is a struggle known to many. One who endured the battles, winning some and losing others to the relentless foe, multiple sclerosis, was B. F. Cummings (1889-1919). In his diary, he documents a rapidly progressive form of the disease until his death at age 28, in 1919, ten years after the first symptoms began.

B. F. Cummings, who wrote under the pseudonym, "W. N. P. Barbellion", was a biologist at the Natural History Museum in London, England. His adopted initials "conceal the bravado" of Wilhelm Nero Pilate. He was born on September 7, 1889 at Barnstable in Devon, the sixth and youngest son of John Cummings, a journalist for the *Devon and Exetor Gazette,* and his wife Maria Elizabeth Richards.

By the time he started writing his diary in 1903 at age 13, it was apparent that he had talents for mathematics and essay writing, and a great appreciation of nature and the outdoors.

His initial hope was to become a naturalist, but he had to refuse opportunities because of his father's ill health. Eventually, he did obtain a position on the staff of the Natural History Museum, over competing university graduates. At this time, however, he began experiencing the early symptoms of multiple sclerosis. He had the appearances of a consumptive and that it was "only a medical nicety which saved him from rejection by the doctors – there were no detectable defects and so they were unable to classify him".

He started at the Natural History Museum with great determination: "I am not going to be beaten, if I develop all the disease in the doctors' index. I mean to do what I set out to do if it has to be done in a bath-chair". Although he was aware of and seriously troubled by his increasing ill health, he had not been told of the serious nature of his illness and, in September 1915 he married Eleanor Benger. She was aware of the doctors' diagnosis and, shortly after their marriage, he also discovered the truth. His physical strength continued to deteriorate and he had to resign from the Natural History Museum in 1917. He died on the 22nd of October, 1919 in a cottage at Gerrard's Cross.

THE LAST DIARY

Cummings called his original journal *A Study in the Nude.* The later publication, *The Journal of a Disappointed Man,* contained his own selections from his journal, but there was a posthumously published *Last Diary.* It was his illness that shaped the journal and made him famous, and this same illness restricted his literacy output so that there is only *Enjoying Life* (1919) and *The Last Diary* (1920) in his bibliography.

The sombre presence of illness and impending death helped him put life in its proper context. He was frustrated by the artificial nature of much of life. He wanted to strip away the walls, the partitions and "walk about with my clothes off, to make a large ventral incision and expose my heart." He wanted to be brutally candid to others and wanted to know everything clearly himself.

His published journal was well received and brought pleasure to his last months. "The kindness everyone has shown the journal and the fact that so many have understood its meaning, have entirely changed my outlook. My horizon has cleared, my thoughts are tinged with sweetness, and I am content." His brother, A. J. Cummings, said of his last days, "never was a half-dead man more alive".

THE JOURNAL

His daily writings began at age 13 and continued until he was age 28, when he made the false entry "Barbellion died on December 32 (1917)." When he began his journal on January 3, 1903 he wrote about his adventures, particularly in the outdoors which he loved. The next year he won the school gymnasium championship for under 15.

On March 17, at age 17, he awoke covered with spots and the doctor confirmed that he had measles. He commented "I have somewhere near 10,000 spots on me." It is interesting to note that there are indications that measles at a late age may be somehow related to MS and age 17 is unusually late for this childhood illness. Six weeks later he was found by "Dr. H." to have chickenpox, another late onset for a childhood illness.

His sombre and contemplative nature made him think often of death, even before his final illness. In August 1907 he wrote "when I feel ill, cinema pictures of the circumstances of my death slip across my mind. I cannot prevent them, and I consider the nature of the disease and all I said before I died – something heroic of course!"

He worked very hard at his studies always with the goal of becoming a naturalist. He outfitted his attic like a laboratory and got up each morning to dissect. During these years his diary records mostly observations of natural history and zoology. He also frequently illustrated his dissections throughout his journal. He held a job as a journalist but retained his interest in science.

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When suffering from a long-standing toothache he made a comment that was appropriate later in his years. "No, I am not a martyr or a saint. Just an ordinary devil who is having a rough time."

On August 8, 1909 he began to describe a series of vague symptoms. He talked about a "*swingeing* inflammation of the eyes", perhaps the early symptoms of optic neuritis.

On Christmas Day he commented "feeling ill-like a sloppy tadpole. My will is paralyzed. I visit the doctor regularly to be stethoscoped, ramble about the stress, idly scan magazines in the library and occasional drink – with palpitations of the heart as a consequence. In view of the shortness, bitterness and uncertainty of life, all scientific labour for me seems futile." Although his symptoms were vague at this point, he seems depressed.

Later, he commented "better but still very dicky: a pallid animal: a weevil in a nut. I have a weak heart, and enervated nervous system."

He mentioned he has been "living in a state of mental ebullition." "Physically I am such a wreck that to carry out the least intention, such as putting on my boots I have to flog my will."

He still had to fight a "weak will" and on June 10th said that "legginess is bad enough in a woman but bandy legginess is impossible." He was becoming self-conscious about his abnormal gait and embarrassed when walking down the High Street on a market day. It would seem from later comments that he was developing leg spasticity

Soon, his enthusiasm returned and he was enjoying his books, his late night studying, his pipe and his tea. He tried for a set of examinations to obtain the position at the British Museum but was unsuccessful. However, he felt that he would soon be busy in his new position at the Plymouth Marine Laboratory and could not afford to be hypochondriacal. Ten days later, however, he is again talking about "heart attacks" and is trying to get over his "visions of sudden death, coffins and obituary notices."

He was informed that his father had another stroke with right-sided paralysis and aphasia. He resigned from his employment to care for him.

He talked of attacks of faintness. He said that when he feels the least bit down he stops what he is doing because the next day, week, or month or year, he may be dead. It seemed a waste of life to work. Zoology and philosophy seemed of no importance against the question of living, but, as soon as he was feeling well again, he forgot all this.

He went for a walk in the country but returned frightened because of violent attacks and palpitations. He described looking at each stranger on the way in terms of how each would react in having to help him home. He had to lean against the river wall and eventually got back to the library, where he sat down and had more severe palpitations. His fact was hot and his hands were shaking. He said his heart went Bang! Bang! and he could feel its beat "in the carotids of the neck and up along the Torcular Herophili and the big vessels in the occipital region of the head." The symptoms sound like an anxiety attack. He got home and had some sal volatile which made him feel better but he was quite demoralized after this event. Two days later he described himself as "an undeveloped negative, or a jellyfish on stilts, or a sloppy tadpole, or a weevil in a nut, or a spitchcocked eel. In other words and in short – ill."

A few days later he talked about the vision of sudden death constantly coming before him, but he felt he was recovering. "Yet these are a few terrible pages in my history." The doctor ordered him to stop his work and he began to rest and spend long periods in bed. He talked about having "inflammation to my eyes twice in three weeks", probably optic neuritis. The doctor thought it was catarrh of the eyes and windpipe.

He declared that if he died he would like to be buried in the Cherry Orchards. He also recorded all the people who had illness in his village and was obviously obsessed by illness and death.

In beginning to understand some of his morbid tendencies he commented "I have come to loathe myself: my finicking, hypersensitive, morbid nature, always thinking, talking, writing about myself for all the world as if the world beyond did not exist!"

He commented "who will rid me of the body of this death? My body is changing – dead weight. It is my warder. I can do nothing without first consulting it and seeking its permission. I chafe at the thongs it binds on me. On this bully I am dependent for everything the world can give me." In the end, too, I know it intends to carry me off .... I should like though to have the last kick, and copying DeQuincey, arrange to hand it over for dissection to the medical men – out of revenge."

In 1912 he was happily and enthusiastically working at the Museum but came down with the flu and his mother and the doctor were frightened by his appearance. The doctor felt that he might be concealing something. Two weeks later he described himself carrying a cane and watching a pretty girl run out of the breakers.

Increased weakness with heat is seen in most MS patients, and on each hot day he sought out ponds and pools to bathe in, spending long periods in the cool water. His obsession with death continued as he said "I decided my death shall be disputed all the way." He regretted that he felt insignificant and did not want to die nameless and without making his mark. He was not happy about an "unobtrusive passing away of the rancorous, disappointed, morbid, and self-assertive entomologist in a West Kensington boarding house, what a mean little tragedy! It is hard to be somebody even in death." He beat at autumn leaves with his cane, because he was angry that they were dead."

Dr. M. was gloomy about his patient's health and talked of South Africa or Labrador, as his patient was not responding to his treatment. He was sent to a Dr. Hawkins, a stomach specialist, who told him he should live on the prairies. Despite this, he began to work feverishly, feeling the shadow of death over him. He began to suspect, however, that his illness was affecting his ability and even his mental powers.

On December 15, 1912 he described a "very bad heart attack" and said "it intermits every three or four beats" suggesting he had some sort of an arrhythmia or ectopic beats. As he was going to sleep his watch stopped and he wondered if this was an omen. He wondered if he would live through the night. The next day he was well but noted he saw a hearse pass in the street.

Shortly after he began to get a new sense of his own existence and the afterlife and said that "when I am dead you can blow me, burn, drown me, scatter me – but you cannot destroy me: my little atoms would merely deride such heavy vengeance. Death can do no more than kill you."

When courting his fiancée he entertained some friends by showing them the newly discovered patellar knee reflex. He tapped his leg, and then crossed the room to tap hers. All were delighted but there was no comment on the fact that his was probably increased.

He saw "Dr. M." again who felt his symptoms were alarming but no definite diagnosis was made. He then was referred to a well-known nerve specialist, "Dr. H.", who asked him suspiciously "if I had ever been with women" and then ordered two months complete rest in the country. Presumably the doctor was suspecting syphilitic involvement of his nervous system. He says that the consultant "chased me around his consulting room with a drumstick tapping my tendons and cunningly working my reflexes."

He wrote "staying at the King's Hotel – Giddiness very bad. Death seems unavoidable. A tumor on the brain?"

He went on to describe the delight in feeling the sensation in his hands, and the feeling of motion as he used his arms and legs. Later, however, he had an acute attack with feeling of depression, decrease in sight in one eye, numbness on one side of his face and weakness in his right arm. His blindness was increasing and he said men look like trees walking and print was becoming hopelessly blurred. He saw a Harley Street oculist who reassured him about the blindness.

All during this time he was convinced he was dying, but he expressed little concern at the lack of any definite diagnosis. He continued to go to physicians, taking medicines without any sense of optimism and was beginning to go blind in both eyes. He again thought of suicide, and continued to take his medicine of arsenic and strychnine. He developed chronic constipation and thereby gained "an unrivalled knowledge of all laxatives, aperients, purgatives, and cathartic compounds." He found that the best relaxation for the toilet was picture puzzles. His medicine began to upset his stomach, gave him cardiac irregularities and made him feel faint.

Despite his ill health he tried to continue his career, and said "I keep flogging my will in the hope of winning though in the end. Yet at the back of my mind there is a great improbability that I shall ever live long enough to realize myself. For a long time past my hope has simply been to last long enough to convince others of what I might have done – had I lived. That will be something."

By the end of 1914 he determined that he would publish an edition of his journal, and his writing style, subject matter, and length of entries improved. He began to write more of authors, musicians and artists, commented less about his own problems and illness and showed less depression and self pity. It was clear that he was beginning to write for a public and even started some paragraphs, "you observant people will notice."

He briefly mentioned going to the Christian Scientists Church, but made no further comment about whether he actually attended, and if he sought any approaches to his illness. He spent the afternoon at the Royal Army Medical College in consultation with the Professor of Hygiene. There is no comment about what transpired.

He noted that he would marry on September 15th. He was quite uncertain about the event but felt that if he could enjoy twelve months of happiness it would be worthwhile.

Two weeks before his marriage he had a fall. He felt that he injured his spinal column and said that his symptoms from 1913 were returning but this time in the left side. He developed some paralysis and vertigo and the feeling that his legs would collapse when he walked. A week later he went to his doctor, expecting to have the marriage forbidden, as he could scarcely hobble to the doctor's house. To his amazement the doctor made light of his paralysis and said that it was just due to a fall on his coccyx.

Despite his past problems, difficulty and concern that he had little time to live, he actually obtained a certificate from his doctor to be taken to a recruiting office where he wanted to join and serve in the First World War. He knew he was totally unfit but not *how* unfit. He was immediately rejected . As the certificate he carried was not needed he returned home with it and opened it. It stated that eighteen months earlier he showed the visible symptoms of disseminated sclerosis. Finally, the diagnosis! This was apparently known to his relatives but not told to him. The doctor had only used the term "nerve weakness" to him. The letter asked the medical officer to continue to respect the confidence, rejecting him without stating the grounds. After reading about the changes in his reflexes, he tore the paper up and threw it out the railway carriage window. He was amazed at the calm way he received the news, but thought he was a fool not to have suspected a serious nervous system disease.

He then attempted to learn more about the disease.He writes that he has a creeping paralysis, and his left leg would go lame after a short walk. He did not know whether his wife was aware of the diagnosis and does not speak about it with her. In his diary, he never used the words multiple sclerosis but always left a blank instead.

It is clear that the journal is of tremendous importance to him. He feels that it is even a competitor to his wife – he tells it secrets that he does not tell her.

He sardonically contemplates how the outbreak of war with Germany in 1914 changed his status from an interesting invalid to a lucky dog. Later, he was hardly noticeable among the numerous tragic lives and survivors of the War.

He then comments "my nerves are giving way under the strain ... one leg (the left) drags ... we shall want a bath-chair as well as a perambulator." He was starting to complain that his mind was going and his memory was poor. The numbness in his right hand was bothering him and his doctor advised him to go to the sea alone for his unstrung nerves. To add to his stressful time his wife was about to have a baby. Soon he was unable to write any longer.

He points out that he hates alarming the doctor, who is such a cheerful man, so he conceals his symptoms. He had another attack and was in bed again, expecting death. He said he wanted music or he would be able to hear the paralysis creeping. As a result he would lie in bed and whistle. He worried about whether the journal will survive accidental loss, and whether it was of any value.

He wrote the hidden dream of most MS patients: "it would be nice if a physician from London, one of these days, were to gallop up Hotspur, tether his horse to the gate post and dash in waving a reprieve – the discovery of a cure!"

His wife then revealed that she spoke to the doctor before his marriage and was told that he would be expected to live only twelve months after becoming bedridden. She felt he knew, and he was not sure whether she knew. He wished he could make some sacrifice for her, but he was entirely in her debit and dependent on her.

He visited a homeopathic therapist in Finsbury Circus. He comments "I could write a book on the doctors I have known and the blunders they have known about me." Later, a doctor was called to see him and commented that he felt he was quite young to have multiple sclerosis, and then suggested he should travel and continue to take arsenics.

He read over his diary and said that his constant preoccupation with himself sickens him. Life also tired him and he was sick of living. He repeatedly visualizes his illness as bacteria gnawing away at his spinal cord producing a creeping paralysis, and feels he can hear the sound of the gnawing.

He later overcomes some of the depression and begins to describe the pleasure at small accomplishments such as penmanship, coaxing a button though a hole, and other simple tasks.

He went to a chemist's shop looking for morphia, but he was unable to obtain this. It was not clear why he wanted it, for pain or suicide.

He began to rewrite and edit his journals for publication and became very pleased with the results. He was still going to the Museum but only doing simple work such as making out labels, and recognized that he would never do any serious research again. He began to regret the possibility of lingering and causing his wife a burden, and begins again to think of death. He had another attack and had to retire from his job. His weak hand was improving but he said "it is a cat and mouse game and so humiliating to be the mouse." It caused him great pain to resign. His gratuity on retiring turned out to be smaller than he had hoped, less than a year's salary.

By September he could not climb the stairs, but on his hands and knees he attempted to search out a half bottle of laudanum (opium) which he heard had been found in the house. His last entries are in very erratic handwriting. "I am only 28 but I have telescoped into those few years a tolerably long life: have loved and married and have a family; I have wept and enjoyed, struggled and overcome, and when the hour comes I shall be content to die."

He made brief entries on October 14th ("miserable") and October 21st ("self-disgust"). He then wrote "finis" and "(Barbellion died on December 31st)". This last entry is puzzling because it is premature. Perhaps he signalled the end for his journal readers. In fact, he lived in a debilitated state a further two years.

W. N. P. Barbellion, a young man who fought a long and losing battle with multiple sclerosis, is still remembered for his open and honest documentation of his illness. In the words of Peter Clifford, he "embodied that rare fusion of scientific and literary genius which can observe nature and self with equal sensitivity, analyzing with scientific detachment, yet feeling with poetic intensity." □

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The Wheelchair as a Mobility Aid for Persons with Multiple Sclerosis

R. Lee Kirby, MD, FRCPC, and Brenda M. Joyce, MD, FRCPC

Halifax, N.S.

Of the impairments that affect people with multiple sclerosis, many limit walking ability. Those most severely affected may benefit by the use of a wheelchair as a mobility aid. The type of wheelchair that is appropriate, and a great many options are available, will depend on the characteristics of the person, the setting and the intended uses of the chair. The natural history of the disease — particularly its frequently progressive course and tendency to relapse and remit — also needs to be considered. Prescription of a wheelchair should be made with care, with input from appropriate members of the team, and after a supervised trial with the chair.

> *One might say that such matters are outside the healing art. Why, forsooth, trouble one's mind further about cases which have become incurable? This is far from the right attitude. The investigation of these matters too belongs to the same science; it is impossible to separate them from one another.*
>
> Hippocrates[1]
> (*c.*460 BC - *c.* 377 B.C.)

Disability is prevalent, affecting 14% of non-institutionalized people, 27% of them severely so.[2] Multiple sclerosis is one of the chronic health conditions most likely to limit activity (Table I). Many of the impairments that limit walking ability (e.g. weakness, spasticity, sensory loss, incoordination and visual disturbances) affect persons with multiple sclerosis. Although rehabilitation of mobility problems is rarely as simple as providing someone with a wheelchair, the wheelchair is a mainstay of rehabilitation medicine. Too often, however, the wheelchair is misunderstood, misused or taken for granted. In this paper we will therefore review some of the factors that affect the prescription of the most appropriate wheelchair from among the many models and options available.

CLINICAL EVALUATION

If you suspect a functional problem with mobility, explore it further until you either are satisfied that the problem is insignificant or you have sufficient information to manage it. Remember that the subjective description of abilities is no more than a starting point; it requires corroboration by observation — yours, the family's or that of an allied health professional such as a physiotherapist. A clear understanding of a mobility problem should include at least two components.

First, determine the level of function. Locomotion (getting from one point to another) may be by a variety of techniques (e.g. walking, crawling, hopping, wheelchair propulsion) and includes locomoting over smooth and rough ground, through doors, ascending and descending inclines, curbs and stairs. Some tasks are consistently more difficult than others. Determine what is possible and what is not. Identify the assistance required, whether in the form of help from another person or from the use of a specific aid or appliance.

Second, identify the limiting factors to that function.[3] Limiting factors are those which preclude a higher level of function. Intrinsic limiting factors may be the impairments due to a disease or condition (e.g. muscle weakness) or the characteristics of the person affected. Extrinsic limiting factors are those in the person's setting or environment (e.g. architectural barriers) which preclude functioning at the limits of one's intrinsic capabilities.

TABLE I

SOME CHRONIC HEALTH CONDITIONS THAT CAUSE ACTIVITY LIMITATIONS

Condition	Percent whose activity is limited
Multiple sclerosis	77.0
Paralysis of extremities	65.7
Intervertebral disc disorders	45.9
Cerebrovascular disease (stroke)	41.2
Deformities, orthopedic impairments	31.6
Arthritis	20.8

Adapted from Craus and Stoddard.[2]

THE PERSON

The type of wheelchair which is best will vary according to a number of personal characteristics (listed in Table II), not the least of which are the person's motivation, and the maturity to accept what cannot be changed. The person must be willing to comply with the trial-and-error and fine-tuning necessary to optimize the prescription. The natural history of the disease also needs to be considered, namely its often progressive nature and tendency to relapse and remit.

Arm strength is needed to propel the chair up inclines and ramps. Hand strength is needed to grip the pushrims, and trunk strength to resist forces (e.g. the tendency to jack-knife when stopping the chair abruptly). Balance is needed to compensate for inclines and direction changes. Leaning can be used to improve the stability of the wheelchair or in order to achieve an objective (e.g. leaning forward to open a door).

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TABLE II

FACTORS TO CONSIDER IN PRESCRIBING A WHEELCHAIR

The Person	The Setting
motivation	intended uses
maturity	architectural barriers
cooperativeness	assistance available
disease course	finances
strength	
coordination	
balance	
spasticity	
range of motion	
posture	

Fair coordination is needed, for instance to grip the rims, or to steer the chair through narrow openings. Many wheelchair users are ill-equipped to protect themselves during a fall due to lack of strength, coordination or range of motion. Can the person sit upright or does he or she need to be tipped back? Does spasticity (e.g. in the form of extensor thrusts) make consistent positioning difficult? Soft tissue contractures are common and affect sitting position and the ability to reach the wheels — is there adequate range of motion? Many persons using wheelchairs because of severe neuromuscular disease have scoliosis and pelvic obliquity, which may affect the distribution of sitting pressures in the chair.

THE SETTING

The intended uses of the chair are also important considerations in wheelchair selection. The activities performed by wheelchair users range from simply sitting, where the only purpose of the wheelchair may be to permit an attendant to transport the user from one room to another, to the highly athletic. Will sports be played in the chair? Which ones? The environment also needs to be considered. Indoor chairs need not have as cushioned a ride as those that will be used outdoors, where sidewalk and other terrain irregularities are encountered. Are the floors where the person lives carpeted? How narrow are the doorways, how tight the turning circles? Is help available for transfers and ramps? Outside, are there sidewalks? Are there curb cuts at corners? Is the road paved?

Financial resources are also important. A bottom-of-the-line wheelchair may cost as little as $500, but sophisticated power chairs may cost twenty times that much. In Nova Scotia, provision of aids and appliances are not insured services, although municipalities and special programs (e.g. vocational rehabilitation) will assist those who meet their eligibility criteria. Furthermore, private organizations (e.g. the Abilities Foundation of Nova Scotia and the Multiple Sclerosis Society) can be approached for support, often in the form of the long-term loan of a chair. The social worker is a valuable member of the rehabilitation team for many reasons, not the least of which is the ability to obtain the prescribed equipment.

THE WHEELCHAIR

In choosing a therapeutic strategy to overcome a specific disability such as in locomotion, one of the most feasible and rewarding components of the management is to change the nature of the task. Aids and appliances improve one's functional capacity by modifying the task. A person with multiple sclerosis may not have the endurance to walk up the hill to visit a friend, but a motorized wheelchair can make the visit possible.

When should one consider a wheelchair? Although some people accept wheeled locomotion prematurely, it is more common to procrastinate. There are a variety of means (e.g. braces, canes) to help people with multiple sclerosis stay on their feet. However, if the involved individuals are so badly fatigued by walking that they are unable to function well once they get to their destination, then using rehabilitation technologies to preserve walking may represent "a triumph of technique over reason". As the patient's physician, you can play a big role in debunking the myths surrounding the use of a wheelchair, noting that people are not "wheelchair bound" or "confined to" wheelchairs; rather, they are freed by them to carry out activities that would otherwise be impossible.

The overall prevalence of wheelchair use in Canada is about 3.2 per 1000 of the non-institutionalized population[4] (or about 2,800 people in Nova Scotia) of which ~28% use electrically powered wheelchairs.[5] The number of wheelchair models and options have increased dramatically in the past decade. Although this has been a generally positive development, a negative consequence is that many patients obtain wheelchairs that are ill-suited to them. No single wheelchair design is suitable for all ages, disorders and activities. The components of a wheelchair that should be considered are listed in Table III, several of which are illustrated in Figures 1-3.

Problems may accompany the freedom provided by wheelchairs, not unlike the side effects that plague other potent therapies.[6] Data documenting the incidence and circumstances surrounding wheelchair accidents are not well established, but such accidents appear to be very common. An estimated 26,000 wheelchair-related accidents that are serious enough to cause the victims to seek attention at an emergency room occur in the United States each year.[7] The consequences of such accidents may be simple sprains and lacerations, but 0.2% of these accidents (50 per year in the US) are fatal.[4]

Therefore, to obtain a wheelchair that is both functional and safe, we suggest that prescription of wheelchairs be made with great care.[8] Seek input from appropriate members of the team, notably the occupational therapist, physiotherapist, social worker, reputable distributor and, if customization appears to be necessary,[9] an orthotist. Allow the patient a supervised trial with the chair.[10, 11] Ensure that the patient is familiar with its use; training is important for first-time users. After the patient has received a wheelchair, regular maintenance and service are needed if the chair is to function well and

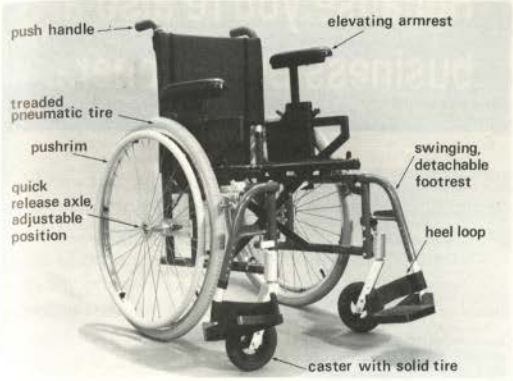

Figure 1

Lightweight wheelchair. Note that the right footrest is in the swung-out position and the left armrest is elevated.

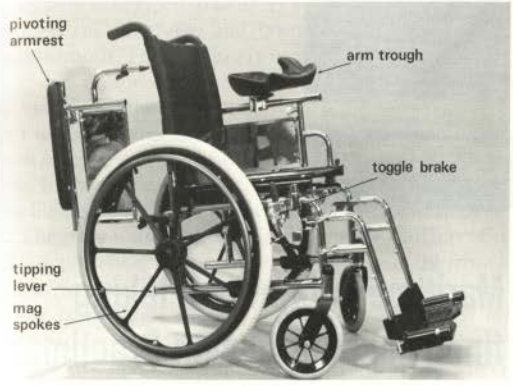

Figure 2

Regular-weight wheelchair. Note that the right armrest is pivoted into the folded-back position.

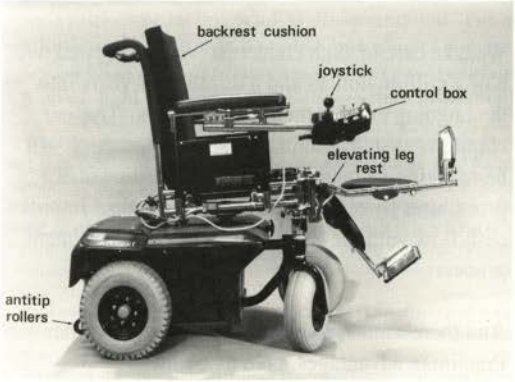

Figure 3

Powered wheelchair. The motor and batteries are under the seat, beneath the cover.

safely;[12] enquire about the chair and examine it at recheck visits.

With these few caveats regarding appropriate prescription, training and maintenance, you will find the wheelchair to be a safe and effective way to help patients with severe multiple sclerosis improve their mobility and the quality of their lives.

TABLE III

CHAIR COMPONENTS AND OPTIONS

Feature	Explanation or Option
All wheelchairs	
weight	conventional vs lightweight chair
frame	size; rigid vs collapsable
push handles	for attendant to push, pull, tip or lift
tipping levers	for attendant's foot, to assist with rear tip
anti-tips	limit the extent of rear or forward tip; with or without rollers
recliner	partial vs full; compensating or not; release mechanisms; powered
rear axle	posterior offset ("amputee"); adjustable position; quick release; camber
wheels	diameter; "mag" vs wire spokes
tires	solid vs pneumatic; non-puncturable; treaded vs smooth
seat	hammock vs solid; fixed vs removable; adjustable position
cushions	foam, air or gel; specify thickness
head rest	removable vs fixed; define direction of restraint
restraints	lap vs chest belts; lateral thoracic pads; user vs attendant release
footrests	regular vs long; bumpers; swinging detachable vs fixed; calf straps; rollers; heel and toe loops
legrests	pads; troughs; elevating
inserts	prefabricated vs custom; base and/or back
armrests	desk- vs full-length; variable height; padded; removable; wrap-around; pivoting fold-backs; arm trough
laptray	for food, communication aids
carrier	knapsack; pouch; luggage rack; crutch attachment
Self-propelled chairs only	
pushrims	chrome vs plastic; vertical or oblique projections; one-arm drive
brakes	lever vs toggle; high vs low profile; grade aid (ratchet for incline ascent)
power	arm(s) and/or leg(s); attendant; crank
Powered chairs only	
power	motors fixed or removable; optional use (booster); stair-climbing
control	joystick controlled by hand, foot; head switchs; mouth; voice controlled
controller	defines performance parameters, may be programmable
batteries	gimballed; different types (e.g. gel)

□

ACKNOWLEDGEMENTS

We thank the Audiovisual Division and the Editorial Service at Dalhousie University, and B.L. Yorke for their assistance.

References on page 53.

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My Life with Technical Aids

Paul Gouett,* BA, MA, BEd

Halifax, N.S.

I know this will not come as a surprise to anyone but we're firmly imbedded in an era of tremendous technological change! For that, we are all winners, especially those of us in the disabled portion of the community.

As an offshoot of that very obvious fact, regard the previous statement as an example of this era: previously I would have referred to "The Disabled Community" as though it was somehow separate from "normal" society. Now with so many advances it has become one community.

The problem now is two fold: 1) To discover a way in which these leaps and bounds of technology can be made available by reasonable means to the disabled persons they were developed to assist. 2) To dispel the widely held notion that disability and bottom-rung are somehow synonymous. The only losers in all of this are those who, for one reason or another, refuse to keep pace and acknowledge the advances.

I'm going to use myself for an example of how important some of these technological advances are in my own life. It's been a long trail but the many aspects that make my life easier weren't always available. Patience has helped.

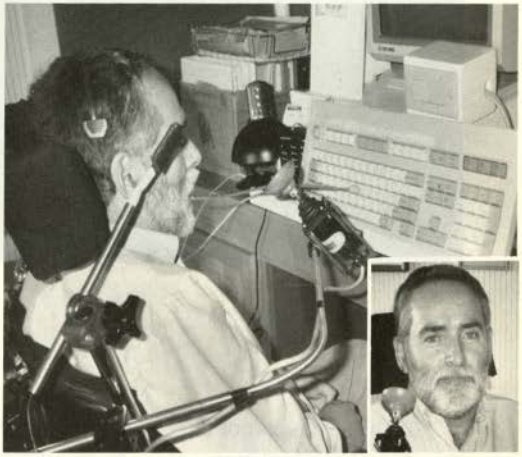
The most noticeable advance in my life which is obvious in presence alone is my wheelchair. From the front it looks like most other electric wheelchairs . . . except that there is a strange suction cup looking affair near my mouth.

In actual fact it's a chin-cup used to drive my wheelchair and direct its many different operations . . . for reasons which I'll come to later it was necessary for it to swing away. That I manage by pressing a concealed button inside my headrest. Easily seen outside my headrest is a popsicle stick size lever which I can reach with my right temple. I can flick it for 3 various modes of operation: 1) drive; 2) recline; and 3) environmental. These are indicated by lights on a control box which I can see. They aren't as obvious to the casual viewer so I'll explain – A green light puts me in drive mode where movement of the chin cup tells the chair to move where the chin cup directs it. – A red light means I can recline (the leg rests rising proportionally as I go back). This is again controlled by up and down movements of the chin cup. – In between the green and red modes is one where no colour is evident. This is environmental control mode. Here with the 4 major directions of the chin cup, up, down, left, right, I can turn on and off: A) my computer; b) stereo; c) light over computer; and d) reading light on desk.

All this is coordinated by a computer mounted on the back. The speed of the chair be it high/low, indoor/outdoor can be regulated. As well, an attendant control for the chair is found. This can be used by a designated individual within the range of the control's reach. The many wires on the back indicate that *something* very interesting is going on!

Thus far, I have given no attention to the *real* computer which makes my life meaningful. To adequately do that, however, I must tell you about another aid which allows me to utilize the computer. (Actually, who am I kidding? My *whole life* is dependant upon support of some sort. Singling out a few items simply means ignoring others which are just as important for different reasons.)

At any rate, to use my computer, because I have no use of my arms or hands, I must use a mouthstick. This apparatus is composed of a metal biteplate fitted with an extending 12" brass rod with a rubber tip. With this aid I can type, operate my telephone and turn pages. (To make room for the utilization of my mouthstick is what I alluded to earlier when I said it was necessary for my chin cup to swing away.) All of this needs some explaining which I won't go into here but would be more than happy to illustrate it to interested parties.



Paul Gouett shown at his computer typing with his mouthstick.

*Paul Gouett is a free lance writer and expert advisor on the disabled and their affairs. He has made valuable contributions as a Board member of many different organisations. He was editor of the Nova Scotia Paraplegic Association journal "The log", advisor to the Rehabilitation Council for the Disabled of Nova Scotia 9(R.C.D.N.S.). He is currently completing two years as a member of the Disabled Persons Commission, and was formerly chairman of the fund raising committee for the Abilities Foundation.

Paul obtained his B.A. and M.A. at St. Mary's University and completed his training at Queens, University with a Bachelor of Education degree.

He taught at Sidney Stephen Junior High and continued his work for five years after the diagnosis of multiple sclerosis was made. In 1980 he finally retired from teaching and took up residence at St. Mary's University.

Despite his disability Paul retains a cheerful personality maintains an active part in current affairs.

I think of myself as a writer. Though with this mouthstick I am slow, that being the case I consistently keep most of my articles and letters to a manageable limit. It saves on jaw fatigue and too great an expansion of neck muscles!

The use of the computer is vital to my sense of participation in life. I have found my niche as a writer and feel I am thus able to contribute on a very worthwhile level. This aspect I emphasize through repetition because it is largely due to the use of technical aids in my life. I am not unusual in this use of technology. Many of us (meaning you and I, not with "Disabled" or "Ablebodied" labels attached) have our lives shaped by technology. As examples, regard the advances in the medical field itself. MRI scans were not even a dream when I was diagnosed. Pocket calculators were unheard of. Engineers used slide rules.

So where does that leave you and me? After all that rhetoric we're still back at square one. You're still ablebodied and I'm not! – Until we break down the barriers that divide us, we'll all stay that way. The ones that say technology costs too much and the ones that equate disability with meaningless existence will just have to wake up and smell the flowers. This is a whole new era. Let's all join it. □

The Dalhousie Multiple Sclerosis Research Unit

The Dalhousie Multiple Sclerosis Research Unit was established in 1980 to provide care and education for people and families with MS in Nova Scotia. In providing such care, it was planned to document all cases in great detail in a computerized data system to aid in research to find answers about the cause and treatment of MS.

Dr. T.J. Murray had been involved in research projects related to multiple sclerosis since 1973 but, a need to have the large group of well documented MS patients was recognized, if further studies were to be effectively organized.

A grant was obtained from the Multiple Sclerosis Society of Canada to initiate the Unit. It was then organized with the unique approach of organizing the clinical care and documentation of patients for a large number of collaborative scientists and clinicians could carry out research programs. Building on this concept, over 30 collaborative investigators have been involved in the Unit over the past decade. These investigators have been at Dalhousie primarily, but also in nationally and internationally organized research projects.

The central concept of the Unit, however, is to provide exemplary care for patients, providing patient education, family education, and public education, and developing extensive computerized documentation as the basis for research.

OBJECTIVES

The Unit has a series of objectives:

- To maintain a close liaison with referral physicians and consultants regarding their patients with MS.
- To act as a resource for educational information for patients, families, and physicians.
- To provide public education about multiple sclerosis.
- To develop and support research programs related to the cause and cure of multiple sclerosis.
- To provide a large group of well documented patients who agree to participate in various projects to find answers in MS.
- To provide clinical support for various basis researchers and clinical researchers in the area of multiple sclerosis.

RESEARCH

Over the past decade, the MS Unit has encouraged collaboration with many scientists, clinicians and health care workers. More than 70 scientific publications have resulted from this research activity. Collaborations have occurred from Psychology, the Trace Metal Laboratory, Urology, Neurosurgery, Rehabilitation Medicine, Nursing, Physiotherapy, Human Communication Disorders, Ophthalmology, Medicine, and many other groups.

Research funding has totalled over a million dollars, and the projects continue to increase.

EDUCATION

An important function of the Unit is to provide education for patients and families, for health professionals and for the public. The staff of the Dalhousie MS Research Unit are involved in medical student lectures, nursing seminars, community physician programs, refresher courses, MS Society programs and various educational programs on TV and radio.

The Unit maintains a resource library for MS books, pamphlets and audio-visual materials available to patients and the public. There is a close liaison with the Atlantic Division of the MS Society who also carry out activities in relation to education of patients and the public. The Unit has been instrumental in setting up self help and support groups for spouses of MS patients and for MS patients, and organizes an annual children's workshop for those who have a parent with MS.

A TEAM APPROACH

Each person with MS has unique treatment needs and can be managed by a team of health professionals. The patient's assessment and evaluation is done by one of three Unit neurologists, Dr. T.J. Murray, Dr. V. Bhan, and Dr. C. Maxner. We have consultant liaison with Neurosurgery, Rehabilitation Medicine, Orthopaedic Surgery, Gynaecology, Urology, Audiology, Psychology and other services.

A nurse/coordinator provides a continuing link with patients. The Unit has effective support from Physiotherapy, Occupational Therapy, Psychology, Pharmacy, Social Work, and dietary consultants.

CLINIC ARRANGEMENTS

Upon receiving a referral from a family physician or other physician, the Unit will arrange an appointment at Camp Hill Hospital. The Clinic is wheelchair accessible, includes examination rooms, and access to physiotherapy and occupational therapy areas, a library of MS information, and the clinic coordinator's office.

A neurologist sees the patient and carries out a neurological and general physical examination, and counsels the patient and provides recommendations regarding therapy. That same day, a letter is dictated to the referring physician who continues the management and care.

MS CARE FOR THE MARITIMES

The Dalhousie Multiple Sclerosis Research Unit is the only centre of its kind in Maritime Canada. It provides consultation, care, education and research, and it has documentation on over 1000 patients with multiple sclerosis.

It is supported by the Department of Health and Fitness of Nova Scotia who provide an annual grant in support of its activities. We are grateful for this support, and the Unit could not continue if it were not for the understanding and support of the Department.

NATIONAL AND INTERNATIONAL LINKS

The Dalhousie MS Research Unit has various links nationally and internationally. It was part of the initial Canadian cooperative study group for MS and initiated the first national project. It was a founding member of the Consortium of MS Centres, headquarters at the Cleveland Clinic, and recently hosted an international meeting of the Centres in Halifax. Dr. Murray has recently completed his term as Chairman of the Medical Advisory Board of the National MS Society, and sits on the International Federation of Multiple Sclerosis Societies, as well as being the founding member and Advisory Board member of the Consortium of MS Centres.

These national and international linkages not only keep the Unit in the forefront of MS activity, but they also involve the Unit in collaborative projects with other Centres in Canada and the United States.

CONCLUSION

The Dalhousie MS Research Unit was organized over 12 years ago to coordinate exemplary clinical care, research and education of MS patients, their families and the public. It has been successful in all these areas, and its activities and programs continue to increase. □

ACKNOWLEDGEMENTS

We acknowledge our debt to the patients and their families, particularly for their continuing collaboration and cooperativeness in our research programs.

We are grateful for the support of the MS Society, and particularly of the Department of Health and Fitness of Nova Scotia.

Finally, we are grateful for our Unit staff, the many supportive staff and administrators at the Camp Hill Medical Centre and to the clinicians, health professionals and scientists who help us search for new answers and improved care of MS patients.

The following is a list of publications available on request from the Dalhousie MS Research Unit, oral presentations are also available.

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Fund Raising for Multiple Sclerosis

"MY THOUSAND DOLLAR T-SHIRT"

Basil Grogono,* MB, BS, FRCS

Halifax, N.S.

Raising money for charity has become a major industry these days. Despite government support for research, payments of unemployment benefits, and many social support systems of the modern welfare state, hundreds of organizations depend on voluntary contributions.

This is particularly true of the Multiple Sclerosis Society. This disease remains an enigma. It is the most common neurological disease affecting active young members of our society and there are some 25,000 suffers in Nova Scotia.

One of those who suffers from this disease is my friend Paul Gouett who is now in a wheelchair and attending St. Mary's University, in Halifax. It was after a visit to him that I decided to participate in the Multiple Sclerosis Bike Ride, being held for the first time, from Mt. Uniacke to Acadia University in Wolfville, a round trip of 150 kilometres.

In the spring of 1990, I salvaged my twenty-year-old Raleigh and practised trekking along the beautiful country side of Nova Scotia. I hadn't ridden a bike, for more than a few miles, for about forty years. However, a bike race in Yellowknife in 1986 had toned up some of my latent muscle fibres.

The ride to Wolfville, that year (1990), for the hundred enthusiasts was a stimulating experience. Many a sporty athlete and many a charming maiden, swished past my bike but I arrived unblemished at Acadia's dazzling heights. The return journey was swathed in rain but the sight of so many happy cyclists cheered my return journey.

Now, in 1991, plans for the Multiple Sclerosis Second Annual Bike Ride was once again underway, however; this project, for me, seemed unrealistic. How would I get enough sponsors, would my ancient muscles respond, was my old Raleigh a fit instrument to compete against a whole armada of magnificent mountain bikes and super light weight racers? Then I hit upon the idea of my T-shirt. I would get a $5 plain white T-shirt and some colored marking pencils, and put the names of my sponsors there upon and raise $1,000.

First I tried the Premier's Office - "Sorry", came the answer, "I would have to do the same for every charity". The Mayor of Dartmouth was my next target – "Yes", he would give a contribution. I then tried Ron Wallace, Mayor of Halifax, and was promised $50. Then I rang all of the doctors I knew as well as medical representatives. They were all generous and none refused. The only problem was, many were away on holiday so I was nowhere near my thousand dollar target. Next I approached several automobile centers, Subaru and Honda both contributed.

At last I had sponsors for my thousand dollars. The great day arrived. My old bike had been carefully tuned by Mr. Beaver of The Trail Shop and it hummed along like a new top. I had practised every morning at 6 am and felt the task should not be impossible.

As we assembled in Mount Uniacke, I felt a little nervous. It reminded me of taking exams, those mental butterflies that flutter before you sit down for an unpredictable task.

Dr. B. Grogono, a young 69, in action wearing his "Thousand Dollar T-Shirt"

*Orthopaedic Surgeon, Halifax Infirmary, Halifax, N.S.

"Have a good ride and drive carefully," remarked our Constable. The chaos of bikes and bodies somehow became transformed and was to be set along the wonderful sloping roads along Windsor and beyond. These were historic road where Haliburton, Eisenhauer and Uniacke all travelled in carriages in Nova Scotia's early days. A century later, automobiles and trucks were regraded to second class vehicles as more than one hundred cycles sped on their way. Hills and hills, my gears worked smoothly but there were always many athletic types speeding past.

The route along the main highway crossed Avonport and Acadia. The Evangeline brought the ride to Grand Pré . Eventually we arrived at Acadia University where we stayed over night for an evenings entertainment.

The return journey was the real test. It seemed to be uphill all the way. I stopped several times along the way for photographs. It's difficult to appreciate the beauty of the countryside as you relentlessly peddle, peddle . . . . peddle!

At last, Mount Uniacke was in sight. I over took a small group of cyclists to reach the final post. It had been over four hours before I spied my wife and grandson on the finish line. "We have been waiting for you for over and hour, but you're not quite the last!"

Now it was time to make those phone calls and visit numerous offices to finally deliver the thousand dollars to the Multiple Sclerosis Society. I hope this wonderful weekend encouraged others to support the much needed help for Multiple Sclerosis.

This Bike Ride raised $60,000 in Nova Scotia and $400,000 across Canada. The idea of an issue of *The Nova Scotia Medical Journal* devoted to Multiple Sclerosis had been hatched! □

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Anti-inflammatory analgesic agent

ACTION and CLINICAL PHARMACOLOGY: Animal pharmacological studies have shown that ketoprofen possesses anti-inflammatory, analgesic and antipyretic properties. The anti-inflammatory action is not mediated through the pituitary adrenal axis. Its therapeutic effectiveness has been demonstrated by a reduction in joint swelling, pain and duration of morning stiffness, and by increased grip strength and an improvement in functional capacity. Clinical trials in patients with rheumatoid arthritis and osteoarthritis have shown that when given in a dose of 200 mg once daily, the anti-arthritic activity of Oruvail is comparable to that of a twice daily administration of ketoprofen (100 mg ketoprofen b.i.d.). Ketoprofen 200 mg daily induced less gastrointestinal bleeding than acetylsalicylic acid 4 g/day. **Pharmacokinetics properties:** Ketoprofen from Oruvail is slowly but almost completely absorbed from the gastrointestinal tract. Mean peak plasma levels of 2.2 and 4.2 mg/L are achieved about 5 hours following single oral doses of Oruvail 100 and 200 mg, respectively. Pharmacokinetics are linear over a dosage range of 100 to 200 mg. The systemic availability of Oruvail is 95% of that of conventional capsules. In a food-effect study, meal composition did not affect the extent of absorption of ketoprofen from Oruvail, although a heavy meal slightly but significantly delayed the absorption of the drug by about 2 hours by comparison to a light meal; in this study, there was no comparison with the fasted state nor with a conventional ketoprofen formulation. Steady-state plasma ketoprofen concentrations are achieved within 4 days with mean peak and trough levels of 4.3 and 0.91 mg/L respectively, after repeated doses of 200 mg once daily. There is some evidence that C_{max} and bioavailability are increased in the elderly as the result of an age-related reduction in volume of distribution since the apparent elimination half-life of about 8 hours is similar in both young and elderly patients. No or negligible accumulation of ketoprofen was found following repeated once daily dosing of Oruvail 200 mg capsules in either young or aged subjects. In arthritic patients treated with Oruvail 200 mg once daily for up to 3 months, the steady-state disposition of ketoprofen remains unaltered during chronic administration. When comparing to a group of healthy subjects, no differences with respect to AUC, C_{max}, and elimination half-life were found, indicating that inflammatory joint disease has no influence on the kinetics of Oruvail capsules.

INDICATIONS and CLINICAL USES: Oruvail (ketoprofen) is indicated in the treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis.

CONTRAINDICATIONS: Oruvail (ketoprofen) is contraindicated in patients with active peptic ulcers or active inflammatory diseases of the gastrointestinal tract. Oruvail is also contraindicated in patients who have demonstrated hypersensitivity to the drug. Because of cross-sensitivity, ketoprofen should not be given to patients in whom acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria. Fatal anaphylactoid reactions have occurred in such individuals.

WARNINGS: Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with nonsteroidal anti-inflammatory drugs (NSAID's), including Oruvail (ketoprofen). Unlike most adverse reactions, which usually manifest themselves in the first month if they are going to occur in an individual, new peptic ulcers keep appearing in patients under treatment with ketoprofen at a rate of greater than 1% per year. Oruvail should be given under close medical supervision to patients prone to gastrointestinal tract irritation particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract. In these cases the physician must weigh the benefits of treatment against the possible hazards. Patients taking any NSAID including this drug should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning symptoms or signs and at any time during the treatment. Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAID's). For such patients, consideration should be given to a starting dose lower than usual, with individual adjustment when necessary and under close supervision. See "Precautions" for further advice. **Use in Pregnancy:** The safety of Oruvail when administered to pregnant or nursing women has not been determined and therefore such use is not recommended. Pregnant rats who received ketoprofen 6 and 9 mg/kg/day p.o. from day 15 of gestation, showed dystocia and increased pup mortality. **Nursing mothers:** In rats, ketoprofen at doses of 9 mg/kg (approximately 1.5 times the maximum human therapeutic dose) did not affect perinatal development. Upon administration to lactating dogs, the milk concentration of ketoprofen was found to be 4 to 5% of the plasma drug level. Data on secretion in human milk after ingestion of ketoprofen do not exist. As with other drugs that are excreted in milk, Oruvail is not recommended for use in nursing mothers. **Use in Children:** The conditions for safe and effective use of Oruvail in children under 12 years of age have not been established and the drug is therefore not recommended in this age group.

PRECAUTIONS: Gastrointestinal system: If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs Oruvail (ketoprofen) should be discontinued, an appropriate treatment instituted and patient closely monitored. There is no definitive evidence that the concomitant administration of histamine H_2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of Oruvail therapy when and if these adverse reactions appear. **Renal function:** As with other nonsteroidal anti-inflammatory drugs, long-term administration of ketoprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state. Ketoprofen and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with great caution in patients with impaired renal function. In these cases lower doses of Oruvail should be anticipated and patients carefully monitored. During long-term therapy kidney function should be monitored periodically. **Hepatic function:** As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful (3 times the upper limit of normal) elevations of ALT or AST occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with this drug as with other nonsteroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), this drug should be discontinued. During long-term therapy, liver function tests should be monitored periodically. If this drug is to be used in the presence of impaired liver function, it must be done under strict observation. **Fluid and Electrolyte Balance:** Fluid retention and edema have been observed in approximately 2% of patients treated with ketoprofen. Therefore, as with many other nonsteroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be born in mind. Oruvail should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention. Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients at risk. **Hematology:** Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when Oruvail is administered. Blood dyscrasias associated with the use of nonsteroidal anti-inflammatory drugs are rare, but could be with severe consequences. Anemia is commonly observed in rheumatoid arthritis and is sometimes aggravated by nonsteroidal anti-inflammatory drugs, which may produce fluid retention or minor gastrointestinal blood loss in some patients. Therefore, patients with initial hemoglobin values of 10 g/dL or less who are to receive long-term therapy should have hemoglobin values determined frequently. **Infection:** In common with other anti-inflammatory drugs, Oruvail may mask the usual signs of infection. **Ophthalmology:** Blurred and/or diminished vision has been reported with the use of ketoprofen and other nonsteroidal anti-inflammatory drugs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time. **Drug Interactions: Methotrexate:** The concomitant administration of ketoprofen and high-dose methotrexate has been associated with prolonged and marked enhancement of serum methotrexate levels resulting in severe methotrexate toxicity. This may also apply to some other nonsteroidal anti-inflammatory drugs. There were no abnormalities in methotrexate kinetics or evidence of toxicity when ketoprofen was given at least 12 hours after completion of high-dose methotrexate infusion. ORUVAIL should not be used in patients receiving high dose methotrexate. The potential for severe toxicity should be kept in mind when prescribing ketoprofen and low-dose methotrexate concurrently. ORUVAIL should not be administered within 12 hours of methotrexate infusion. **Acetylsalicylic acid (ASA):** concurrent administration of ASA decreased ketoprofen protein binding and increased its plasma clearance. The overall result was a 40% reduction in the AUC of ketoprofen. **Oral anticoagulants:** Ketoprofen has been shown to depress platelet aggregation and it can prolong bleeding time by approximately 3 to 4 minutes from baseline values. However, a study conducted in twenty patients undergoing therapy with coumarin and simultaneously receiving ketoprofen, failed to demonstrate potentiation of anticoagulant effect. Nevertheless, close monitoring of patients is recommended when Oruvail is given concomitantly with anticoagulants. **Diuretics:** hydrochlorothiazide, given concomitantly with ketoprofen, produces a reduction in urinary potassium and chloride excretion compared to hydrochlorothiazide alone. Patients taking diuretics are at greater risk of developing renal failure secondary to a decrease in renal blood flow caused by prostaglandin inhibition. **Antacids:** concomitant administration of magnesium hydroxide and aluminum hydroxide does not interfere with the rate or extent of the absorption of ketoprofen. **Lithium:** nonsteroidal anti-inflammatory agents have been reported to increase steady-state plasma lithium levels. It is recommended that plasma lithium levels be monitored when Oruvail is coadministered with lithium. **Probenecid:** concurrent administration of probenecid increases both free and bound ketoprofen through reducing the plasma clearance of ketoprofen to about one-third as well as decreasing its protein binding. ORUVAIL is not recommended in association with probenecid. Ketoprofen is extensively (99%) protein bound to human serum albumin and may compete for binding sites with drugs such as sulfonamides, oral hypoglycemic agents, phenytoin or lithium. Although no significant interaction has been documented, patients with such combination therapy should be monitored. **Clinical Laboratory Test:** The presence of ketoprofen and its metabolites in urine has been shown to interfere with certain tests which are used to detect albumin, bile salts, 17-ketosteroids or 17-hydroxycorticosteroids in urine and which rely upon acid precipitation as an end point or upon colour reactions for carbonyl groups. No interference was seen in the tests for proteinuria using Albustix, Hema-Combistix or Labstix Reagent Strips. Ketoprofen decreases platelet adhesion and aggregation. Therefore, it can prolong bleeding time by approximately 3 to 4 minutes from baseline values. There is no significant change in platelet count, prothrombin time, partial thromboplastin time, or thrombin time.

ADVERSE REACTIONS: Gastrointestinal: Gastrointestinal effects were the most frequently observed adverse reactions and were seen in approximately 13% of patients receiving Oruvail (ketoprofen). Ulceration and gastrointestinal bleeding have been observed in a few patients receiving Oruvail therapy (approximately 0.3%). Other adverse reactions in order of decreasing frequency were: gastrointestinal pain, dyspepsia, constipation, nausea and/or vomiting, diarrhea and flatulence. Such symptoms led to the discontinuation of treatment in 6.8% of patients. **Central Nervous System:** Central nervous system adverse reactions were next in frequency and included headache, fatigue, drowsiness, dizziness, depression, restlessness and nightmares. **Skin:** rash, eczema, flushing, pruritus, sweating and loss of hair were occasionally observed. **Allergic:** These were seen infrequently and included urticaria, angioedema and asthma. **Cardiovascular:** Mild peripheral edema, palpitation, bruising, arrhythmia, chest pain and exacerbation of circulatory disturbances were reported. **Auditory:** Tinnitus and deafness were reported on rare occasions. **Mouth:** The following symptoms were reported: dry mouth, mouth ulcers, sore tongue and inflammation of the mouth and gums. **Laboratory tests:** Abnormal alkaline phosphatase lactic dehydrogenase, glutamic oxaloacetic transaminase and blood urea nitrogen values were found in some patients receiving ketoprofen therapy. The abnormalities did not lead to discontinuation of treatment and, in some cases, returned to normal despite continuation of the drug. There have been sporadic reports of decreased hematocrit and hemoglobin values without progressive deterioration on prolonged administration of the drug.

SYMPTOMS AND TREATMENT OF OVERDOSE: Symptoms: Of 20 cases of overdosage (up to 5,000 mg) reported in Great Britain (5 children, 14 adolescents or young adults, and 1 elderly), only 4 had mild symptoms (vomiting in 3, drowsiness in 1 child). **Treatment:** Administer gastric lavage or an emetic and treat symptomatically: compensate for dehydration, monitor urinary excretion and correct acidosis if present. The drug is dialyzable; therefore, hemodialysis may be useful to remove circulating drug and to assist in case of renal failure.

DOSAGE AND ADMINISTRATION: Adults: The usual dosage is 150 to 200 mg once daily. The capsules should be taken with food and can be administered in the morning or evening. **Elderly and debilitated patients:** The dosage should be reduced in patients with impaired renal function and the elderly. The lower strength should be used in those cases. **Children:** Oruvail is not indicated in children under 12 years of age because clinical experience in this age group is insufficient. **Composition:** Non medicinal ingredients: colloidal silicone dioxide, ethyl cellulose, gelatin, maize starch, shellac, sucrose, talc. Colouring agents: ORUVAIL 150 mg: erythrosine, titanium dioxide. ORUVAIL 200 mg: brilliant blue, erythrosine, titanium dioxide.

AVAILABILITY: Oruvail 150 capsules: each transparent pink capsule with opaque white cap (each half printed "Oruvail 150" in black) contains ketoprofen 150 mg as white pellets. Available in bottles of 100 and 250. **Oruvail 200 capsules:** each transparent pink capsule with opaque blue cap (each half printed "Oruvail 200" in yellow) contains ketoprofen 200 mg as white pellets. Available in bottles of 100 and 250.

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INDICATIONS AND CLINICAL USE
Short term symptomatic relief of excessive anxiety in patients with generalized anxiety disorder (psychoneurotic disorder).

Eight three-way, short term, controlled clinical trials involving buspirone, diazepam and placebo are considered central to the evaluation of buspirone as an anxiolytic agent. In four of the eight clinical trials, buspirone demonstrated a significant difference from placebo. In the other four trials, there was no significant difference between buspirone and placebo, but a significantly greater improvement was observed with diazepam than with placebo. The adverse effect profiles of buspirone and diazepam in these clinical trials were, however, different.

CONTRAINDICATIONS
BuSpar (buspirone hydrochloride) is contraindicated in patients hypersensitive to buspirone hydrochloride.

BuSpar is contraindicated in patients with severe hepatic or severe renal impairment.

WARNINGS
The occurrence of elevated blood pressure in patients receiving both BuSpar (buspirone hydrochloride) and a monoamine oxidase inhibitor (MAOI) has been reported. Therefore, it is recommended that buspirone should not be used concomitantly with a MAOI.

Since buspirone can bind to central dopaminergic receptors, the possibility of acute and chronic changes in dopamine mediated neurological function (e.g. dystonia, pseudo-parkinsonism, akathisia and tardive dyskinesia) should be considered. (SEE PRECAUTIONS)

Since the effects of buspirone have not been evaluated in patients with a history of convulsive disorders and since it lacks anticonvulsant activity in animals, buspirone is not recommended for patients with seizure disorders.

Use of Buspirone in Patients Previously Treated with a Benzodiazepine: Patients who have previously taken benzodiazepines may be less likely to respond to buspirone than those who have not. In two clinical studies to date, substitution of buspirone did not ameliorate or prevent withdrawal symptoms in either abrupt or gradual withdrawal from various benzodiazepines following long-term use. Therefore, if it is considered desirable to switch a patient who has been receiving benzodiazepine therapy to buspirone, the benzodiazepine should first be withdrawn gradually. A drug-free interval is desirable between withdrawal of the benzodiazepine and initiation of buspirone, in order to increase the likelihood of distinguishing between benzodiazepine withdrawal effects and unrelieved anxiety due to possible failure of buspirone in this category of patients.

Benzodiazepine rebound or withdrawal symptoms may occur over varying time periods depending in part on the type of drug and its effective half-life of elimination. These symptoms may appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever and, occasionally, seizures, and should be treated symptomatically.

Use in Pregnancy and Lactation: The safety of buspirone during pregnancy and lactation has not been established and, therefore, it should not be used in women of childbearing potential or nursing mothers, unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus. Buspirone and its metabolites are excreted in milk in rats. The extent of excretion in human milk has not yet been determined.

PRECAUTIONS
Effects on Cognitive and Motor Performance: In controlled studies in healthy volunteers, single doses of buspirone up to 20 mg had little effect on most tests of cognitive and psychomotor function, although performance on a vigilance task was impaired in a dose-related manner. The effect of higher single doses of buspirone on psychomotor performance has not been investigated.

Ten (10) mg of buspirone given three times daily for seven days to healthy volunteers produced considerable subjective sedation but no significant effect on psychomotor performance (no vigilance tasks were used in this study). It also caused transient dizziness, especially on standing and walking.

Until further experience is obtained with buspirone, patients should be warned not to operate an automobile or undertake activities requiring mental alertness, judgement and physical coordination, until they are reasonably certain that buspirone does not affect them adversely.

Significant Interactions: In laboratory studies in healthy volunteers, buspirone in doses up to 20 mg did not potentiate the psychomotor impairment produced by relatively modest doses of alcohol. However, decreased contentedness or dysphoria was observed with a combination of alcohol and a 20 mg single dose of buspirone. Since no data are available on concomitant use of higher doses of buspirone and alcohol, it is prudent to advise patients to avoid alcohol during buspirone therapy.

Food increased the bioavailability of unchanged buspirone in healthy subjects, possibly due to a reduced first-pass effect.

Concomitant use of monoamine oxidase inhibitors and buspirone has been reported to cause an increase in blood pressure. Therefore, concomitant use of these medications is not recommended.

In a study in normal volunteers, no interaction of buspirone with amitriptyline was seen. A similar study with diazepam showed an increase in the levels of nordiazepam.

In another study in normal volunteers, concomitant administration of buspirone and haloperidol resulted in increased serum haloperidol concentrations. The clinical significance of this finding is not clear.

There is one report suggesting that the concomitant use of trazodone and buspirone may have caused 3- to 6-fold elevations in SGPT (ALT) in a few patients. In a similar study, attempting to replicate this finding, no interactive effect on hepatic transaminases was identified.

Because the effects of concomitant administration of buspirone with most other psychotropic drugs have not been studied, the concomitant use of buspirone with other CNS active drugs should be approached with caution.

In vitro, buspirone does not displace tightly bound drugs like phenytoin, propranolol and warfarin from serum proteins. However, there has been one report of prolonged prothrombin time when buspirone was added to the regimen of a patient treated with warfarin. The patient was also chronically receiving phenytoin, phenobarbital, digoxin and Synthroid. In vitro, buspirone may displace less firmly bound drugs like digoxin. The clinical significance of this property is unknown.

There have been no reports to date of interference of buspirone with commonly employed clinical laboratory tests.

Drug Abuse and Dependence: Although preliminary animal and human investigations suggest that buspirone may be significantly devoid of potential for producing physical or psychological dependence, only extensive clinical experience with the drug will provide conclusive evidence. Meanwhile, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse and abuse.

Use in Patients with Impaired Hepatic or Renal Function: Since it is metabolized by the liver and excreted by the kidneys, buspirone should be used with caution in patients with a history of hepatic or renal impairment. It is contraindicated in patients with severe hepatic or renal impairment.

Use in Children: The safety and effectiveness of buspirone in individuals below the age of 18 years have not been established.

Use in the Elderly: Buspirone has not been systematically evaluated in older patients. Although it would appear from limited pharmacokinetic and clinical studies that buspirone does not behave differently in the elderly, there is little known about the effects of buspirone in this age group at doses above 30 mg/day. Therefore, it is recommended that buspirone should be used in the elderly at doses not exceeding 30 mg/day for a duration not exceeding 4 weeks.

Neuroendocrine Effects: Single doses of 30 mg or higher of buspirone resulted in significantly elevated plasma prolactin and growth hormone concentrations in normal volunteers. No effect was seen at lower doses. In another study, no such increases were observed after buspirone was administered in divided doses (10 mg t.i.d.) for 28 days.

Possible Concerns Related to Buspirone's Binding To Dopamine Receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudo-parkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). Obviously, the question cannot be totally resolved at this point in time. Generally, long-term sequelae of any drug's use can be identified only after several years of marketing.

ADVERSE REACTIONS
The most common adverse reactions encountered with BuSpar (buspirone hydrochloride) are dizziness, headache, drowsiness and nausea. During premarketing clinical trials, approximately 10% of the patients discontinued treatment due to an adverse event.

Adverse reactions reported include the following:

CNS: Dizziness, headache, drowsiness, lightheadedness, insomnia, fatigue, nervousness, decreased concentration, excitement, depression, confusion, nightmares/vivid dreams, anger/hostility. Infrequently (<1%) depersonalization, noise intolerance, euphoria/feeling high, dissociative reaction, fear, loss of interest, dysphoria, hallucinations, seizures, suicidal thoughts. Rarely, slurred speech, claustrophobia, cold intolerance, stupor, psychosis.

Neurologic: Paresthesia, weakness, incoordination, tremor, numbness. Infrequently, muscle cramps and spasms, rigid/stiff muscles, involuntary movements, akathisia, slowed reaction time. Rarely, tingling of limbs, stiff neck, rigidity of jaw, ataxia.

Autonomic: Dry mouth, sweating/clamminess, blurred vision, constipation. Infrequently, urinary frequency, retention and burning, flushing.

Cardiovascular: Tachycardia, chest pain, palpitations. Infrequently, syncope, hypotension, hypertension. Rarely, congestive heart failure, cerebrovascular accident, myocardial infarction, cardiomyopathy, bradycardia, EKG change.

Gastrointestinal: Nausea, G.I. distress, diarrhea, vomiting. Infrequently, flatulence, increased appetite, anorexia, hypersalivation, rectal bleeding, irritable colon. Rarely, burning tongue.

Respiratory: Nasal congestion. Infrequently, shortness of breath, chest congestion, difficulty breathing, hyperventilation. Rarely, epistaxis.

Endocrine: Infrequently, decreased and increased libido, weight gain, weight loss, menstrual irregularity/breakthrough bleeding. Rarely, delayed ejaculation, impotence, galactorrhea, amenorrhea, thyroid abnormality.

Allergic or Toxic: Skin rash, sore throat. Infrequently, edema/facial edema, pruritus, chills/fever. Rarely, photophobia, erythema, flu-like symptoms.

Clinical Laboratory: Infrequently, increases in liver enzymes. Rarely, eosinophilia, leukopenia, thrombocytopenia.

Miscellaneous: Tinnitus, muscle aches/pains. Infrequently, redness/itching of eyes, altered taste/smell, roaring sensation in head, malaise, easy bruising, dry skin, arthralgia, blisters, hair loss. Rarely, acne, thinning of nails, sore eyes, inner ear abnormality, pressure on eyes, nocturia, enuresis, hiccups; voice loss, alcohol abuse.

Post Introduction Clinical Experience: Post-marketing experience in the United States has shown an adverse experience profile similar to that given above. Additional reports have included rare occurrences of allergic reaction, cogwheel rigidity, dystonic reaction, ecchymosis, emotional lability and tunnel vision. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to buspirone treatment has not been determined.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
Symptoms: In clinical pharmacology trials, BuSpar (buspirone hydrochloride) up to 400 mg/day was administered to healthy male volunteers. As this dose was approached, the following symptoms were observed in descending order of frequency: drowsiness, ataxia, nausea and vomiting, dizziness, clammy feeling, difficulty thinking, feeling "high", "rushing" sensation, gastric distress, headache, itching, miosis, hypotension, tremor, incoordination, insomnia and hallucinations. In a dose ranging study in acute psychotic patients, up to 2400 mg/day was administered. Dizziness, nausea and vomiting were the most common adverse effects. One patient developed extrapyramidal symptoms at 600 mg/day.

Treatment: There is no specific antidote for buspirone. Management should, therefore, be symptomatic and supportive. Any patient suspected of having taken an overdose should be admitted to a hospital as soon as possible, and the stomach emptied by gastric lavage. Respiration, pulse and blood pressure should be monitored, as in all cases of drug overdosage. As with the management of intentional overdosage with any drug, the ingestion of multiple agents should be suspected. In six anuric patients, hemodialysis either had no effect on the pharmacokinetics of buspirone or decreased its clearance.

DOSAGE AND ADMINISTRATION
BuSpar (buspirone hydrochloride) dosage should be individually adjusted, according to tolerance and response.

The recommended initial dose is 5 mg two to three times daily. This may be titrated according to the needs of the patient and the daily dose increased by 5 mg increments every two or three days up to a maximum of 45 mg daily in divided doses. The usual therapeutic dose is 20 to 30 mg daily in two or three divided doses.

Elderly Patients: Limited pharmacokinetic and clinical data have shown no difference in the effects of buspirone between elderly patients and healthy adult volunteers. However, until more information has accumulated in the elderly, it is recommended that the maximum daily dose should not exceed 30 mg for a duration not exceeding 4 weeks.

Note: If buspirone is administered to patients with compromised hepatic or renal function, careful monitoring will be required together with appropriate dosage adjustment.

AVAILABILITY
BuSpar (buspirone hydrochloride) Tablets, 10 mg, are white tablets. Bottles of 100.

Product Monograph available upon request.

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†Until further experience is obtained with buspirone, patients should be warned not to operate an automobile or undertake activities requiring mental alertness, judgement or physical co-ordination until they are reasonably certain that buspirone does not affect them adversely.

††Since no data is available on concomitant use of higher doses of buspirone and alcohol, it is prudent to advise patients to avoid alcohol during buspirone therapy.

*T.M. Authorized user, Bristol-Myers Squibb Canada Inc.

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BRISTOL

A division of Bristol-Myers Squibb Canada Inc.
2365 Côte-de-Liesse
Montréal, Québec H4N 2M7

Atrovent®

(ipratropium bromide)

INHALATION SOLUTION 250 µg/mL

THERAPEUTIC CLASSIFICATION

Bronchodilator

INDICATIONS AND CLINICAL USES

Atrovent (ipratropium bromide) solution is indicated for the therapy of acute exacerbations of chronic bronchitis. Atrovent solution, when used in conjunction with a β_2-adrenergic stimulant solution such as fenoterol or salbutamol, is indicated for acute asthmatic attacks. It is to be administered by compressed air or oxygen driven nebulizers.

CONTRAINDICATIONS

Known hypersensitivity to Atrovent (ipratropium bromide), to any of the product ingredients, or to atropinics.

WARNINGS

Atrovent (ipratropium bromide) solution in the 20 mL multidose bottle contains preservatives (benzalkonium chloride and disodium ethylene diamine tetraacetic acid - EDTA-disodium). It has been reported that these preservatives may cause bronchoconstriction in some patients with hyperreactive airways.

The 2 mL unit dose vial does not contain preservatives.

Atrovent should not be used alone for the abatement of an acute asthmatic attack since the drug has a slower onset of effect than that of an adrenergic β_2 agonist.

Care should be taken to ensure that the nebulizer mask fits the patient's face properly and that nebulized solution does not escape into the eyes. There have been isolated reports of ocular complications (i.e., mydriasis, increased intraocular pressure, angle closure glaucoma) when nebulized ipratropium bromide either alone or in combination with an adrenergic β_2 agonist solution has escaped into the eyes. In the event that glaucoma is precipitated or worsened, treatment should include standard measures for this condition.

PRECAUTIONS

General:

-Patients should be instructed in the proper use of the nebulizer.

-Caution is advised against accidental release of the solution into the eyes.

-In patients with glaucoma, prostatic hypertrophy or urinary retention, Atrovent (ipratropium bromide) should be used with caution.

-If a reduced response to Atrovent becomes apparent, the patient should seek medical advice.

-Atrovent solution, when administered to patients with acute severe asthma, should be used with concomitant β_2-adrenergic stimulant therapy.

Use in Pregnancy:

The safety of Atrovent in pregnancy has not been established. The benefits of using Atrovent when pregnancy is confirmed or suspected must be weighed against possible hazards to the fetus. Studies in rats, mice and rabbits showed no embryotoxic nor teratogenic effects.

Use During Lactation:

No specific studies have been conducted on excretion of this drug in breast milk. Benefits of Atrovent use during lactation should therefore be weighed against the possible effects on the infant.

Use in Children:

The efficacy and safety of Atrovent in children younger than 5 years has not been established.

Use with Other Drugs:

In patients receiving other anticholinergic drugs, Atrovent should be used with caution because of possible additive effects.

In patients with glaucoma or narrow anterior chambers, the administration by nebulizer of combined Atrovent-β_2 agonist solution should be avoided unless measures (e.g., use of swimming goggles) are taken to ensure that nebulized solution does not reach the eye. Exposure of the eyes of such patients to a nebulized combination of Atrovent and a β_2 agonist solution has been reported to result in increased intraocular pressure and/or acute angle closure.

Atrovent solution with preservatives (i.e. from the 20 mL multidose bottle) should not be mixed with sodium cromoglycate, as this produces a cloudy solution caused by complexation between the preservatives and sodium cromoglycate. If the patient's condition requires the administration of sodium cromoglycate, it should be given in combination with Atrovent solution without preservatives (i.e., from the unit dose vial).

ADVERSE REACTIONS

The frequency of adverse reactions recorded in 214 patients receiving Atrovent (ipratropium bromide) solution was as follows, given by percentage of patients reporting: Dry mouth or throat, 9.3; Bad taste, 5.1; Tremor, 4.2; Exacerbation of symptoms, 4.2; Burning eyes, 0.9; Nausea, 0.9; Sweating, 0.9; Cough, 0.9; Headache, 0.5; Palpatations, 0.5.

The adverse effect judged to be most severe was exacerbation of symptoms. This occurred in 8 patients treated with Atrovent solution alone, 6 of whom withdrew from the clinical studies.

Bronchospasm occurred in 3 patients with acute severe asthma who received Atrovent solution alone. In two patients, this was reversed after therapy with β_2 sympathomimetic solution. The third patient received no other therapy.

The following table compares the incidence of adverse effects of the combination of Atrovent and a β_2 agonist (either fenoterol or salbutamol) solution with that of the β_2 agonist alone.

ADVERSE EFFECT	ATROVENT + β_2 AGONIST (% of 94 patients)	β_2 AGONIST (% of 96 patients)
Tremor	31.9	26.0
Dry mouth	16.0	28.1
Bad taste	16.0	13.5
Vomiting	2.1	2.1
Palpitations	2.1	1.0
Headache	1.1	2.1
Cough	1.1	0.0
Flushing	1.1	0.0
Dizziness	0.0	1.0
Numbness in leg	0.0	1.0

There have been isolated reports of ocular effects such as mydriasis, increased intraocular pressure, and acute glaucoma associated with the escape of nebulized ipratropium bromide-alone or in combination with a β_2 agonist solution into the eyes.

DOSAGE AND ADMINISTRATION

In adults, the average single dose is 1-2 mL of Atrovent (ipratropium bromide) solution, containing 250-500 µg of ipratropium. In children, aged 5-12 years, the recommended dose is 0.5-1 mL (125-250 µg of ipratropium). This should be diluted to 3-5 mL with preservative free sterile Normal Saline [Sodium Chloride Inhalation Solution, USP 0.9%] or with a bacteriostatic sodium chloride solution, 0.9% preserved with benzalkonium chloride (see PHARMACEUTICAL INFORMATION).

Nebulization should take place using a gas flow (oxygen or compressed air) of 6-10 L/minutes and the solution nebulized over a 10-15 minute period. The Hudson Updraft™, Bennett Twin Jet® and Inspiron Mini-Neb® nebulizers, with facemask or mouthpiece have been used. The manufacturers' instructions concerning cleaning and maintenance of the nebulizer should be strictly followed.

Treatment with Atrovent solution may be repeated every 4-6 hours as necessary.

PHARMACEUTICAL INFORMATION

Stability and Storage Recommendation:

20 mL Bottle: Unopened bottles of Atrovent (ipratropium bromide) solution should be stored at controlled room temperature (below 30°C). Solutions diluted with preservative free sterile Sodium Chloride Inhalation Solution, USP 0.9% should be used within 24 hours from time of dilution when stored at room temperature and within 48 hours when stored in the refrigerator.

Dilutions may also be made with a bacteriostatic sodium chloride solution 0.9% which contains benzalkonium chloride as the bacteriostatic agent (see WARNINGS). This diluted solution may be stored at room temperature and used within 7 days.

Controlled laboratory experiments using mixtures of Atrovent solution with Alupent® (orciprenaline sulfate), Berotec® (fenoterol hydrobromide) or salbutamol sulfate (6mg/mL preserved with benzalkonium chloride) solutions and diluted with a sterile bacteriostatic sodium chloride solution 0.9% (i.e. normal saline), preserved with benzalkonium chloride, indicated that such mixtures were stable for 7 days at room temperature. For the preparation of such mixtures, it is recommended that only sterile solutions of bacteriostatic sodium chloride 0.9% preserved with 0.01% benzalkonium chloride be used to maintain the level of preservative in the mixture.

The safety of preservatives other than benzalkonium chloride has not been established.

Incompatibilities: Atrovent solution with preservatives (i.e. from the 20 mL multidose bottle) should not be mixed with sodium cromoglygate solution, as this produces a cloudy solution caused by complexation between the preservatives and sodium cromoglycate. If the patient's condition requires the administration of sodium cromoglycate, it should be given in combination with Atrovent solution without preservatives (i.e., from the unit dose vial).

2 mL Unit Dose Vial: Unopened unit dose vials of Atrovent solution should be stored at controlled room temperature (below 30°C) and protected from light. If required, the solution should be diluted with a preservative free sterile sodium chloride solution 0.9% and used immediately. Any solution remaining in the vial must be discarded.

The solution is physically compatible with Alupent® (orciprenaline sulfate), Berotec® (fenoterol hydrobromide) or salbutamol sulfate (6 mg/mL) solutions. If such mixtures are prepared, they should be diluted with preservative free sterile sodium chloride solution 0.9% and used immediately. Any unused portion of such combined solutions must be discarded.

AVAILABILITY

20 mL Bottle: Atrovent (ipratropium bromide) solution is provided as 20 mL clear, colourless or almost colourless solution containing 250 µg/mL (0.025%) Atrovent in isotonic solution. This solution is preserved with benzalkonium chloride 250 µg/mL and EDTA-disodium 500 µg/mL at pH 3.4 in an amber glass bottle with screwcap.

2 mL Unit Dose Vial: Atrovent solution is also provided as 2mL of clear, colourless solution containing 250 µg/mL (0.025%) ipratropium bromide in isotonic solution, presented in a plastic single use vial. One vial contains a total of 500 µg of ipratropium bromide.

The complete Product Monograph for Atrovent (ipratropium bromide) Inhalation Solution is available to health professionals on request. Patient Information/ Instructions are provided with the solution.

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Boehringer Ingelheim

Dedicated to Respiratory Care

Boehringer Ingelheim (Canada) Ltd./Ltée
5180 South Service Rd., Burlington, Ontario L7L 5H4

B-020/92

TILADE®

Nedocromil Sodium Inhalation Aerosol
2mg/metered dose

THERAPEUTIC CLASSIFICATION
Bronchial Anti-inflammatory Agent

ACTIONS AND CLINICAL PHARMACOLOGY
TILADE (nedocromil sodium) is a new chemical entity that inhibits the release of inflammatory mediators from a variety of cell types occurring in the lumen and in the mucosa of the bronchial tree. When it is administered topically to the bronchi, it displays specific anti-inflammatory properties. Laboratory experiments have shown that nedocromil sodium prevents the release of inflammatory chemotactic and smooth muscle contracting mediators, which are preformed or derived from arachidonic acid metabolism by both the lipoxygenase and cyclo-oxygenase pathways, in a range of human and animal leucocytes. Nedocromil sodium prevents the release of mediators, such as, histamine, Leukotriene C_4 (LTC_4) and Prostaglandin D_2 (PGD_2) from the cellular population of the chronically inflamed bronchus, especially from mast cells of the mucosal type. There is growing evidence that these mediators are important in human lung disease, and TILADE may, therefore, be expected to have more scope in the management of chronic reversible obstructive airways disease in which allergy, inflammation and bronchial hyperresponsiveness are significant pathophysiological factors.

After inhalation, TILADE is deposited throughout the respiratory tract where about 5% of the dose is absorbed. Because TILADE is inhaled much of the delivered dose is either swallowed directly or subsequently due to mucociliary clearance from the large airways. A small amount of nedocromil sodium (2 to 3%) is then absorbed from the gastrointestinal tract. Since the absorption rate constant from the respiratory tract is lower than the elimination rate constant in bile and urine, the terminal half-life (1.5 to 2 hours) reflects the absorption rate of the lungs. The drug is cleared rapidly enough from the circulation such that successive doses in the recommended dosing regimen do not accumulate.

Nedocromil sodium is bound reversibly (80%) to human plasma proteins and to a lesser extent in animals. It is not metabolized in man or in animals. In man it is excreted unchanged in the urine (approximately 70%) and in faeces (approximately 30%). While the plasma concentration falls rapidly (i.e., to 10% of peak levels in 8 hours) and urinary excretion is 90% complete within 12 hours, faecal elimination may take up to 3 days to be completed.

The pharmacokinetic profile of nedocromil sodium is similar in healthy volunteers and in patients with reversible obstructive airways disease. In challenge studies, a single dose of TILADE provided protection against bronchospasm provoked by stimulants such as, inhaled allergens, cold air, exercise and atmospheric pollutants.

INDICATIONS AND CLINICAL USE
TILADE (nedocromil sodium) is indicated as an adjunctive in the treatment of mild to moderate reversible obstructive airways disease, including bronchial asthma and bronchitis, particularly where allergic factors may be present.

TILADE can also be used on a maintenance or on an occasional basis in the prevention of bronchospasm provoked by stimulants, such as, inhaled allergens, cold air, exercise and atmospheric pollutants.

TILADE may be used safely with other anti-asthma drugs. The addition of TILADE may permit reduction of concomitant therapy.

CONTRAINDICATIONS
Known hypersensitivity to TILADE (nedocromil sodium), to sorbitan trioleate or to propellants such as dichlorotetraflourethane and dichlorodiflouromethane.

WARNINGS
TILADE (nedocromil sodium) should not be used for the relief of an acute attack of bronchospasm.

PRECAUTIONS
IN THE TREATMENT OF ASTHMA, TILADE (nedocromil sodium) SHOULD NOT BE USED AS AN ALTERNATIVE TO BRONCHODILATORS. However, addition of TILADE to the treatment regimen can reduce the need for concomitant medications. **This reduction should be done slowly and under close supervision. The requirements for the reduction of corticosteroids have not been established.**

To ensure optimal delivery to the bronchial tree patients should be carefully instructed in the proper use of the inhaler. For maximum benefit, patients should be reminded of the necessity to take TILADE regularly, as prescribed.

Abuse of fluorocarbon propellants may be hazardous. Deliberate inhalation of propellants in high concentrations, particularly under conditions of hypoxia, has resulted in toxic cardiovascular effects, severe CNS disturbances, and death. Acute toxic effects of TILADE would be restricted to propellant overdose or to aerosol induced bronchoconstriction. Nedocromil sodium itself has an extremely low acute toxicity.

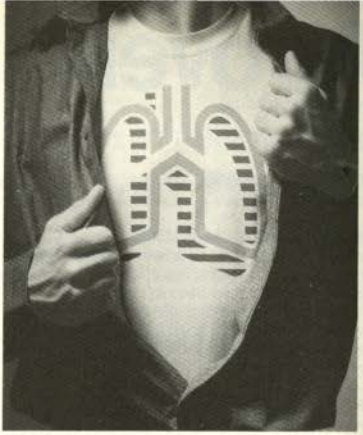
Use in Pregnancy Safety in human pregnancy and the absence of adverse effects on the human reproductive process have not been established. Small amounts are known to cross the placenta but without effect in animals. In fact, in reproductive studies, nedocromil sodium at up to 100mg/kg (more than 800 times the human maintenance dose) has shown no teratogenic or embryotoxic effects, nor has it interfered with reproductive performance, gestation, parturition, or suckling. Nedocromil sodium did not affect male or female fertility nor did it alter the development of progeny.

Although there is no reason to suspect that nedocromil sodium affects the fetus or mother, as with any drug, caution must be exercised. The benefits of treatment to the mother must be weighed against the potential risk to the fetus before proposing its use.

Nursing Mothers Safety in breast-fed infants has not been established. Animal studies have indicated no toxicity of nedocromil sodium in suckling newborns receiving drug from the parent or directly by injection. The concentrations of nedocromil sodium in milk of animals were very low but have not been measured in human milk.

The benefits of treating a nursing mother must be weighed against potential risk to the infant.

Use in Children The safety and efficacy of TILADE in children under twelve years of age has not yet been established.



Drug Interactions TILADE has been used in association with other antiasthmatic drugs in man including β_2-adrenergic agonists, inhaled and oral corticosteroids, theophylline and other methylxanthines and, with ipratropium bromide. No drug-drug interactions have been observed in humans or in animals.

ADVERSE REACTIONS
Few side effects have been reported, principally unpleasant taste, headache and nausea, that have been mild and transient and insufficient to require discontinuation of treatment in nearly all cases.

Specific side effects and their frequencies of occurrence with chronic dosing are unpleasant taste 13.4%, headache 4.8%, nausea 3.8% and vomiting 1.1%.

SYMPTOMS AND TREATMENT OF OVERDOSE
There have been no reported cases of overdosage in humans. Animal studies have not shown evidence of toxic effects of TILADE (nedocromil sodium), even at high dosage. If overdosage is suspected, treatment should be supportive and directed to the control of the relevant symptoms.

DOSAGE AND ADMINISTRATION
TILADE (nedocromil sodium) is intended for regular daily usage and should not be used for relief of symptoms during an acute attack.

The therapeutic benefits of repeated doses of TILADE will be apparent in most patients within one week of starting treatment, but it may take longer on occasion.

Adults and children over 12 years of age: In initial and maintenance therapy, two actuations (4mg of nedocromil sodium) four times daily. Some patients can be maintained with two actuations twice daily.

TILADE in a single dose of two actuations (4mg) a few minutes before exposure provides protection against bronchospasm provoked by stimulants, such as, inhaled allergens, cold air, exercise and atmospheric pollutants.

DOSAGE FORM
Each 17mL pressurized, aluminium canister contains nedocromil sodium and sorbitan trioleate as surfactant with dichlorotetrafluorethane and dichlorodifluoromethane as propellants. Units are filled with material to provide a minimum of 112 metered actuations, delivering 2mg of nedocromil sodium. The pack consists of an aerosol canister with a plastic adaptor and a patient instruction sheet.

Product monograph available upon request.

REFERENCES: 1. Bianco S et al, *Respiration* 1989; 56:204-11. 2. Tilade product monograph 1990.

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NEDOCROMIL SODIUM

GENERAL INDEX

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