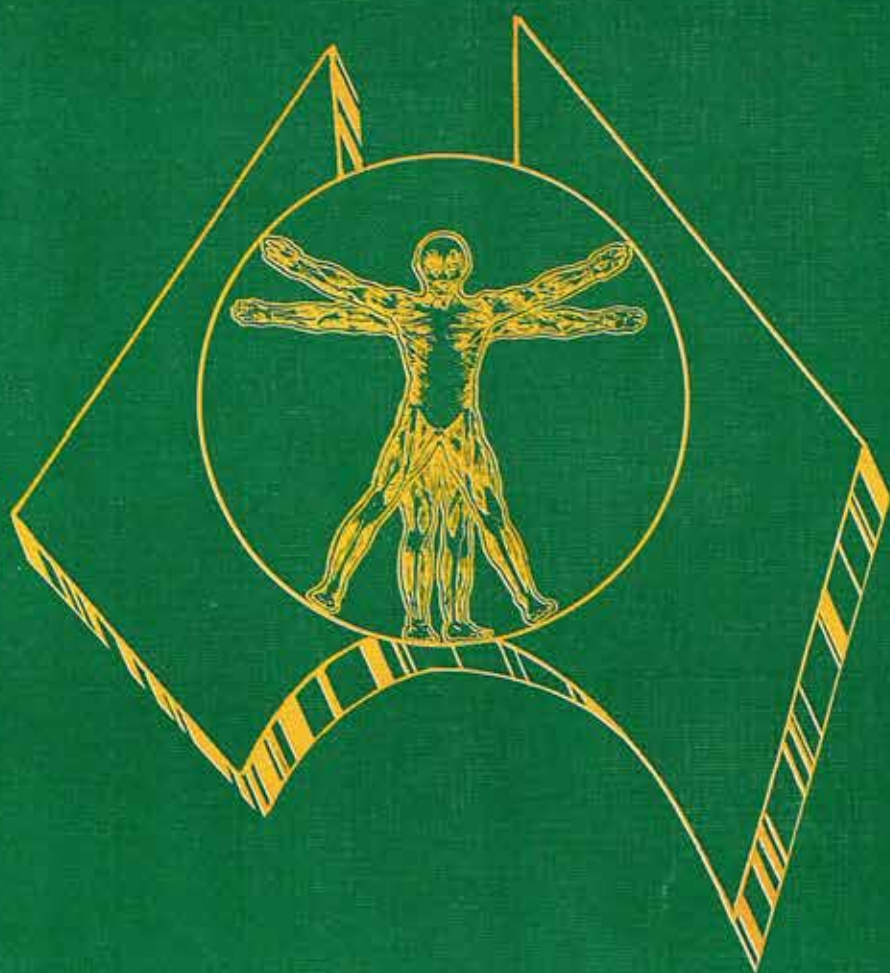


Australian
Association of
Musculoskeletal
Medicine

Bulletin



Special Feature: the newer N.S.A.I.D.s

Australian Association of Musculoskeletal Medicine



Bulletin

Vol. 1 No. 2

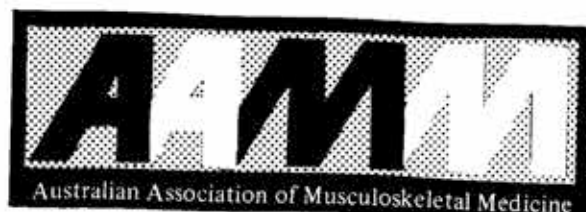
June 1985

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The A.A.M.M. Bulletin is published by the Australian Association of Musculoskeletal Medicine for medical practitioners interested in the aetiology and management of musculoskeletal disorders. Opinions expressed are those of the authors and not necessarily those of the editor or the Association. Editorial comment may reflect the opinions of the editor alone. Contributions on any relevant topic are welcome for submission to the editor, Dr. Wade King, 454 Peel Street, Tamworth, NSW, 2340, telephone (067) 66 6166, a.h. (067) 67 8262.
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About the



The Australian Association of Musculoskeletal Medicine is comprised of medical practioners interested in disorders of the musculoskeletal system.

The Association was formed on 6th December, 1971, when thirteen doctors met in Melbourne to discuss their common interest in the conservative management of back pain and other musculoskeletal problems. Ten others sent their apologies and these twenty-three became the foundation members of the association. The name Australian Association of Manipulative Medicine (A.A.M.M.) was chosen to reflect the common interest in manipulation, especially of the spine, as one form of conservative physical management. The name was distinctive, as most doctors then professed no interest in spinal manipulation and the scientific basis for such treatment was known to few. Several founding members of the new association were already members of the British Association of Manipulative Medicine (B.A.M.M.), which had been formed some ten years previously with similar objectives.

The fledgling A.A.M.M. held clinical meetings and annual conferences and encouraged members to present and publish scientific papers on relevant subjects. For several years the annual conferences were held in conjunction with the Australian Association of Physical and Rehabilitation Medicine (A.A.P. & R.M.), another group with some interests in common and to which some A.A.M.M. members also belonged (as indeed some still do).

By 1978 membership of A.A.M.M. had grown to 130 and organisation was strong enough to sponsor a large meeting with international guest speakers. Professor Malcolm Jayson of Manchester and Professor Justin Lehmann of Washington joined Australian academics and clinicians in a three day conference on back pain research. The meeting was well reported in the Australian medical press and the activities of the Association were seen to be providing leadership in an important area of need in medical practice. The A.A.M.M. seemed to have come of age.

In 1982 the Association met to consider a change of name. By then membership had reached 200 and encompassed a range of interests not adequately described by the term "Manipulative". After considerable discussion the name Australian Association of Musculoskeletal Medicine was chosen,

with the same initials as used previously. At the same time the constitution of the Association was amended to give better expression to the interests of members in all aspects of conservative management of musculoskeletal disorders.

Today the A.A.M.M. has a membership of approximately 300 doctors in all states of Australia. Their activities are spread over a broad range of musculoskeletal disciplines including orthopaedic medicine, manipulative medicine, osteopathic medicine, physical medicine, rehabilitation, rheumatology, acupuncture, neurology and orthopaedic surgery. The Association fosters interests in all musculoskeletal treatments consistent with scientific principles and encourages a wide range of treatment options with the use of the least invasive method appropriate to the management of each individual patient. In addition, the Association is active in the fields of education and research.

Local meetings are held regularly in a number of centres and annual conferences now usually feature international guest speakers. As well, the Association often sponsors speakers of high standing in other countries to come to Australia for lecture tours and instruction courses, which members and other doctors are encouraged to attend.

The Association conducts its own courses for medical graduates to learn or improve particular skills in musculoskeletal management. It also co-operates with other bodies active in postgraduate medical education, such as the University of Sydney's Coppleson Postgraduate Medical Institute and the Royal Australian College of General Practitioners. Some members of the A.A.M.M. are involved in the education of medical undergraduates and physiotherapists.

Dissemination of information about musculoskeletal medicine is another area of activity. Through its own publication, the A.A.M.M. Bulletin, and through letters and articles in other medical publications, members' perceptions are shared with a wide medical audience. The Association also acts in an advisory capacity to professional organisations and government bodies when musculoskeletal issues arise.

Some members are engaged in research, both laboratory projects and clinical studies. The Association encourages this and a committee on research and education meets regularly to consider ways of facilitating research and to develop better methods of spreading musculoskeletal knowledge and skills. A research proforma, to assist in the collection of comparable data by practitioners engaging in clinical studies, is available to members on request.

The A.A.M.M. liaises with other groups with similar interests, both in Australia and overseas. In this country, the Association is affiliated with the Australian Medical Association and maintains relationships with the A.A.P. & R.M. (as mentioned above), the Australian College of Rehabilitation Medicine and the Royal Australian College of General Practitioners, as well as numerous universities, hospitals and other bodies. Outside Australia, the A.A.M.M. has close ties with its sister organisations the New Zealand Association of Musculoskeletal Medicine (N.Z.A.M.M.) and the British Association of Manipulative Medicine (B.A.M.M.). All three, together

with some twenty other national bodies, are affiliated with the International Federation of Manual Medicine (F.I.M.M.). By correspondence, and when possible by direct contact at meetings and conferences, members share in a world-wide movement towards improved management of musculoskeletal disorders.

The A.A.M.M. is not an association of specialists. Some members, certainly, are registered specialists in physical medicine, rehabilitation, rheumatology, neurology and orthopaedic surgery. Some others practise full-time in the fields of orthopaedic medicine, physical medicine and manipulative medicine. The majority of members, however, are general practitioners interested in the problems of musculoskeletal disorders and many have been drawn to the Association by the inadequacy of some widely-practised methods of management of these conditions. Membership of the A.A.M.M. is open to all medical practitioners who share the desire to improve methods of alleviating the suffering caused by some of the most common and most painful afflictions of mankind.



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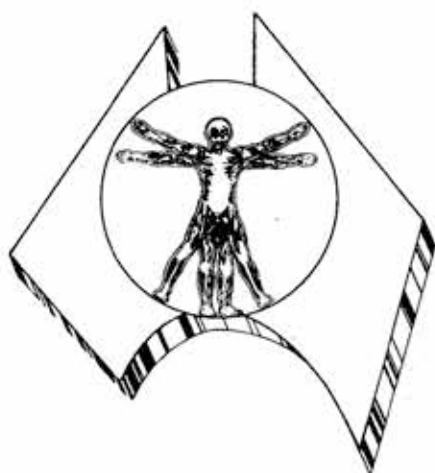
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1. Bjelima, A. Scand. J. Rheumatol., 1978, Suppl. 22, 74.
2. Uthgenant, H. Symp. Proc. of VII Eur. Rheumat. Congress Helsinki, 1975.
3. Schlumpf, U. Schweiz. med. Wochschr., 1978, 108, 28.

Logo Rhythms



The muscle-man logo presented in the first issue of the Bulletin drew only a few comments and did not spark any great controversy. Whether this indicates a general acceptance or simply apathy is hard to say but it does suggest at the least that no-one was so moved to repulsion as to express it to the editor. Perhaps this reflects a proper order of priorities: there is certainly much more to life than the shape of a logotype.

One comment that was made by several members was that the central figure of the device was quite familiar and had been seen in different forms in other applications. This invites some explanation of the origin of the imagery and its relevance to musculoskeletal medicine.

The central figure of the logo is termed a Vitruvian man, after the Roman polymath Marcus Vitruvius Pollio (first century B.C.). Vitruvius was trained as a military engineer and as such he campaigned with the armies of Julius Caesar and Octavian. His diverse interests included various aspects of military science and this led him to investigations into the physical abilities of a man to fight in the close combat of the time. His writings record studies of musculoskeletal function which make him one of the earliest authors on the subject and the figure in the circle was devised by him to demonstrate some of the ideas put forward.

The theme was taken up in the fifteenth century by Leonardo da Vinci (1452-1519), who in the spirit of the Renaissance explored the works of the ancient authors and used them to expand his own ideas. Leonardo was, amongst other things, a dedicated anatomist who dissected at every opportunity and recorded his findings in notebooks liberally illustrated with drawings and diagrams. These show his particular interests in the attachments of muscles and the relationships between muscle contractions and joint movements. He wrote a treatise on body mechanics and the effects of postural changes and used an embellished Vitruvian man to illustrate the manuscript. This is the form in which the figure is now best known.

As a possible logo for the A.A.M.M., the image of the Vitruvian man has appeal for several reasons. It has strong links with the history of man's investigations into the mechanics of his body. The depiction of postural balance and of joint movement, as shown by the limb positions, and the element of measurement suggested by the circle all seem appropriate symbols of the Association's objectives. Changing the figure to a muscle-man served to emphasise the musculoskeletal system and to make the image more distinctive. The stylised map outline distinguishes the Association's nationality and lends further visual imagery of movement. It also adds the concept of the Association reaching out over Australia. As a whole, the logo symbolises the elements of art and science that have contributed to musculoskeletal medicine from its beginnings in the ancient world to its modern expression in practice in present-day Australia.

On a more serious note, one further comment was received from a somewhat bashful member who would prefer to remain anonymous (and this wish will be respected, as all the President's wishes should be). After studying the logo, he made the observation that he did not remember Leonardo's drawing having quite so much of the modern emphasis on "person" rather than on gender specificity. This criticism is accepted with some extenuation. The muscle-person in the logo does have most of the muscles visible from an anterior aspect, including the cremasters. Certainly the dartos has been omitted, but purely because it was technically difficult to illustrate. There was no attempt at editorial suppression of sensitive material nor to deny the importance of a muscle held by many to initiate some of the most significant reflexes of all. Members encountering difficulties in this area, and especially with the trying problem of dartos hypotonicity, are assured that the Association is always ready to lend its support.

The subject of the logo is not closed. Further comments are invited and will be reported in future issues of the Bulletin.

AUSTRALIAN ASSOCIATION OF MUSCULOSKELETAL MEDICINE

OFFICE-BEARERS 1985

The following members were elected to office at the annual general meeting in Melbourne on 25th November, 1984.

PRESIDENT:

Dr. Conrad Winer LLB, MB, BS, MRCS, LRCP, DRCOG, DPRM, FACRM, MLCO, MRO.

Director, Department of Rehabilitation Medicine,
Royal Prince Alfred Hospital, Sydney, NSW, 2050.
telephone (02) 27 8926



HON. SECRETARY:

Dr. David Vivian MB, BS
441 Bay Street, Brighton, Vic., 3186
telephone (03) 596 7211



HON. TREASURER:

Dr. Alex Ganora MB, BS, FRACGP, DPRM, FACRM
72 Phillip Street, Thirroul, NSW, 2515
telephone (042) 67 2811



COMMITTEE MEMBERS:

Dr. Nikolai Bogduk	Brisbane, Qld.	(07) 377 2702
Dr. Bunt Burnell	Adelaide, S.A.	(08) 45 0222
Dr. Clive Kenna	Melbourne, Vic.	(03) 568 8166
Dr. Wade King	Tamworth, NSW.	(067) 66 6166
Dr. Goff Nelson	Canberra, ACT.	(062) 95 6773
Dr. Jeffrey Phillips	Toowoomba, Qld.	(076) 38 4800
Dr. Vern Vivian	Point Lonsdale, Vic.	(052) 52 2009

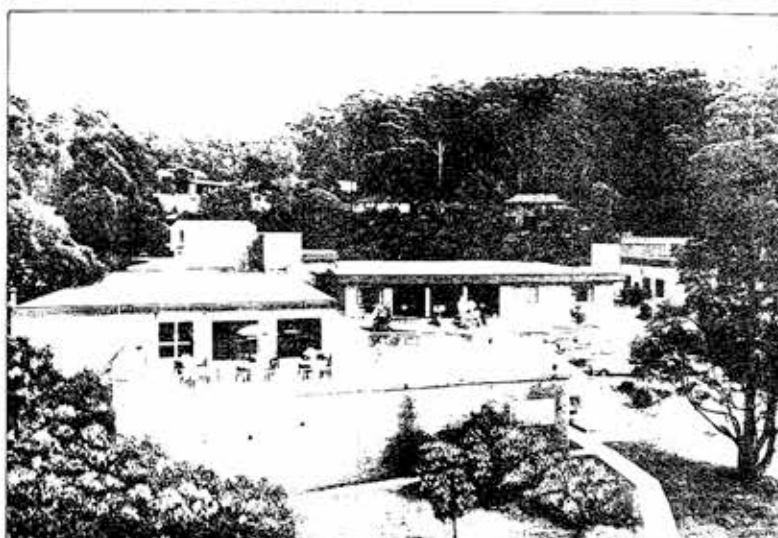
STATE REPRESENTATIVES:

ACT:	Dr. Goff Nelson	(062) 95 6773
NSW:	Dr. Wade King Dr. Howard Rivett	(067) 66 6166 (02) 439 1335
NT:	Dr. Paul Condon	
QLD:	Dr. Gordon Byth Dr. Jeffrey Phillips	(07) 391 5049 (076) 38 4800
SA:	Dr. Norm Broadhurst Dr. Bunt Burnell	(08) 278 4139 (08) 45 0222
TAS:	Dr. Roger Bodley Dr. Gordon Rich	
VIC:	Dr. John Piesse Dr. David Vivian	(03) 890 0549 (03) 596 7211
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For further information on the services and facilities available please contact the Administrative Director, Mr. Phil King, Illawarra Rehabilitation Centre, 72 Phillip Street, Thirroul, N.S.W. 2515. Tel: (042) 67 2811.

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Editorial

This issue of the Bulletin focuses attention on the non-steroidal anti-inflammatory drugs and in particular the newer preparations. The prescription of anti-inflammatory medication is one treatment modality used by all members of the Association. It is basic first-line therapy in the management of many musculoskeletal disorders and adjunctive to other forms of treatment in the management of many others. The ability to prescribe drugs is one major advantage doctors have over others who treat musculoskeletal conditions. Yet, while this valuable form of treatment is often appropriately used it is also often misused.

Inappropriate prescribing of anti-inflammatory drugs causes the type of disaffection among patients which turns them away from doctors and is manifest in the plethora of "alternative remedies", from charms to coloured lights. This disaffection is not always unjustified by any means. A patient who presents with a backache or joint pain is no more likely to obtain a cure from a doctor who invariably prescribes drugs than he is from another practitioner who invariably treats with manipulation or exercises or whatever. Doctors with a special interest in musculoskeletal disorders are aware of this, of course, and generally employ a range of treatment modalities, including medication, used singly or in combination as indicated by a specific diagnosis. They know that medication correctly prescribed is one of the most dramatically successful forms of treatment available. They also know that inappropriate medication leads to unrealistic treatment goals, unmet patients' expectations and often unwanted iatrogenic problems. Such effects are rarely the fault of the drug itself. Failure of a medication regime is usually based on the failure of the prescriber to understand specific musculoskeletal diagnosis and the indications for and limitations of drug therapy. These problems do not only occur with the inexperienced or the careless. There is a real danger that doctors' familiarity with potent drugs may lead to a form of contempt for the finer points of their use. It is important for all of us to review our prescribing habits from time to time, especially when new drugs become available, to make sure we understand the uses of these drugs and can employ them appropriately and effectively.

The four papers presented in this issue have been reprinted (with permission) from recent pharmaceutical research journals. Because of their clinical significance they were considered worthy of reproduction in this Bulletin for our members' attention. As a group the papers compare three NSAIDs in the treatment of the two major inflammatory arthroses, rheumatoid arthritis and osteoarthritis. The long-used "standard" drug indomethacin is compared with the newer diclofenac, which in turn is compared with another relatively new drug, naproxen. If there appears to be some bias in the subject matter, in that all four studies include diclofenac in their trials, it is because the papers were supplied by the manufacturers of that drug, Ciba-Geigy. This was not the result of any unfair dealing between that company and the editor. In fact, all companies marketing NSAIDs in Australia were approached to supply scientific papers for a feature issue on these drugs. Ciba-Geigy was the only company to respond with suitable material.* The company has also generously supported the Bulletin with its advertising. Other drug companies are warmly invited to follow this example.

There is no bias in the studies themselves. The trials described have been properly constructed and the results are presented with appropriate statistical evidence to support the findings. From this point of view the papers have another value other than their actual subject matter. They are good examples of well-conducted and relatively simple clinical trials such as members of the A.A.M.M. could carry out on all sorts of subjects. Clinical research has been an objective of the Association since its foundation, yet few members seem to be able to find the time to become actively involved. In a field of medicine in which much is yet to be discovered and clarified, the opportunities for valuable clinical research are almost limitless. Perhaps the examples of these four papers will serve to remind us of the need.



Footnote to editorial (with asterisk* in text).

* To be absolutely fair, Syntex Australia also sent material and the editor was grateful to receive it. However, although of high quality and quite objective, it was mostly of a descriptive nature and thus not as suitable for the present purpose as the controlled studies herein. It may well appear in future issues.

From The Hon. Secretary's Desk



The first issue of the Bulletin was a great success. We can all appreciate the work involved in putting together such a publication and that it ought to be a shared effort. In order to maintain the standard set, and indeed to improve on it if possible, we will need input from as many of our members as possible. Our Association now has over three hundred members, many of whom must be interested and creative, so it is hoped that ample contributions will be forthcoming.

It has been interesting recently to observe the television performances of a number of doctors. The two Sydney surgeons have perhaps had the most extensive coverage during 1985. I feel they have done nothing at all for the image of the medical profession. Their appearance and inability to state coherently the facts as they see them, so that the general public can understand them, has hindered their course of action continually. Recently, a forum on cigarette advertising was held; on one side were 2 doctors and on the other side two spokesmen from a cigarette company. The doctors mainly used emotional argument to justify their position rather than referring to any scientific studies, whereas the cigarette people were far more logical and came across so much better in the public's eye.

In both instances the doctors concerned are probably being introduced to television and public speaking without much advice from professionals in this area. In this age of increasing media exposure, it would seem appropriate that medical spokesmen have adequate training in the areas of public relations and speaking.

Over my years of work in this field I have had increasing exposure to the manipulative disciplines of physiotherapy, osteopathy and chiropractic. I have always been struck by some members of these professions who have a high degree of antagonism towards doctors practising or teaching in the area of musculoskeletal medicine. The letters to the editor in the March edition of this Journal, and talking to Dr. Clive Kenna, have prompted this comment.

Dr. Kenna and Dr. John Murtagh have recently begun a correspondence course through the Australian Family Physician. They have had letters from the manipulative therapists of Australia and from the chiropractors criticizing them for teaching this subject to doctors. I have talked to members of the Manipulative Therapy Association of Australia who feel that doctors should not even be taught how to examine a back or neck properly. Conversely, I have talked to other members of the MTAA who feel that doctors of course should be involved fully in this area.

It is only logical that the medical profession should have a comprehensive knowledge of this field, both in the diagnostic and application senses. I am unsure as to what percentage of work in general practice is musculoskeletal. If you accept that a considerable proportion of headaches and other painful conditions indeed come from the musculoskeletal system, it is probably around about a quarter of all general practice consultations. It is probably second only to viral illness in all consultations. Therefore, to say that the doctors should not have a thorough working knowledge of this field is ridiculous and impractical.

At the present time there is little or no education in medical undergraduate courses in regard to common musculoskeletal complaints. When I went through university the only mention we had about back or neck injuries was that if someone presents with a disc prolapse we should send them to an orthopaedic surgeon. While this may indeed be true, I feel that they missed out in talking about 99.9% of all back or neck presentations.

Eventually proper musculoskeletal skills will be part of the university curriculum. Dr. Murtagh works in this area at Monash University and he finds that the students enjoy these sessions as much or more so than any other.

The major benefit a patient has when going to a doctor who understands backs is that the patient can obtain a proper working diagnosis and a sensible treatment plan. Frequently, unnecessary investigations will not have to be undertaken. A prime example is the patient who presents with loin pain. I have seen a number of patients who have already been sent for urine analysis, blood investigations and often an I.V.P. The tests have shown no abnormality. After some months the patient filters into a musculoskeletal clinic, and treatment is directed to the affected lower thoracic segment. It is obvious that the patient and the community would have been much better served if the doctor had merely turned the patient onto his or her stomach and felt the back. If any stiffness was found in an appropriate segment and especially if palpation over this area reproduced the patient's pain, then a short session of treatment would have produced at least some temporary alleviation of pain, indicating that the source of pain was most likely the back. After taking up to 80 people a year through introductory courses in musculoskeletal medicine, I have gathered that about 90% of medical graduates would have no ability to have discovered this unless they had done a course in musculoskeletal medicine.

Of far less importance to the patient, but obviously of more importance to the manipulative therapist, is that the number of patients available for manual therapy will be vastly increased when more doctors can diagnose and understand musculoskeletal complaints. In addition, the patient will feel far more affinity with the doctor, as the doctor begins to use a more "hands-on" approach. Instead of confining some problems to the general practitioner and other problems to other therapists, the patient will find that the general practitioner indeed has a general knowledge of health matters and the ability to refer to appropriate therapists when necessary.

I, therefore, feel that it is imperative that the medical profession becomes increasingly involved in all aspects of musculoskeletal medicine for the simple reason that it will improve the overall health and treatment of the population.

Editorial footnote:

The Hon. Sec. makes mention of the series currently running in the Australian Family Physician as a "correspondence course in spinal manipulation". This series is a private project of the authors and the A.A.M.M. is not officially involved with it in any way. However, the nature of the material presented is of considerable interest to those already practising in the field.

Whilst most members of the Association will applaud Clive Kenna and John Murtagh for their fine effort in raising the awareness of general practitioners in this way, some would also have reservations about the feasibility of teaching manipulative skills by correspondence. The same criticism could of course be levelled at authors who illustrate journal articles with pictures of surgical operations and their defence would be that the pictures were presented for information only, not to encourage their readers to perform the procedures without appropriate training. Perhaps the problem some have with the series is not with the information presented but with the title: "correspondence course" may be a misnomer.

These comments are not intended to denigrate the work of Clive and John; they are two of the Association's most active and dedicated members and together have done a great deal to further the causes of musculoskeletal medicine in Australia. Rather, the intention is simply to stress that it is the policy of the A.A.M.M., and of the international body F.I.M.M., that manipulative techniques should not be used on patients unless the practitioner has received an adequate practical training in their application and has a thorough knowledge of their indications, contraindications and dangers.

□ □ □

New members are always welcome. If you have colleagues who have expressed interest in musculoskeletal topics, why not share this Bulletin with them? You might also care to send their addresses to the Treasurer: membership application forms will be speedily dispatched.



MAIL BAG Letters to the editor

"I had written him a letter...."



When the mailbag was opened this month it was found to contain an account from Australia Post, three Bulletins returned "address unknown" and a small quantity of lint. Letters to the editor were conspicuous by their absence. Members are warned that if they do not move quickly to correct this situation the editor will have to resort to writing scandalous letters to himself and publishing them over members' names. One way or another, a full page (at least) of letters will appear in the next issue. Act now to save embarrassment! Letters on any subject will be gratefully received. What do you think of R.S.I.? or intrathecal steroids? or manipulation under anaesthesia? or orgone therapy? or the Hon. Sec.'s wife? or...?



NEWS

"heard on the bush telegraph"

The 1985 annual conference will be held in Adelaide. This is absolutely the last word on the venue for this meeting which has wandered like an albatross half-way around the southern hemisphere before finally settling.

The combined conference with the New Zealand association is not to be: or at least not this year. After an enthusiastic start the organisers ran into a series of problems. All looked well for a gathering in Noumea until political troubles erupted in New Caledonia. Doubts arose about the safety of meeting in such a place and after negotiations with Club Med the venue was changed to Moorea, Tahiti. This seemed to remove the potential problems but somehow confidence in the project was not universally restored. When the committees of the two associations decided to canvass members' feelings about the conference, in April, Australian support was strong but was not matched by that in New Zealand. No doubt local political and economic factors added to the burden of uncertainty for the New Zealanders and their committee decided that they had insufficient numbers to make such a gathering a success. As they had originally proposed the joint meeting, the Australian committee deferred to their wishes and the combined conference was cancelled.

The final washup of plans is that the New Zealanders' annual conference will now be held in Rotorua, the A.A.M.M. annual conference will be held in Adelaide and a meeting will still be held in Tahiti to accommodate the keen group of Australian members whose enthusiasm, once raised, has grown rather than diminished (see Meetings, Conferences and Courses).

The idea of a South-West Pacific Conference remains a good one and perhaps can be brought to fruition sometime in the future.

□ □ □

*A par in the last Bulletin suggested that we should all go and eat crow. With the annual conference to be held in Adelaide that expression now has an extra meaning. The croweaters have certainly set the pace for the other states this year and now all the rest of us have the chance to go there and see what they have been up to. The S.A. branch formed in January 1985 now has twenty-six members and another fifteen doctors attended a recent introductory course. With regular meetings, practical sessions, liaison with the M.T.A.A. and now a national conference to organise, **Norm Broadhurst** must be wondering what he did with his time before he became an A.A.M.M. state rep. **Bunt Burnell** has experienced it all before but even during his term as President of the Association in 1977-78 he can hardly have been busier.*

□ □ □

Another former President, **Gordon Byth** of Brisbane, must have heaved a sigh of relief recently. At one stage of the conference discussions it looked as though he might have the honour of organising it again. Still, his respite may only be very temporary. There would be worse places than the Sunshine State to meet in 1986.

□ □ □

The eighth international congress of the F.I.M.M., to be held in Madrid in June 1986, is shaping up well. The provisional scientific programme has three main themes and thirteen main topics, any one of which would be worth a trip to Spain to hear presented and discussed in such an international forum. The social programme looks just as good. One of the many interesting activities planned is a "bull fight semblance" in a mediaeval village, with congress delegates invited to try their hands (and feet) as matadors.

□ □ □

Melbourne members take the prize for involvement in teaching and diversity of teaching methods. **Clive Kenna**, **John Piesse** and **David Vivian** combine to run three courses each year in conjunction with the Family Medicine Programme of the R.A.C.G.P. **John Murtagh**, who has been active for some time in undergraduate teaching at Monash University, has combined with Clive to write a series for the Australian Family Physician and conduct practical sessions to back it up.

□ □ □

Overseas lecturers invited to Australia in the next twelve months include Professor Vladimir Janda, Dr. Hans Schmid, Professor Rene Cailliet and Dr. Karel Lewit.

Professor Vladimir Janda, of Prague, will be here from June to September for further lectures and demonstrations of his muscle techniques. This will be the last of a series of annual visits and those wishing to hear him should not miss the opportunity to do so.

Dr. Hans Schmid, of Berne, is Director of the Department of Physical Medicine in a large Swiss teaching hospital. He is also the Treasurer of the F.I.M.M. He will be here in August - September to speak about his recent work on sacro-iliac joint problems and other aspects of musculoskeletal medicine.

Professor Rene Cailliet needs little introduction as most members will be familiar with his books on musculoskeletal topics. As Professor of Rehabilitative Medicine at the University of Southern California, Los Angeles, he is an authority many will look forward to hearing. His visit is planned for February, 1986.

Dr. Karel Lewit comes, like his colleague Professor Janda, from Prague. He is an acknowledged expert in his own right on muscle dysfunction and related problems. He will be here in February - March, 1986.

All of these visitors will be speaking at meetings and some will give brief courses while they are in Australia. Dates and venues of their engagements will be found on the Meetings, Conferences and Courses pages of the Bulletin.

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Hans Schmid and his wife Renata will be travelling in Queensland, New South Wales and the A.C.T. in the fourth week of September, partly by air and partly by road. They are keen to see as much of Australia as possible while they are here. It would be a nice gesture if members along their way could spare a little time meeting them and perhaps even offer hospitality. Anyone who might be able to help in these ways is invited to contact the President.

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Research grants are available from the Association. Some aspects of research work, such as the collating and processing of information, are difficult or impossible without expenditure of funds. To facilitate research by members, the Committee decided at its last meeting to make money available for such purposes. Applicants should submit to the Committee, via the Hon. Sec., an outline of the project to be undertaken with an estimate of the funds required and the way the money is to be spent.

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Subscriptions for 1985 should now have been paid. Members who are unfinancial are respectfully reminded of their obligations. Anyone in doubt about whether they have paid or not should send a cheque for \$15 to the Treasurer. If you are not in arrears it will be credited to your account for next year.

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Proceedings of the Back Pain 1984 Conference, held in Melbourne last November, are now available. A bound transcript of the entire scientific programme, including discussions and questions from the floor, can be yours for a mere \$20. Re-live the drama of Bogduk versus the ignorant! Overload your coping system with facts and fantasies! Cheques, made out to A.A.M.M., to the Hon. Sec. please.

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The Arthritis Foundation has for sale proceedings of two professional seminars, one on Repetition Strain Injuries (55 pp.) and the other on Back Pain and other Strains (48pp.). These are available for \$10 each, including postage, from the Education Co-ordinator, Arthritis Foundation of Australia (NSW), 12th Floor, 291 George Street, Sydney, NSW, 2000.

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MEETINGS, CONFERENCES AND COURSES

Regular meetings are held in a number of centres around Australia for local members to come together and discuss matters of common interest. Some of these groups conduct courses, both introductory and more advanced, from time to time. Others focus their activities on case discussions, exchanges of techniques and the like. Groups are known to be meeting regularly in Adelaide, Melbourne and Geelong, Sydney, Tamworth and Wollongong. If you are involved in, or know of, a group meeting elsewhere, please communicate with the editor so we can all share in the secret.

In **Adelaide**, regular meetings are conducted by the South Australian branch of the Association and the next is to be held at 7p.m. on Wednesday, 14th August at the Department of Physical Medicine, Queen Elizabeth Hospital. It will be one of a series of practical sessions conducted by Dr. Bunt Burnell to follow up the recently-completed introductory course. Other activities planned include joint meetings with the M.T.A.A. later in the year. Enquiries should be directed to Dr. Norm Broadhurst, telephone (08) 295 1890.

In **Melbourne and Geelong**, members meet at a number of places for discussions and practical sessions. Three courses are conducted each year. There will be meetings in Melbourne on 27th and 28th July and 10th August and meetings in Geelong on 30th November and 1st and 8th December. For details of these, contact Ann at the R.A.C.G.P. on (03) 240 8671.

An evening seminar on cervical headaches will be held on Tuesday, 3rd September at 441 Bay Street, Brighton. For information about this meeting contact Dr. David Vivian on (03) 596 7211.

In **Sydney**, meetings are held at 7.30p.m. on the third Monday of each month in the Department of Rehabilitation Medicine, Royal Prince Alfred Hospital. These meetings are designed as practical sessions for those who have attended the introductory course in spinal manipulation. Those wishing to attend are asked to telephone Dr. Conrad Winer on (02) 27 8926 during the preceding three working days to confirm the arrangement.

The next Coppleson Institute introductory course in spinal manipulation will begin on Monday 19th August, 1985. Enquiries should be directed to Miss Licitis at the Coppleson Postgraduate Medical Institute, University of Sydney, telephone (02) 692 3526.

Professor Vladimir Janda will be giving an advanced course on his muscle techniques in Sydney on the 6th and 7th September. The group will be restricted for practical reasons. As the course is designed for those who have already attended one of Professor Janda's introductory courses, they will be given preference, but others may be accommodated if places are available. Anyone wishing to attend is asked to ring Dr. Conrad Winer on (02) 27 8926 as soon as possible.

The Arthritis Foundation of Australia is holding a seminar for health professionals on "Aches and Pains in Childhood" on Saturday, 12th October, 1985 at The Shore Inn, Artarmon. Musculoskeletal disorders in childhood will be discussed by a panel including paediatricians, rheumatologists and an orthopaedic surgeon, with practical demonstrations by physiotherapists. For details of the programme and registration, contact Elizabeth Rich on (02) 969 1400.

A day-long seminar on "Differentiation and Management of Lumbar Spine, Hip and Sacro-Iliac Joint Problems" will be held at the Stephen Roberts Lecture Theatre, University of Sydney, on Saturday 19th October. Sponsored by the M.T.A.A., the meeting will feature physiotherapists, rheumatologists and an orthopaedic surgeon discussing various aspects of the subject and demonstrating relevant practical procedures. A full programme and registration details are on the leaflet enclosed.

In **Tamworth**, meetings are held at 5p.m. each Thursday in the Outpatients Department of Tamworth Base Hospital. An introductory course in musculoskeletal medicine, with emphasis on spinal and peripheral joint mobilisation and manipulation, is being conducted over a period of twelve months. Further information can be obtained by contacting Dr. Wade King, telephone (067) 66 6166.

In **Wollongong**, introductory courses are run over a period of ten weeks. The organiser is Dr. Alex Ganora, who can be contacted on (042) 67 2811.

Dr. Hans Schmid will be holding three evening sessions in different centres after he completes his commitment at the University of Queensland in September. He will speak in **Townsville** on Monday 23rd September [for local arrangements contact Dr. Roger Watson on (077) 71 3084], in **Canberra** on Thursday 26th September [contact Dr. Goff Nelson on (062) 95 6773] and in **Sydney** on Friday 27th September [contact Dr. Conrad Winer on (02) 27 8926].

There will be an A.A.M.M. meeting in **Tahiti** on 4th - 11th October, 1985. The questionnaire enclosed with the last Bulletin produced an excellent response. Strong support was shown for the planned South-West Pacific Conference and despite its cancellation, and the change of the main A.A.M.M. annual conference venue to Adelaide, a number of members were keen to go ahead with plans for a Tahiti meeting, albeit a smaller gathering than that originally envisaged. Details of travel arrangements, costs and the scientific programme can be obtained from the Hon. Sec.

Two other overseas meetings this year may be of interest to members.

The New Zealand Association of Musculoskeletal Medicine is holding its annual conference at **Rotorua** on 1st - 3rd November, 1985. The principal speaker will be Dr. Robert Burns of the U.K., who will also be giving an advanced course in manipulative techniques over the three days prior to the main meeting. A.A.M.M. members are welcome to attend both the conference and the course. For further information contact Dr. Graham Perry, 36 Kitchener Road, Milford, Auckland 9, New Zealand.

A five day international conference on Back Pain: Current Concepts and Recent Advances will be held at the International Hotel, **Vienna** on 4th - 8th November, 1985. The conference chairman will be Professor Malcolm Jayson of Manchester supported by a large faculty of eminent speakers including Professor Wilbert Fordyce of Seattle, Professor Alf Nachemson of Goteburg, Professor Barrie Vernon Roberts of Adelaide and Professor Patrick Wall of London. An impressive programme is scheduled and the conference is highly recommended to members able to make the trip. Further details may be obtained from the Hon. Sec. Contact address for the conference is Congress Team International (U.K.) Ltd., 30 Deane Way, Ruislip, Middlesex. U.K.

see you in...

Adelaide



The annual conference of the Australian Association of Musculoskeletal Medicine will be held this year in Adelaide, rather than as a combined conference with the New Zealand association as previously advertised. An interesting programme has been arranged with papers, discussions and demonstrations on a number of topics including "whiplash injury", chymopapain, spinal exercises, back pain in pregnancy, upper limb tension testing, referred pain, trigger points, etc.

Proceedings commence on Friday, 22nd November, 1985, with a morning meeting for those involved in teaching musculoskeletal medicine and manipulative techniques. A meeting of the A.A.M.M. Committee will be held on the Friday afternoon. The main programme begins on Saturday, 23rd November, with registration of delegates at 8.30a.m., and runs through until the afternoon of Sunday, 24th November, when the Annual General Meeting of the Association will be held. Venue is the St. Leonards Motor Inn, Glenelg, with accommodation available there and also at the Patawalonga Motor Inn, Glenelg.

As usual, members are invited to present free papers at the conference. All papers will be examined by the conference committee and will only be accepted if they meet objective criteria. Anyone wishing to present a paper is asked to submit a complete text, with a synopsis suitable for inclusion in the registration handout, before 1st October.

Programmes and registration forms are enclosed with this Bulletin. Enquiries should be addressed to the conference convenor, Dr. Norm Broadhurst, 4a Byron Street, Glenelg, South Australia, 5045, Telephone (08) 295 1890.

Madrid



The next tri-ennial congress of the F.I.M.M. (International Federation of Manual Medicine, with which A.A.M.M. is affiliated) will be held in Madrid on 24th to 28th June, 1986. For members able to travel to Spain, this will be another experience not to be missed.

8. INTERNATIONALER KONGRESS
8th INTERNATIONAL CONGRESS
8ème CONGRES INTERNATIONAL



FIMM Fédération Internationale de Médecine Manuelle Madrid 24.-28.6.1986

DICLOFENAC SODIUM (VOLTAREN) AND INDOMETHACIN: A MULTICENTRE COMPARATIVE STUDY IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

By C.G. Barnes¹, H. Berry², M.E. Carter³, M.E. Downie⁴, P.D. Fowler⁵, J.M.H. Moll⁶, J.D. Perry⁷, M.S. Sawaf⁸, and Prof. V. Wright⁹

¹The London Hospital, London

²Kings's College Hospital, London

³St. Mary's Hospital, London

⁴Leeds General Infirmary

⁵CIBA-GEIGY (UK) Limited

⁶Nether Edge Hospital, Sheffield

Paper presented by P.D. Fowler

ABSTRACT

A five-centre double-blind crossover trial of two two-week periods using diclofenac and indomethacin showed that both drug groups (51 patients) with rheumatoid arthritis responded similarly in relation to pain scores and morning stiffness. It was noted that the response was better in inpatients than in outpatients, despite differences in disease severity. In the osteoarthritis trial (58 patients) it was shown that neither drug significantly reduced resting pain, although both drugs were significantly better in reducing pain on movement; however, patient preference was for diclofenac. Three patients treated with indomethacin withdrew owing to side-effects, compared with one on diclofenac. A slight but significant decrease in haemoglobin levels was observed in both treatment groups with osteoarthritis, but this did not appear to be symptom-related.

INTRODUCTION

The aim of this study was to compare the efficacy and tolerability of diclofenac and indomethacin in patients with rheumatoid arthritis and osteoarthritis. Five hospitals were involved, three in London and two in Yorkshire, all using the same protocol.

METHOD

Patients were recruited for the study in two diagnostic groups: (i) inflammatory polyarthritis with laboratory data supporting a diagnosis of rheumatoid arthritis, and (ii) osteoarthritis of the hip or knee joints.

All standard NSAID/analgesic drugs were discontinued immediately before the start of the trial, but patients with rheumatoid arthritis stabilized on gold, penicillamine and corticosteroids were included. The plan was a double-blind crossover trial of two x two-week periods using matched tablets and a fixed dosage of 25 mg four times daily of diclofenac or indomethacin, the order of administration being randomized separately for groups (i) and (ii). In regard to the indomethacin tablets used in the trial, pharmacokinetic studies showed these to be indistinguishable from the marketed capsule so far as absorption and blood levels were concerned.

The patients were seen on the day of entry to the trial (Day 0) and at the end of each two-week treatment period (Day 14 and Day 28). At each visit clinical and laboratory data were accumulated, and efficacy and tolerability were assessed at Days 14 and 28. Laboratory examinations included blood (haemoglobin, WBC, platelets, ESR), serum (SGPT, SGOT, AST, alkaline phosphatase, bilirubin, total proteins and albumin, urea, creatinine, uric acid), and urine (protein and sugar).

† The criteria of efficacy were:

(1) *Pain*, estimated on a 0-4 scale ranging from "no pain" through "mild", "moderate", "severe" and "very severe pain", subdivided in osteoarthritis patients for pain at rest and pain on movement.

(2) *Morning stiffness*, recorded in minutes.

(3) *Rescue analgesic requirements*: Paracetamol was allowed ad lib. The amount taken by the patient each week was recorded on a diary card and checked by a returned tablet count.

(4) *Global assessment*: Patients' and doctors' opinions in 5 grades, from "very poor" to "very good", and change from "much worse" to "much better". At the end of the trial the preference for either treatment was sought.

(5) *Joint tenderness (rheumatoid arthritis only)*, assessed by a minor modification of the articular index (Ritchie et al., 1969).

(6) *Joint range (osteoarthritis only)*: The worst affected joint was selected. Knee range was measured with a goniometer, and hip range by the maximum intermalleolar distance (in cm).

All spontaneously volunteered side-effects were noted after posing the indirect questions: "Did the tablets suit you?" and "Did the tablets upset you?"

Statistical analysis

The Chi-square test was used to analyse categorical data. When the data were normally distributed the Student's *t*-test was used, but otherwise the non-

parametric Mann-Whitney U-test was applied. Friedman's two-way analysis of variance was used to determine if there were any changes over time in the study, the Binomial test to analyse treatment preference, and McNemar's test to determine whether the number of side-effects was equal with both drugs.

RESULTS

Rheumatoid arthritis

(a) *Patients and drop-outs.* Sixty-six patients were entered, of whom 17 were inpatients. Fifteen dropped out for the reasons shown in Table I.

TABLE I
DROP-OUTS AND WITHDRAWALS

Unsuitable for analysis	1
Side-effects in first period, no second treatment	5
Neither treatment satisfactory	3
One period satisfactory, not the other	6

Not included in side-effects are one patient who developed hemiplegia and one who developed post-menopausal bleeding, whilst taking indomethacin.

(b) *Comparison of treatment order groups.* Initial data, analysed according to whether patients received diclofenac first (D-I) or vice versa (I-D), showed that the two groups were matched.

(c) *Effect of treatment.* The responses were similar, regardless of order of treatment. In both groups pain scores improved significantly ($P < 0.05$); morning stiffness improved significantly on all but the indomethacin period in the D-I group; joint tenderness diminished significantly with both treatments in the I-D, but neither in the D-I group. Paracetamol requirements were similar.

It was thus considered justifiable to combine the results for each drug from the first and second periods (Table II).

TABLE II
Summary of Mean Scores

	Initial	After diclofenac	After indomethacin
Pain	2.3	2.0	1.8
Morning stiffness (mins.)	128	67	79
Joint tenderness	12	10	9

(d) *Global and comparative assessment.* There were no differences between the treatments (Table III).

TABLE III
preferences

	diclofenac	indomethacin	Same
Patients*	14	18	19 (N.S.)
Doctors*	15	12	22 (N.S.)

(c) *Unwanted effects.* Nine patients (three on diclofenac and six on indomethacin) dropped out because of side-effect, which were mainly gastric with diclofenac and mainly dizziness, vomiting and headache with indomethacin. Four of these six patients with side-effects on indomethacin tolerated diclofenac. The others did not receive it. Side-effects not requiring withdrawal of treatment were reported in nine patients on diclofenac and 18 on indomethacin (Table IV).

TABLE IV
Side-effects in 51 Rheumatoid Patients

	Central nervous system	Gastro-intestinal	GI and CNS	Skin	Other	Total
Diclofenac	5	2	0	1	1	9
Indomethacin	6	6	4	0	2	18

Heartburn, headache or dizziness occurred with diclofenac; headache and vomiting or headache and nausea and dizziness were more common with indomethacin.

(f) *Comparison of inpatients and outpatients with rheumatoid arthritis.* As response to treatment is usually much better in inpatients, an analysis to compare the 17 inpatients and 49 outpatients was performed.

Although mean age and length of history were similar, withdrawals were much less frequent with inpatients (1:14), and the proportion with severe symptoms was higher, the latter being reflected in scores for disease activity (Table V), significantly so in many cases.

TABLE V

Initial Disease Activity in Rheumatoid Arthritis: Comparison of in and outpatients.

	Inpatients	Outpatient	P
Mean pain score	2.6	2.2	0.074
Median duration of morning stiffness	120 min	75 min	
Joint tenderness score	18.0	8.0	0.001
Mean grade of general condition*	By Doctor 3.5 By Patient 2.9	2.8 2.75	0.036 0.023

*Based on 1-5 grade scoring. P values calculated on distribution of grades.

Improvement in pain scores with both drugs was significantly greater in the inpatients than the outpatients, but without differences between the drugs. Morning stiffness improved significantly in all groups, with no statistical difference between inpatients and outpatients, or between treatments. Joint tenderness improved significantly more in inpatients, without significant differences between drugs. Overall improvement was judged to be much commoner in inpatients, but again there were no significant differences between the treatments.

Thus, although there was a marked difference both in initial severity and response between the inpatients and outpatients, neither group responded better to either drug.

The two groups of patients may therefore be combined when comparing the response to drug treatment.

Osteoarthritis

(a) *Patients and drop-outs.* Fifty-eight osteoarthritis outpatients entered the study, of whom 10 dropped out.

Drop-outs were divided into four categories, five being unsuitable for analysis, two having side-effects in the first period and no second treatment, and three finding one period satisfactory but not completing the other. Side-effects caused withdrawal in three patients on indomethacin and one on diclofenac.

(b) *Comparison of treatment order groups.* Initial data were again analysed according to treatment order, and the findings show that the two groups were comparable.

(c) *Effect of treatment.* The initial pain scores and responses were similar, regardless of treatment order. The only significant improvement was for pain on movement, when diclofenac was the second treatment. Combination of the two treatment periods (Table VI) shows that neither treatment significantly reduced pain at rest, whereas both significantly improved pain on movement. Paracetamol usage was similar in the two treatment groups.

TABLE VI

Mean Pain Scores

	Initial	After diclofenac	After indomethacin
At rest	1.5	1.1	1.2
On movement	2.6	1.7**	2.0*

* $P < 0.05$

** $P < 0.01$

Knee joint range was slightly improved, and intermalleolar range slightly decreased during both treatment periods, the latter being statistically significant for indomethacin ($P < 0.05$).

(d) *Global assessments and preferences.* Global and comparative assessments showed marginally more improvement with diclofenac, but preferences (Table VII) were very clearly in favour of diclofenac.

TABLE VII

Preferences

	diclofenac	indomethacin	Same	P
Patients*	24	9	15	0.01
Doctors*	20	9	17	0.06

(c) *Unwanted effects.* Three patients withdrew because of side-effects on indomethacin (combinations of headache, nausea, vomiting and dizziness) and one on diclofenac (epigastric pain and tiredness).

Side-effects not requiring withdrawal of treatment were reported by 10 patients on diclofenac and 18 on indomethacin (Table VIII), the actual symptoms being similar to those in the rheumatoid patients. CNS symptoms were responsible for the larger number of side-effects with indomethacin.

TABLE VIII

Side-effects in 48 Patients with Osteoarthritis

	CNS	GI	CNS+ GI	Skin	Totals
Diclofenac	2	7	1	0	10
Indomethacin	9	7	0	0	16

LABORATORY INVESTIGATIONS

The number of items of laboratory data (refer †), repeated on three occasions, meant an analysis of nearly 6000 results, with resultant problems in analysing this type of data.

Haemoglobin levels

In osteoarthritis, both treatment groups showed slight but significant changes in haemoglobin level (from 13.6 to 13.3 and 13.2 g/dl) but both groups were unchanged in rheumatoid arthritis.

Fourteen patients showed a decrease and eight an increase of more than 1g/dl. Decreases were evenly divided between the treatment groups and not related to symptoms, particularly to dyspepsia.

Total white cell and platelet counts

The initial mean WBC value in rheumatoid arthritis patients was significantly higher than in the osteoarthritis patients ($P < 0.0001$). None of the mean changes were significant, nor were there individual changes of importance.

ESR

The initial mean value was significantly higher in rheumatoid arthritis patients than in osteoarthritis patients ($P = 0.0003$). Many individual patients showed marked variation, so that group changes were not meaningful.

Serum proteins

These showed no important changes.

Renal function tests

Sixteen rheumatoid arthritis patients had initially raised blood urea levels, which did not change during either treatment period. A few scattered elevations developed in both treatment periods. Similar findings were present in osteoarthritis patients.

In rheumatoid arthritis patients, both drugs reduced mean creatinine levels. Neither affected other tests, whereas in osteoarthritis patients creatinine was not affected, but increases in blood urea levels were present in both treatment groups.

Liver function tests

These showed a number of inconsistent abnormalities with both treatments, but were related more to the trial centre than to the treatment. The majority of abnormal liver function tests were present initially, and there was a marked relationship between abnormal tests and centres. Only one patient developed a high SGOT (101 U/l), which occurred during the indomethacin treatment period only.

The value of diclofenac as a useful alternative preparation for some patients can only be assessed by considering both tolerance and efficacy.

Side-effects have been described in detail under rheumatoid arthritis and osteoarthritis, and may be divided into two groups: severe, requiring withdrawal from the trial, and less severe, allowing treatment to continue. There were three withdrawals from diclofenac and six from indomethacin on account of severe side-effects plus one from each group due to a combination of poor effect and a mild side-effect. Four of the patients with severe effects with indomethacin tolerated diclofenac; the other two did not receive diclofenac.

Poor effect or intolerance of some degree occurred in 32 patients with indomethacin only, 11 with both drugs and 57 with neither. Side-effects were mainly gastrointestinal, headache and dizziness, although indomethacin produced a far higher incidence of CNS effects. The incidence was similar in all five centres. The multitude of laboratory tests can be summarized by saying that no firm evidence of any definite or progressive biochemical or haematological abnormality was detected with either drug.

In patients with osteoarthritis there was no improvement in rest pain, but pain on movement decreased significantly with both drugs. Both patients and doctors expressed significantly more preferences for diclofenac.

In rheumatoid arthritis, both in inpatients and outpatients, there was no difference in the preferences, nor any appreciable difference in the other parameters assessed.

Thus, this five-centre trial was performed on the basis that indomethacin is an accepted and proven anti-inflammatory analgesic. Trials of diclofenac versus placebo have been reported indicating the analgesic effect of diclofenac, and its anti-inflammatory action has also been demonstrated (Doreen et al., 1978). It could be argued that a placebo period should have been incorporated into this trial, although at least one of the centres would have declined to participate. Nevertheless, little difference in efficacy between diclofenac and indomethacin has been shown in this two x two-week crossover trial. Furthermore, during this period no clinically important laboratory abnormality was detected. The quality of side-effects was similar with both drugs, but they were less frequent and less severe with diclofenac.

On this basis it seems likely that diclofenac could reasonably join the group of non-steroidal anti-inflammatory analgesics.

REFLECTIONS AND COMMENTS ON TRIAL METHODOLOGY

Although diclofenac had been used widely in many countries, and a considerable body of data on its efficacy and tolerance was available, this study was designed particularly to provide information on its use in rheumatoid arthritis and osteoarthritis for the UK registration authorities; accordingly, although efficacy is an important feature, much greater stress was placed on tolerance and safety.

One of the main aims in the treatment of osteoarthritis is the relief of pain, whereas in rheumatoid disease reduction of inflammation is also important. In all treatment situations, and particularly in clinical trials, there is always a considerable placebo response, both in regard to effectiveness (particularly pain relief) and to side-effects. So far as this study is concerned the two trial drugs were shown to be equally effective. It could be argued that a placebo group should have been included to prove that this was a real effect, even though previous studies (e.g. Doreen et al., 1978) have already shown both compounds to be superior to placebo and though indomethacin is firmly established as a most effective treatment for these conditions. Certainly there is disagreement amongst the clinicians; at least one centre would have refused to participate had a placebo-treated group been included.

The length of the treatment could also be criticized. Although effectiveness in providing symptomatic relief can be demonstrated in short-term studies, long-term studies are required to establish safety and tolerance. (These have, however, been reported elsewhere: Ciccolunghi et al., 1978.) As always in trial design, the value of a wash-out period between treatments should be considered. Although both drugs in this study have short half-lives, both produce an effect on the disease which may persist for some time after withdrawal of treatment.

The assessments of effect used were simple and clinical; it could be said that a precise measurement of anti-inflammatory effect should have been incorporated, such as colour thermography or radioisotope scanning. These techniques, however, are useful only in very experienced units; moreover, changes can only be demonstrated in patients with more florid types of inflammation, and in any case do not reflect changes in the main symptom of rheumatic diseases—pain. Also, a different basis of patient selection would have been required, which would have militated against the object of the study. "Relief of morning stiffness" was used as a criterion, although whether this aspect, and ring size changes, are the best measures of anti-inflammatory activity has not yet been established, and new and better techniques are still being looked for. Of course, none of these symptomatic measurements would be needed if we had a drug comparable in its action to penicillin, although this seems unlikely to be developed until we have a fuller understanding of the disease process and its pathogenesis.

The presentation of the results of a clinical trial becomes much more meaningful if, as in this instance, "real" data are presented. Although much of the analysis was based on specialized statistics, the results are presented as "means" and changes in means. Although not used as a basis for statistical analysis, this presentation is much more realistic for the non-mathematical clinician.

Thought should also be given to the statistical tests used, and to the interpretation of the results. In this study each drug effect was assessed at two fixed points in time, whereas rheumatoid arthritis, in particular, is an ever-changing disease with its remissions and exacerbations. Furthermore, the more sophisticated statistical tests which can be used for analysis of categorical or non-normally distributed data may show up apparent

differences which cruder old-fashioned tests would not, though the latter might more truly represent the clinical situation. Does, therefore, "no statistically significant differences" really mean that the two drugs are equally effective, or does it mean, in the absence of placebo control, that the trial design and the analytical methods are equally insensitive? This latter point raises the question of how many patients should be included in a study. A small but highly significant statistical difference in a large group of patients may be less meaningful clinically than a large, non-statistically significant difference in a small group of patients.

This study included a significant number of inpatients with rheumatoid arthritis, all from one centre. One would expect that these were the patients with the most active disease, and therefore with the most scope for improvement, and the results presented show that this was the case. Many clinicians accept that when a rheumatoid patient is kept in bed, no matter what treatment is given, the joint symptoms and measurements will improve, and this may blur differences between more and less effective compounds. However, one study at least has shown diclofenac to be more effective than placebo in patients with rheumatoid arthritis (Ghazi and Fowler, 1973).

Another hazard of multicentre trials is inter-observer error. This, however, is less likely to cause problems in a crossover study such as this was. It does have the great

advantage that the use of many centres allows the rapid collection of data.

Finally, what further studies should now be carried out with diclofenac? Should studies be done with higher dosage, or in comparison with other compounds? If so, should placebo-treated groups be included? Does diclofenac have any long-term action which influences the pathogenetic mechanisms?

At present, diclofenac appears likely to become established as a useful, well-tolerated compound with a reasonable margin between efficacy and toxicity, and one which should provide a useful alternative to existing drugs.

REFERENCES

- Ciccolunghi, S. N., Schubiger, B.I. and Reddrop, R. (1979) "Comparisons of Tolerability Findings in International Clinical Trials", *Rheumatol. Rehabil. Suppl.* pp. 122-32.
- Doreen, M.S., Boardman, P.L., Fowler, P.D. and Poole, P.H. (1978) "Diclofenac (Voltarol) in Rheumatoid Arthritis: a Report of a Double-blind Trial", *Rheumatol. Rehabil.* 17, 95-102.
- Ghazi, S.A. and Fowler, P.D. (1973) "A Clinical Trial of a New Anti-inflammatory/Analgesic Compound in Rheumatoid Arthritis — GP 45,840", *J. int. med. Res.* 1, 591-9.
- Ritchie, D.A., Boyle, J.A., McInnes, J.M., Jasani, M.K., Dalakas, T.G., Grieve, P. and Buchanan, W.W. (1969) "Evaluation of a Simple Articular Index for Joint Tenderness in Rheumatoid Arthritis", *Ann. Rheum. Dis.* 28, 196.



A cheerio call to someone selected at random from the membership barrel

Our winter coo-ee is to **Roger Watson**, who passes his days in the balmy coastal climate of tropical Queensland. Roger conducts a specialist musculoskeletal practice in Townsville and lives on beautiful Magnetic Island. His year-round suntan attests to his devotion to research: most of his valuable spare time is spent unselfishly lying on the beach, braving the dangers of keratosis and eyestrain, to study the spinal curvatures so freely displayed there. If he ever publishes his findings it should be a paper containing some very interesting statistics.

THE LONG-TERM EFFICACY AND TOLERABILITY OF VOLTAREN (DICLOFENAC SODIUM) AND INDOMETHACIN IN RHEUMATOID ARTHRITIS

A. Bijlsma

"De Wever" Hospital, Heerlen, Netherlands

ABSTRACT. A report is given on a long-term controlled trial in which diclofenac sodium (Voltaren®) was compared with indomethacin in 36 patients with rheumatoid arthritis, both drugs being administered in a dosage of 75–125 mg daily. In this trial, planned as a double-blind study, each patient was to participate for six months, after which the patients treated with diclofenac sodium were to be followed up for a further six months. By the end of the first six months, diclofenac sodium had proved to be clearly superior to indomethacin in terms of therapeutic efficacy. Moreover, unwanted effects referable to either the central nervous system or the gastro-intestinal tract were less common and less severe in the patients treated with diclofenac sodium than in those receiving indomethacin. These results demonstrate that, when given as long-term treatment to patients suffering from rheumatoid arthritis, Voltaren is both effective and well tolerated.

In short-term clinical trials, diclofenac sodium (Voltaren®) has been shown to be an effective and well-tolerated non-steroid anti-inflammatory agent for the treatment of rheumatoid arthritis. In these trials, which lasted for six weeks or less, comparisons were made with placebo and indomethacin (1, 2, 4, 6, 7, 14), acetylsalicylic acid (8, 12), and ibuprofen (5).

So far, only one long-term trial with diclofenac sodium in rheumatoid arthritis appears to have been published (9). In this publication the investigators reported the results of a three-month, double-blind, multicentre, between-patient study in which diclofenac sodium was compared with indomethacin in 48 patients with "classic" or "definite" rheumatoid arthritis of adult onset. No statistically significant differences were observed between the two drugs in respect of therapeutic efficacy—i.e. in their effect on morning stiffness, grip strength, joint tenderness, number of clinically active joints, and status of rheumatoid condition. On the other hand, diclofenac sodium tended to be better tolerated than indomethacin in that it was associated with a lower

incidence of, in particular, gastro-intestinal and central nervous symptoms.

In an initial double-blind, between-patient trial conducted with diclofenac sodium at our own hospital—which lasted three months and involved 45 patients with rheumatoid arthritis—similar results were obtained, insofar as no significant differences were found in the therapeutic efficacy or tolerability of diclofenac sodium and indomethacin. But the degree of therapeutic response observed with both preparations was disappointing: only two patients in the diclofenac sodium group and no patients in the indomethacin group showed an improvement in the status of their rheumatoid condition at the end of the trial.

In order to determine whether the efficacy and tolerability of the two preparations after six months of treatment might be different as compared with the findings after three months, and in an attempt to gain a clearer impression of the long-term efficacy of diclofenac sodium in rheumatoid arthritis, a second double-blind, between-patient trial comparing diclofenac sodium and indomethacin was therefore undertaken. The present paper describes the results obtained in this six-month trial, as well as in a six-month follow-up period during which the patients treated with diclofenac sodium were kept under further observation.

PATIENTS AND METHODS

Thirty-six cooperative out-patients with rheumatoid arthritis of adult onset were admitted to the trial. No patient was considered for inclusion if he was suffering from severe hepatic or renal disease, cardiac failure or severe hypertension, ulcerative colitis, or known or suspected peptic ulcer, or if laboratory findings suggested the presence of some disorder requiring specific treatment. Also excluded were alcoholics presenting physical signs of alcoholism, pregnant women, and patients who had had a serious infection or had undergone any major

Table 1. Data on the trial population

	Diclofenac sodium (N=18)		Indomethacin (N=18)		Total (N=36)	
Mean age (years)	41.3		43.3		42.2	
Mean body weight (kg)	61.0		65.3		63.1	
	No.	%	No.	%	No.	%
Proportion of females	15	83.3	13	72.2	28	77.8
Mean duration of rheumatoid arthritis						
<1 year	3	16.7	8	44.5	11	30.5
1-5 years	13	72.3	9	50.0	22	61.1
5-10 years	1	5.5	1	5.5	2	5.6
>10 years	1	5.5	-	-	1	2.8
Previously treated for rheumatoid arthritis	14	77.8	12	66.7	26	72.2
Concomitant disease present	-	-	1	5.5	1	2.8
Dosage of trial medication						
75 mg daily	2	11.0	5	27.8	7	19.4
75 mg → 125 mg after 2 weeks	12	66.7	11	61.2	23	63.9
75 mg → 125 mg after 4 weeks	4	22.3	2	11.0	6	16.7
Concomitant medication	3	16.7	6	33.3	9	25.0

surgical procedure within the previous month. Likewise excluded were all patients who had received penicillamine in the previous 12 months, gold therapy or antimalarial agents within the previous three months, or ACTH or corticosteroids within the six weeks prior to the start of the trial. Known intolerance to indomethacin, as well as concomitant anticoagulant therapy, were similarly taken as grounds for exclusion. All patients eligible for admission to the trial had to fulfil at least five of the American Rheumatism Association's diagnostic criteria for rheumatoid arthritis (11).

Of the 36 patients admitted, 28 were female and eight male. Their mean age was 42.2 years and their mean weight 63.1 kg. Eleven of the patients had had symptoms for less than one year, whereas all but three of the remaining 25 had been suffering from rheumatoid arthritis for 1-5 years. Approximately three-quarters of the patients had received previous treatment.

Prior to the commencement of the trial, each patient was assessed for duration of morning stiffness (3), bilateral grip strength (3), number of clinically active joints (3), grades of joint tenderness (10), functional activity (13), and general rheumatoid status (3). Laboratory investigations of haemoglobin, haematocrit, ESR, total leucocyte and differential count, platelet count, bilirubin, SGOT, SGPT, alkaline phosphatase, blood urea nitrogen, and random serum glucose were performed, in addition to which urinalyses (albumin, glucose, acetone, and sediment) were carried out. The assessments were repeated after 2, 4, 8, 12, 16, 20, and 24 weeks of therapy.

All patients initially received diclofenac sodium or indomethacin in a dosage of 25 mg t.i.d. after meals. Allocation to treatment was randomised. In cases where the therapeutic effect proved inadequate, the trial plan permitted an increase in the dosage after two weeks to 125 mg daily, administered in three fractional doses (50 mg, 25 mg, and 50 mg), and if necessary a further in-

crease to a maximum of 50 mg t.i.d. Concomitant administration of other antirheumatic agents, analgesics, or psychotropic drugs was forbidden. Any other drugs or physiotherapy considered to be of vital importance to the patient could be continued, provided that such measures had been started before the trial and that they were continued without modification throughout the entire trial period.

RESULTS

The characteristics of the two treatment groups, which were homogeneous, are outlined in Table 1. Three patients in the diclofenac sodium group received concomitant medication (diazepam as an hypnotic for the entire treatment period in two cases, and penicillin for five days as treatment for intercurrent tonsillitis in one case).

In the indomethacin group, six patients received concomitant medication. In four cases this was prescribed for a pre-existing condition or an intercurrent illness that developed during the trial period: one of the patients, suffering from nervousness, took 150 mg Prominal® daily for 24 weeks, one was given 5 mg diazepam daily for 24 weeks as treatment for sleep disturbances, and one patient with bronchitis had a seven-day course of 1500 mg Penbritin® daily; the fourth patient, a 51-year-old woman, had pre-existing vascular headache, for which she took Bellergal®. The other two patients required medication for unwanted effects which occurred during indomethacin therapy (see below).

Table 2. Status of rheumatoid condition in both treatment groups at Day 0, Week 12, and Week 24

Status of rheumatoid condition	Day 0		Week 12		Week 24	
	Diclofenac sodium	Indomethacin	Diclofenac sodium	Indomethacin	Diclofenac sodium	Indomethacin
	No. %	No. %	No. %	No. %	No. %	No. %
Very good or good	— —	— —	5 27.8	4 22.2	14 77.8	6 33.3
Fair	3 16.7	6 33.3	11 61.1	10 55.6	2 11.1	8 44.5
Poor or very poor	15 83.3	12 66.7	2 11.1	3 16.7	2 11.1	— —
Not reported ^a	— —	— —	— —	1 5.5	— —	4 22.2
Total	18	18	18	18	18	18

^a Not reported because patient stopped treatment prematurely owing to inadequacy of therapeutic effect and/or to unwanted effects.

As already mentioned, all the patients commenced the trial with a daily dosage of 75 mg. Two patients in the diclofenac sodium group and five in the indomethacin group remained on this dosage throughout the trial period. All the other patients had their daily dosage increased after either two or four weeks to 125 mg. Four patients, all of them belonging to the indomethacin group and all receiving 125 mg daily, were dropped from the trial because they failed to respond adequately to the treatment. In two of these cases severe unwanted effects also played a role. Neither lack of therapeutic efficacy nor the occurrence of unwanted effects made it necessary to withdraw any of the patients in the diclofenac sodium group from the trial. Since four poorly responding patients had to be dropped from the indomethacin group, the totals in respect of reported therapeutic efficacy do not always add up to 36 cases.

Therapeutic efficacy

The physician's assessments of status of rheumatoid condition at Day 0, Week 12, and Week 24 are summarised in Table 2. At Week 12 one patient, a 42-year-old male, had stopped therapy with indomethacin because of a deterioration in his rheumatoid condition. With the exception of this patient, the general status of rheumatoid condition after three months of treatment was similar in both treatment groups. By Week 24, however, three further patients in the indomethacin group had discontinued treatment owing to inadequacy of the therapeutic effect: one of them was a 21-year-old female who stopped at Week 16 because of worsening of her disease, while the other two patients were a 56-year-old male and a 24-year-old female

who stopped at Week 20 and Week 24, respectively, because of unwanted effects and because their condition had not improved. Thus, after six months 14 (77.8%) out of the 18 patients in the diclofenac sodium group showed a "good" or "very good" status of rheumatoid condition, as compared with only six (33.3%) in the indomethacin group.

As can be seen from Figure 1, all the patients participating in the trial had a functional capacity of either Class II or Class III (13) before the start of treatment.

Although the functional capacity of the patients in the diclofenac sodium group was initially somewhat worse than in the indomethacin group, by Week 12 significantly more of the patients receiving diclofenac sodium had improved their functional capacity by one class or more. Six of them at Week 12 and eight at Week 24 were no longer

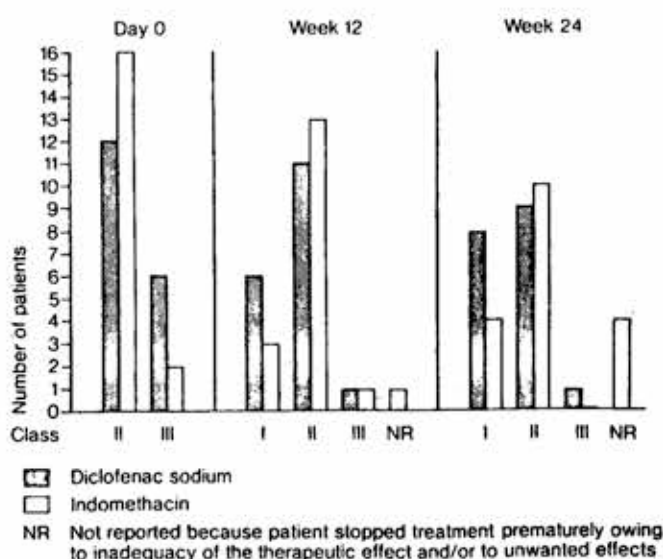



Fig. 1. Functional capacity of the patients in both treatment groups at Day 0, Week 12, and Week 24.



Claims made for anti-arthritic agents are not always borne out. A recent Australian survey showed that only 32% of doctors were satisfied with anti-arthritic drug therapy, while 90% believed that there was significant room for improvement in the area of side-effects. **Voltaren is at least as effective as the agents you use now.**

Some results of clinical comparisons:

"Diclofenac sodium was the most effective drug in all variables and was significantly more effective than naproxen."¹

"Our study indicates that diclofenac in a standard dose of 50mg b.i.d. is more efficacious than naproxen in a standard dose of 250mg b.i.d."²

"In those patients with osteoarthritis diclofenac was shown to be significantly better than ibuprofen in all clinical parameters measured."³

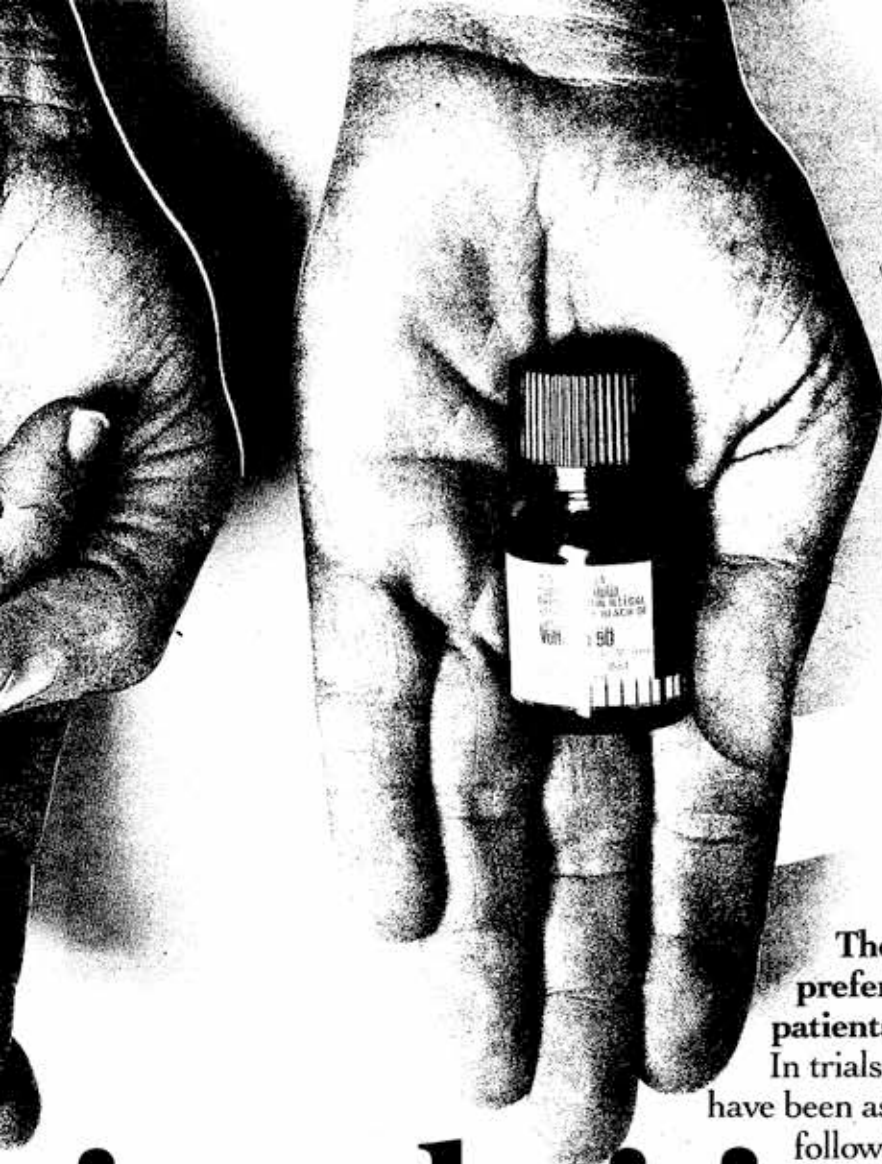
At last, an an which keeps t others ha

"By the end of the first six months, diclofenac sodium has proven to be clearly superior to indomethacin in terms of therapeutic efficacy."⁴

Voltaren offers improved tolerability.

Clinical investigations have also shown that Voltaren is less likely to cause the gastric and CNS side-effects that can limit

1. Amundsen T. et al. *Curr. Ther. Rev.*, Vol. 33(5), 1983, pp.793-801. 2. Eidsaune W. et al. *Curr. Ther. Rev.*, Vol. 33(6), 1983, pp.966-975. 3. Brooks P.M. et al. *Med. J. Aust.*, 1, 1980, pp.29-30. 4. Bijlsma A. *Scand. J. Rheum. Suppl.* 22, 1978, pp.74-80. 5. Siraux P. J. *Int. Med. Rev.*, Vol. 5, 1977, pp.169-174. 6. Sipponen P. Lehtola J. *Scand. J. Rheum.*, Vol. 6, 1977, pp.97-102. 7. Uthgenannt H. Proceedings of a symposium held during the VIII European Rheumatology Congress, Helsinki, 1975. 8. Barnes C.G. et al. *Rheum. Rehab.*, Suppl. 2, 1979, pp.135-146.



The final evidence. Voltaren preferred by both doctors and patients.

In trials where patients and doctors have been asked to make a choice the following results have emerged.

Compared with naproxen – 27 out of 39 doctors who stated a preference, specified Voltaren;

20 out of 29 patients agreed.¹

Compared with indomethacin – 24 out of 33 doctors stating a preference, preferred

Voltaren; 20 out of 29 patients agreed.⁸

Excellent clinical results, good tolerability and convenient b.d. dosage all make Voltaren a most suitable choice for both initial and long-term treatment of arthritic conditions.

ti-arthritic he promises ve made.

the use of other anti-arthritics.

It has been shown to be better tolerated than either indomethacin⁴, or naproxen⁵.

Damage to gastric mucosa⁶, and gastric blood loss⁷ have also been reported to be significantly less with Voltaren than with naproxen.

Voltaren[®]

diclofenac sodium

Unrestricted NHS Benefit.

50mg tablets – 50, 2 repeats.

Table 3. Grades of joint tenderness in both treatment groups at Day 0, Week 12, and Week 24

Grades of joint tenderness	Day 0		Week 12		Week 24	
	Diclofenac sodium (No.)	Indomethacin (No.)	Diclofenac sodium (No.)	Indomethacin (No.)	Diclofenac sodium (No.)	Indomethacin (No.)
0-3	0	2	5	3	13	5
4-6	10	7	12	7	4	6
7-9	7	8	1	6	0	3
10-13	1	1	0	1	1	-
Not reported ^a	-	-	-	1	-	4
Total	18	18	18	18	18	18

^a Not reported because patient stopped treatment prematurely owing to inadequacy of therapeutic effect and/or to unwanted effects.

considered to have any limitation in their functional capacity (Class I), whereas in the indomethacin group only three patients at Week 12 and four at Week 24 no longer had any functional limitation.

Severity of morning stiffness at Day 0 was practically identical in the two treatment groups (Figure 2). From Week 4 onwards, however, proportionally more patients in the diclofenac sodium group had morning stiffness lasting less than one hour. By Week 24, the duration of morning stiffness had been reduced to less than one hour in over three-quarters of the patients receiving diclofenac sodium, and none of them had to stop treatment because the therapeutic effect had proved inadequate. In the indomethacin group, by contrast, the number of patients with morning stiffness lasting less than one hour was 10 (55.6%) at Week 24, and four (22.2%) had to stop the treatment owing to inadequacy of therapeutic effect and/or to unwanted effects.

Grip strength, assessed as the mean of three tries for each hand, improved in both groups, the patients in the diclofenac sodium group showing a more positive tendency in this respect. In this group, ten patients (55.6%) had achieved a clinically significant increase in grip strength (>5 mmHg) at Week 12 and twelve (66.6%) at Week 24, whereas in the indomethacin group the corresponding figures were seven (39%) at Week 12 and ten (55.6%) at Week 24.

The frequency distribution of grades of joint tenderness at Day 0 were similar in the two treatment groups. By Week 12, however, 17 of the patients in the diclofenac sodium group had a score of 6 or less for joint tenderness, as compared with ten patients in the indomethacin group. At Week 24, the corresponding figures were 17 and 11,

respectively. The striking difference between the two treatment groups in this respect is largely explained by the fact that four patients had broken off the treatment with indomethacin owing to inadequacy of therapeutic effect, whereas in the diclofenac sodium group eight patients had attained a further decrease in their score for joint tenderness (Table 3).

Similar findings were obtained with regard to the number of clinically active joints. At Day 0, the two treatment groups were homogeneous in this respect, whereas at Week 12, the number of patients with 11 or fewer clinically active joints in the diclofenac sodium group was 14, as compared with six in the indomethacin group. At Week 24, the respective figures were 16 and nine (four patients in the indomethacin group having meanwhile discon-

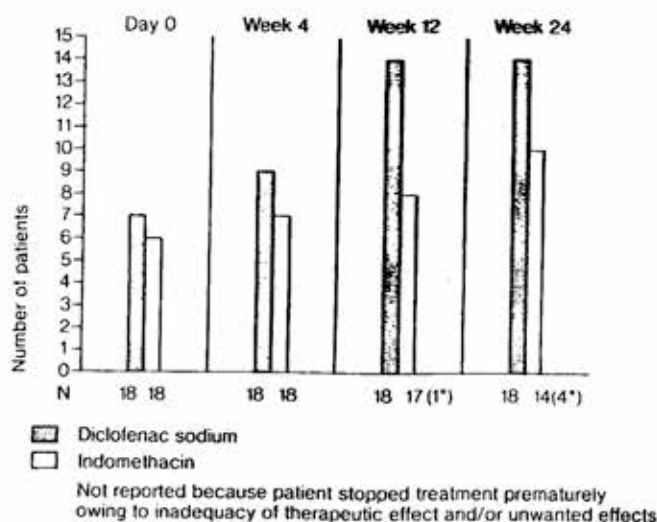


Fig. 2. Morning stiffness of less than one hour's duration in both treatment groups at Day 0, Week 4, Week 12, and Week 24.

Table 4. *Nature and frequency of non-rheumatic signs and symptoms reported in the two treatment groups*

Signs or symptoms	Diclofenac sodium (N=18)		Indomethacin (N=18)	
	No.	%	No.	%
<i>Gastro-intestinal effects</i>				
Nausea	3		6	
Heartburn	—		5	
Vomiting	—		1	
Gastric haemorrhage	—		1	
Diarrhoea	1		—	
Number of patients with one or more unwanted gastro-intestinal effects	4	22.2	8	44.4
<i>CNS effects</i>				
Headache	2		6	
Dizziness	2		4	
Number of patients with one or more unwanted CNS effects	4	22.2	9	50.0
<i>Other unwanted effects</i>				
Pruritus	—		1	
Feeling "hot"	1		—	
Number of patients with one or more other unwanted effects	1	5.6	1	5.6
Total number of patients with one or more non-rheumatic signs or symptoms	5	27.8	13	72.2
Total number of different unwanted effects	9	—	24	—

tinued treatment prematurely owing to inadequacy of therapeutic effect).

The pre-treatment erythrocyte sedimentation rate had decreased by 10 mm or more in six of the patients receiving diclofenac sodium at Week 12 and in ten at Week 24, whereas in the indomethacin group only one patient achieved a decrease of this order of magnitude.

Tolerability

1. *Non-rheumatic signs and symptoms.* As can be seen from Table 4, five (27.8%) of the patients in the diclofenac sodium group, as compared with 13 (72.2%) in the indomethacin group, reported non-rheumatic signs and symptoms ($P<0.05$). In the diclofenac sodium group, the unwanted effects encountered were mild and transitory and usually occurred at the onset of therapy; in no case did reduction of the dosage or discontinuation of the

treatment prove necessary, and subsequent increases in the dosage produced no aggravation or recurrence of the complaints.

The larger number of non-rheumatic signs and symptoms observed in the indomethacin group was accounted for by a higher incidence not only of central nervous system symptoms but also of gastro-intestinal problems. The mean duration of the commoner unwanted effects (headache, nausea, and dizziness) was also longer in the indomethacin group (Table 5).

While under treatment with indomethacin, three patients developed unwanted effects which in two cases were deemed sufficiently severe to necessitate premature discontinuation of the medication. One of these two patients was a 24-year-old woman who had been suffering from moderately severe nausea for ten weeks, pruritus for four weeks, and headache and dizziness for two weeks. The other patient, in whom the unwanted effects were to prove more serious, was a 56-year-old man who developed moderately severe nausea of 48 days' duration and vomiting of three days' duration while undergoing treatment with 125 mg daily. After 20 weeks of treatment his dosage was reduced to 75 mg daily. One week later he had to be admitted to hospital because of gastro-intestinal bleeding; X-ray examination disclosed a gastric ulcer.

2. *Laboratory findings.* A gradual decrease in the haemoglobin values throughout the trial period (from 9.2 mmol/l to 7.5 mmol/l) occurred in one patient (the 56-year-old man mentioned above). This patient had no concomitant disease except for an intercurrent bout of bronchitis and fever which set in after one month of treatment and for which he was given a course of Penbritin. In view of the time relationship it seems likely that the decrease in his haemoglobin values was attributable to treatment with indomethacin. No other patients from

Table 5. *Duration of non-rheumatic signs and symptoms most frequently reported in the two treatment groups*

Sign or symptom	Mean duration (days)	
	Diclofenac sodium	Indomethacin
Headache	13	24
Dizziness	8	18
Nausea	19	29
Heartburn	—	16

either group showed any clinically significant changes in the blood picture, liver function, blood urea nitrogen, or urine tests.

DISCUSSION

Certainly the most interesting finding emerging from the results of this trial was the fact that—as in our previous three-month trial and in the three-month trial reported by Pinheiro et al. (9)—no significant difference in therapeutic efficacy could be discerned between diclofenac sodium and indomethacin at the end of the third month. After six months, however, diclofenac sodium was found to be clearly superior to indomethacin. By the end of the trial, four patients had discontinued treatment with indomethacin because their response to the treatment had been inadequate or because of unwanted effects. The remaining 14 patients responded less well than the 18 patients in the diclofenac sodium group. At week 24, for example, only six (33.3%) of the indomethacin-treated patients showed a "very good" or "good" status of rheumatoid condition, as compared with 14 (77.8%) of the patients receiving diclofenac sodium. This difference in therapeutic effect cannot be ascribed to differences in the dosages of the two trial medications, because roughly equal numbers of patients in both treatment groups were given dosages higher than 75 mg daily. It is also worth noting that the level of therapeutic efficacy observed in the diclofenac sodium group, in which about three-quarters of the patients showed an improvement, bears out the findings reported by Pinheiro et al. and contrasts strikingly with the results of our own previous three-month trial in which hardly any patients appear to have derived benefit from the treatment.

In this six-month trial, a marked difference between the two trial preparations was found with respect not only to the number of unwanted effects but also to their duration. One or more unwanted effects were reported by five (27.8%) of the patients in the diclofenac sodium group, as compared with 13 (72.2%) in the indomethacin group. Two patients in the indomethacin group and none in the diclofenac sodium group discontinued treatment prematurely because of unwanted effects. One of these patients was a 56-year-old man in whom nausea, vomiting, and a gradual decrease in haemoglobin values occurred, which a reduction in the dosage of indomethacin failed to arrest. One week after

the dosage had been lowered, he developed gastrointestinal bleeding which was found upon X-ray examination to have been caused by a gastric ulcer. The unwanted effects from which this patient suffered are considered to have all been related to the treatment with indomethacin, since no ulcer was present at the start of the trial and no other medication which might have provoked them had been taken.

The good gastro-intestinal tolerability which diclofenac sodium exhibited in this trial has been confirmed in a separate study in which five patients with rheumatoid arthritis were treated with the drug for eight weeks. Examinations of their faeces, using the benzidine reaction, were performed both before treatment and every two weeks thereafter; at no time was a positive stool test obtained.

At fortnightly intervals, blood samples were also obtained from these patients, as well as from a further seven patients with spondylarthritis, and analysed for the plasma levels of unchanged active substance. The results clearly indicated that no accumulation of diclofenac sodium occurred over the period of eight weeks of treatment (Bijlsma, A., Stegink, A. J. & Brombacher, P. J.: unpublished findings).

Follow-up examinations (carried out every two months) of the patients treated with diclofenac sodium in this six-month trial revealed that, after the treatment had been in progress for 12 months, five (33.3%) out of 15 patients were still in a "fair to good" condition and the remaining ten (66.7%) in a "good to very good" condition. Three patients dropped out during the follow-up period for reasons not connected with the therapy: one because of an intercurrent illness (glandular fever) and another because of an operation; the third patient stopped the treatment at the end of the first six months because she had by then already achieved an almost complete remission. During this follow-up period, none of the patients complained of any unwanted effects and there were no pathological changes in the blood picture or in liver function, blood glucose, blood urea nitrogen, or urine tests.

At present, i.e. some two and a half years since the start of the trial itself, eight of the 15 patients are still undergoing treatment with Voltaren. Of the remaining seven patients, three stopped the treatment because their rheumatic complaints had either greatly improved or actually disappeared, one stopped after 18 months because she had become

pregnant, and the other three patients had to change over to gold therapy after 12–18 months because their rheumatoid arthritis was progressively worsening.

In conclusion, it would appear from the overall experience we have acquired with diclofenac sodium that, in response to long-term treatment with this drug, an improvement can be expected to occur in about three out of every four cases of rheumatoid arthritis. In the six-month trial described here—in contrast to findings obtained during a three-month period of treatment—diclofenac sodium proved significantly more effective from the clinical standpoint than indomethacin. Unwanted effects, referable both to the central nervous system and to the gastro-intestinal tract, occurred less frequently with diclofenac sodium than with indomethacin and were also less severe.

Long-term treatment for periods ranging from 12 to 30 months has also confirmed the good efficacy and tolerability of this new antirheumatic preparation.

REFERENCES

1. Badía-Flores, J., García Rubio, R. & Muñoz Barradas, F.: Efecto sintomático y tolerabilidad del diclofenac sódico en la artritis reumatoide. *Invest Méd Int (Mex)* 2: 194, 1975.
2. Ciccolunghi, S. N., Levi, B. & Chaudri, H. A.: Klinische Erfahrungen mit Voltaren, einem neuen, nicht-steroiden Antirheumatikum. *Wien Med Wochenschr* 125: 66, 1975.
3. Co-operating Clinics Committee of the American Rheumatism Association: A seven-day variability study of 499 patients with peripheral rheumatoid arthritis. *Arthritis Rheum* 8: 302, 1965.
4. Dürriegl, T., Vitaus, M., Pucar, I. & Miko, M.: Diclofenac sodium (Voltaren): results of a multi-centre comparative trial in adult-onset rheumatoid arthritis. *J Int Med Res* 3: 139, 1975.
5. Houli, J., Klein, B. & Coimbra, F. A.: Efficacy and tolerability of Voltaren (diclofenac sodium GP 45,840) in rheumatoid arthritis. *Folha Méd. (Rio de Janeiro)* 71: 685, 1975.
6. Kátóna, G. & Robles-Gil, J.: Método doble ciego, a corto plazo, para evaluar la eficacia del diclofenac sódico en la artritis reumatoide. *Rev Méd Hosp Gen (Mex)* 38: 93, 1975.
7. Kirchheiner, B., Trang, L. & Wollheim, F. A.: Diclofenac sodium (Voltaren) in rheumatoid arthritis: a double-blind comparison with indomethacin and placebo. *Int J Clin Pharmacol Biopharm* 13: 292, 1976.
8. Meyers, O. L., Quantock, O. P., Joubert, P. G., Louw, D. F. du P., Marais, D. F., Scott, W. A. McD. & Müller, F. O.: A multicentre trial of Voltaren in the treatment of rheumatoid arthritis. *S Afr Med J* 48: 2013, 1974.
9. Pinheiro, G. C., Gouveia, O. S., Moreira Filho, J. M. L., Amorim, E. H. & Rodrigues, J. A.: Comparative double-blind trial with GP 45,840 (Voltaren) and indomethacin in rheumatoid arthritis. In *Voltaren, a New, Non-Steroid Antirheumatic Agent (Diclofenac)*, Proceedings of a Symposium held during the VIIIth European Rheumatology Congress, Helsinki, 1975 (ed. F. J. Wagenhäuser), p. 35. Huber, Berne, Stuttgart and Vienna, 1976.
10. Ritchie, D. M., Boyle, J. A., McInnes, J. M., Jasani, M. K., Dalakas, T. G., Grieverson, P. & Buchanan, W. W.: Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *Quart J Med* 37 (N.S.): 393, 1968.
11. Ropes, M. W., Bennett, G. A., Cobb, S., Jacox, R. & Jessar, R. A.: 1958 revision of diagnostic criteria for rheumatoid arthritis. *Arthritis Rheum* 2: 16, 1959.
12. Solomon, L. & Abrams, G. J.: Voltaren in the treatment of rheumatoid arthritis. *S Afr Med J* 48: 949, 1974.
13. Steinbrocker, O., Traeger, C. H. & Batterman, R. C.: Therapeutic criteria in rheumatoid arthritis. *JAMA* 140: 659, 1949.
14. Tausch, G., Eberl, R. & Tuschl, P.: Klinische Erfahrungen und Ergebnisse klinisch experimenteller Untersuchungen mit Voltaren bei rheumatischen Erkrankungen. *Wien Med Wochenschr* 126: 132, 1976.

The Committee on Education and Research has been working on ways of facilitating the teaching of musculoskeletal medicine. The task is made more challenging by the diversity of views and the multiplicity of techniques favoured by different practitioners and by the rapid movement of the research frontier. A tentative syllabus for an introductory course (or set of courses) on musculoskeletal medicine has been put together and will be discussed at the next meeting of the committee. Members wishing to make suggestions or comments are encouraged to send them to the President (as convenor of the committee) and/or to the editor for publication in the Bulletin.

VARIATION IN RESPONSE TO NAPROXEN AND DICLOFENAC IN PATIENTS WITH OSTEOARTHRITIS

T. Amundsen, M.D.,¹ L. Bleken, M.D.,² B. Borkje, M.D.,³
W. Eidsaunet, B.A.,⁴ P. Eidsbo, M.D.,⁵ S. Larsen, D.Sc.,⁴
R. Finstad, M.D.,⁶ T. Quamme, M.D.,⁷ L. Sandvik, M.Sc.,⁴
P.H. Staff, M.D.,¹ J. Sorlie, M.D.,⁶ and J. Utne-Sorensen, M.D.,³

¹Ullevål Sykehus, Oslo 1,

²N-2600 Lillehammer,

³Hatlestad Sykehus, N-5210 Kalandseidet,

⁴CIBA-GEIGY Pharma A.s. N-2011 Strommen,

⁵Kirkevn, Oslo3,

⁶Sor-Odal Revmatismesykehus, N-2100 Skarnes, and

⁷Hjellestadklinikken, N-5066 Hjellestad, Norway

ABSTRACT

In a double-blind, randomized multicentre, cross-over in 52 patients with osteoarthritis, diclofenac (D) 50 mg bid was compared with naproxen (N) 250 mg bid and placebo (P) given for 10 days in one of four sequences: DPN, NPD, PDN, PND. Because of a significant period effect for placebo, placebo effects were estimated based on the first period only. A significant placebo effect was seen in one variable only. Diclofenac was significantly more effective than naproxen, and was preferred significantly more often ($p = 0.02$). The difference was greatest in patients with an initial ESR 18 mm/hr . Nine out of 22 patients with little effect or unwanted effects obtained good effect without unwanted effects, when changing from naproxen to diclofenac (41%) compared with 1 out of 13 (8%) changing from diclofenac to naproxen. Unwanted effects occurred in 13% of patients on placebo, 6% on diclofenac and 8% on naproxen.

INTRODUCTION

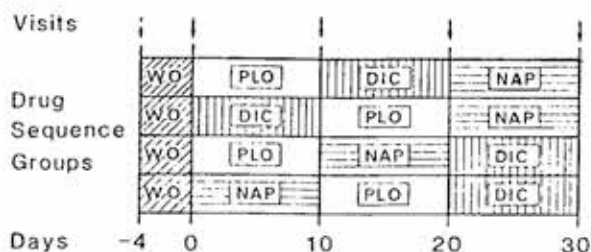
Patient response to non-steroidal anti-inflammatory drugs (NSAID) has been shown to vary considerably, particularly in rheumatoid arthritis.¹ Huskisson in his study of four new NSAID-propionic acid derivatives¹ found naproxen to be the most effective drug. In order to test whether the same variation occurs in osteoarthritis (OA) and whether another recently introduced NSAID diclofenac sodium could be shown to be complementary to naproxen and vice versa, we designed this multi-centre trial basically in the same way as described in Huskisson's studies^{1,2} and by others.^{3,4} A further purpose was to assess the efficacy and tolerability of each drug, hence placebo was also used.

METHODS

Design

The study was designed as a cross-over study using reduced orthogonal latin squares in order to achieve a balanced design. After a washout period of minimum four days for patients on previous treatments, patients were randomly assigned to one of four treatment sequences (Fig. 1) with three 10-day treatment periods. Assessments were carried out on days 0, 10, 20 and 30, i.e. before and after each treatment period. Daily dose of naproxen was 250 mg bid and of diclofenac sodium 50 mg bid. Blindness was achieved by means of the double-dummy technique. Paracetamol up to 1 g qid was allowed as a rescue analgesic, the patients recording daily the number of tablets taken.

Figure 1 — Design of the cross-over study of Diclofenac (DIC), Naproxen (NAP) and Placebo (PLO).



Assessment Methods

All assessments were based on subjective variables using 100 mm visual analogue scales (VAS). Patients assessed their start difficulties after rest, pain on movement and their status of disease (from very good to very poor), before and after each period. The physicians also assessed the patients' status of disease. Patient and physician both assessed overall efficacy by the same method, the scale going from no effect to very good, best possible. Patients were asked at each visit about the presence of symptoms and complaints other than those caused by their disease. If present, the severity of any symptom was assessed by means of visual analogue scales with end points not present and extremely severe, unbearable. Period preference was indicated by physicians and patients at the end of the trial. Laboratory examinations were carried out according to each centre's normal routine with haemoglobin and erythrocyte sedimentation rate (ESR) as the only tests reported for the trial.

Patients

Fifty-two patients, 13 in each sequence were included. Data on sex, age, weight and duration of disease as well as distribution of diagnoses are given in Tables I and II. Only patients with osteoarthritis having acute synovitis with pain necessitating treatment with an NSAID were included. Patients with severe hepatic or renal disease, peptic ulcers, severe infection, previous intolerance to either drug, salicylate-sensitive asthma or patients who had undergone surgery within the last month were not included. There were no drop-outs; all patients completed the trial. All patients received verbal and written information about the study before informed consent was obtained.

Table 1 — Patient characteristics

	MEAN	RANGE
AGE (YEARS)	61	34-78
WEIGHT (KG)	70	48-96
DURATION OF DISEASE (YEARS)	10	48-96

Table 2 — Distribution of diagnoses (Figures in brackets denote number of patients with bilateral disease.)

SEQUENCE	Osteoarthritis of Knee	Osteoarthritis of Hip	Osteoarthritis of Several Joints
NPD	4 (3)	8 (4)	1
DPN	3 (2)	10 (5)	0
PND	3 (2)	10 (6)	0
PDN	4 (2)	7 (3)	2
SUM	14 (9)	35 (18)	3

*N: naproxen; P: placebo; D: diclofenac

Statistical Analysis

Statistical analyses were based on one-tailed non-parametric tests.^{5,6} The Wilcoxon signed rank test was used for testing of treatment effects⁶ and period effects.⁷ Initial analyses and treatment comparisons were based on the Wilcoxon rank sum test.⁶ When testing for differences in frequency of unwanted effects, as well as period differences a one-sided sign test was used.⁶ A significance level of 5% was applied. Correlation analyses were based on Kendall's method.⁸

There was a significant period effect for placebo, but not for the active drugs. Placebo was more effective when given before an active drug than when given after. Because of the significant period effect, estimation of placebo effects were based on the 26 patients receiving placebo in the 1st period (sequences PDN and PND).

The initial correlation analysis showed a significant positive correlation between patients' evaluation of status of disease and ESR ($\tau = 0.35$) and a significant negative correlation between status of disease and haemoglobin ($\tau = -0.26$). There was significant correlations between patients' and physicians' evaluation of status of disease and pain on movement and start difficulties, indicating that both are relevant variables for efficacy evaluation.

RESULTS

The only variable where there was a significant placebo effect was start difficulties ($p = 0.02$) (Fig. 2). Both active compounds caused significant improvement in all variables (Figs. 2 to 5). The difference between active drugs and placebo were all significant, with the possible exception of naproxen in start difficulties ($0.05 < p < 0.08$) (Fig. 2).

Diclofenac sodium was the most effective drug in all variables and was significantly more effective than naproxen (Figs. 2 to 5). The overall evaluation on efficacy showed both drugs to be rated as significantly more effective than placebo and again diclofenac sodium was significantly better than naproxen ($p < 0.05$) (Fig. 6).

Figure 2 Patients' assessment of "Start Difficulties after Rest" using 100 mm Visual Analogue Scales (VAS). Shaded areas indicate initial and columns post-treatment

95% confidence limits. Heavy lines indicate median scores. P-value inside columns for comparison with initial scores, p-values outside, comparison between treatments.

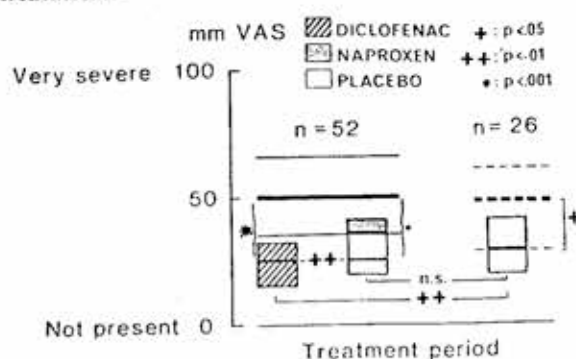


Figure 3 — Patients' assessment of "Pain on Movement" using 100 mm VAS. See Fig. 2 for explanation of details.

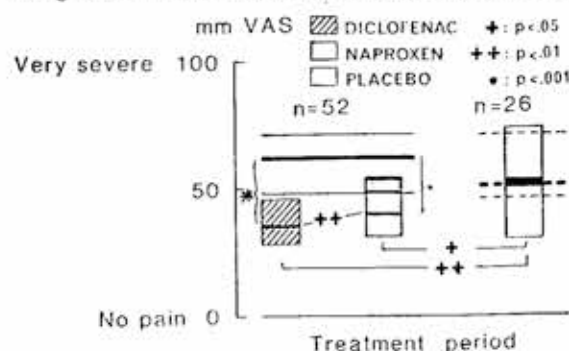


Figure 4 — Physicians' assessment of "Status of Disease" using 100 mm VAS. See Fig. 2 for explanation

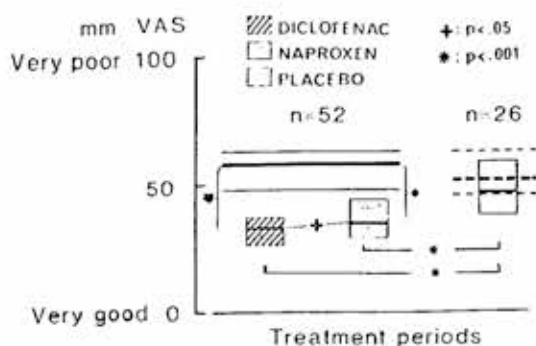


Figure 5 — Patients' assessment of "Status of Disease" using 100 mm VAS

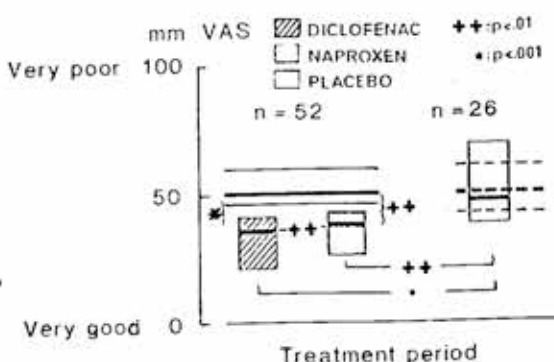
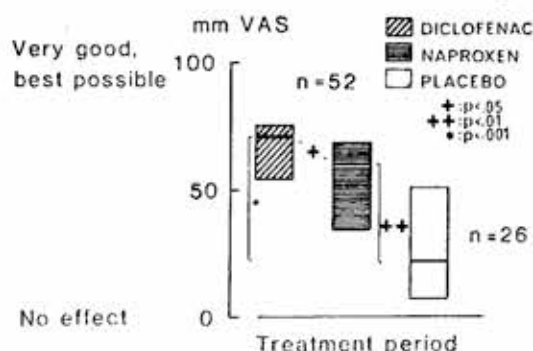


Figure 6 - Patients' assessment of overall efficacy using 100 mm VAS. P-values given for comparison of each active drug with placebo and between active drugs.



Preference indicated by patients and physicians at the end of the trial significantly favoured diclofenac ($p < 0.02$) (Table III) and 83% of patients and physicians preferred active drugs to placebo. Consumption of rescue analgesic did not differ significantly on D, P and N. Diclofenac sodium caused a significant reduction of ESR compared with placebo ($p < 0.001$) and naproxen ($p = 0.02$) and there was a tendency towards a reduction on naproxen ($p = 0.07$). Diclofenac sodium caused a reduction in haemoglobin compared with placebo (141 g/l vs 140 g/l) which was statistically significant whereas naproxen did not. The difference between the drugs was not significant. Seven patients (13%) reported unwanted effects on placebo, compared with 3 on diclofenac sodium (6%) and 4 on naproxen (8%). All were mild or moderate and were related to the gastrointestinal tract with the exception of vertigo in one patient on placebo. In no case was treatment interrupted because of unwanted effects.

TABLE III - Treatment preference

	PATIENTS	PHYSICIANS
DICLOFENAC	28*	27*
NAPROXEN	13	12
PLACEBO	2	1
NO PREFERENCE	9	12

*Diclofenac preferred significantly more often ($p = 0.02$)

Table IV Overall efficacy in relation to initial ESR (VAS-score in CM)

Initial ESR* MM 1. Hour	Overall Efficacy	
	Diclofenac	Naproxen
6 (n= 12)	6.5	7.2
6-8 (n= 14)	5.5	4.8
9-17 (n= 14)	5.7	5.3
18 (n= 12)	6.7	2.5

*Erythrocyte sedimentation rate

There were no significant correlations between patient factors or laboratory variables and efficacy on diclofenac sodium. The only significant correlation on naproxen was a negative correlation between overall efficacy and initial ESR ($r = -0.34$, $p \leq 0.01$). Patients with a high ESR initially did thus have a smaller effect on naproxen. The distribution of initial ESR-values can be divided into 4 classes (Table IV) and when overall efficacy for each

group is estimated, diclofenac sodium appears to be equally effective in all classes, and naproxen is approximately equieffective up to an ESR of 17 mm 1 hr. For patients with an initial ESR of 18 mm or above, naproxen was much less effective.

Complementarity

Two of seven patients with unwanted effects on active drugs reacted to both compounds.

Twenty-two patients had little effect (efficacy score below 3.3 on the VAS) or unwanted effects on naproxen. Nine of these patients (41%) had a good effect (efficacy score above 6.6) without any unwanted effects on diclofenac sodium. Thirteen patients had little effect or unwanted effects on diclofenac sodium and one of these patients (8%) had good effect and no unwanted effects on naproxen.

DISCUSSION

Comparative trials carried out prior to this study have indicated that diclofenac sodium in a dose of 50mg bid might be more effective than naproxen 250 mg bid in osteoarthritis^{9,10} and two studies reported significant differences in favour of diclofenac sodium.^{11,12} All cited studies were based on smaller groups than the present study. In addition we used a very sensitive method for assessment of symptoms and overall efficacy. It is interesting to note that the placebo effect was minimal, with a significant placebo response in only one variable. In addition, the only significant period effect was seen for placebo, which was more effective when given before either active drug. This also means that the size of the placebo effect has been conservatively estimated since only placebo data from the 1st period were used.

The role of synovial inflammation in cartilage destruction in osteoarthritis and the effects of NSAIDs on each remains controversial. Recent experimental research in a spontaneous osteoarthritis model in C-57 black mice¹³ may be seen to support the anecdotal implication of some NSAIDs in the development of osteoarthritis.^{14,15} In the spontaneous OA-model in mice, on the other hand, diclofenac was shown to reduce the rate as well as the severity of joint destruction.¹³ In the present study the entire difference between diclofenac and naproxen can be explained by the difference in the group whose initial ESR was 18mm 1 hr. or more. Presumably these were the patients with the most "severe" inflammation. This may be seen to indicate a greater potential for diclofenac to combat synovial inflammation, but whether this has any relation to the results seen in the experimental model cited above, cannot be determined on the basis of this short-term study. We do feel, however, that the results are interesting enough to warrant further investigation.

On the basis of all efficacy variables used in this study we conclude that, on the average, diclofenac sodium is more effective than naproxen in the present dosage in the short-term treatment of osteoarthritis presenting with an acute episode of synovitis. This difference in mean efficacy was particularly large in patients with a high ESR initially. More can be gained by changing from naproxen to diclofenac sodium than the other way. Both drugs appear to be well tolerated at the dosage used.

References:

1. Huskisson, E.C., Woolf, D.L., Balme, H.W., Scott, J., and Franklyn, S.: Four New anti-inflammatory drugs: responses and variations. *Brit. Med. J.* 1:1048, 1976.
2. Huskisson, E.C.: In the Principle and Practice of Clinical Trials (Ed. C.S. Good) Edinburgh: Churchill Livingstone, p. 188-194, 1976.
3. Amor, Brouhlet, Delbarre, Giroud, Kahan, Di Rosa, Velo, Turk, Willoughby, Timsit, Franchimont, Balme, Berry, Glynn and Huskisson: New Approaches to the Evaluation of Anti-Rheumatic Drugs in Agents and Actions, Basel: Birkhauser Verlag, vol. 3/4 pp. 169-17, 1974.
4. Lee, P., Wehh, J., Anderson, J., and Watson Buchanan, W.: Method of Assessing Therapeutic Potential of Anti-inflammatory Antirheumatic Drugs in Rheumatoid Arthritis. *Brit. Med. J.* 2:685, 1973.
5. Sverdrup, E.: Significance Testing in Multiple Statistical Inference. *Scand. J. Stat.* 3:73, 1976.
6. Lehmann, E.L.: Non-parametrics: Statistical Methods Based on Ranks. San Francisco: Holden-Day Inc., 1975.
7. Koch, G.G.: The use of Non-Parametric Methods in Statistical Analysis of Two-period Change-over Design. *Biometrics* 28:577, 1972.
8. Kendall, M.: Rank Correlation Methods, London: Charles Griffin & Co. Ltd, 1975.
9. Car, A., Jajic, I., Krampac, J., Vitaus, M., Zenic, N., and Zivkovic: A double-blind multicentre comparison of diclofenac sodium and naproxen in osteoarthritis of the hip. *Scand. J. Rheumatol. Suppl.* 22:63, 1978.
10. Siegmeth, W., and Placheta, P.: Langzeitvergleichsstudie: Diclofenac (Voltaren) and Naproxen (Proxen) bei Arthrosen. *Schweiz. med. Wschr.* 108(9):349, 1978.
11. Siraux, P.: Diclofenac (Voltaren) for the treatment of Osteo-Arthrosis. A double-blind comparison with Naproxen. *J. Int. Med. Res.* 5:169, 1977.
12. Bach, G.L.: Comparative clinical trials with Diclofenac sodium (Voltarol) and Naproxen in Rheumatic conditions: Investigations of possible changes in Diclofenac dose and dose interval. *Rheumatol Rehabil. Suppl.* 2:69, 1979.
13. Maier, R., and Wilhelmi, G.: Special pharmacological findings with Voltaren. In Voltaren — New Findings, Ed., E. Kass, Bern: H. Huber Publishers, p. 11-18, 1982.
14. Solomon, L.: Drug induced arthropathy and necrosis of the femoral head. *J. Bone Joint Surg.* 55B:246, 1973.
15. Rommigen, H., and Langeland, N.: Indomethacin treatment in osteoarthritis of the hip joint. *Acta. Orthop. Scand.* 50:169, 1979.



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RESPONSE TO TWO NSAIDs: DICLOFENAC AND NAPROXEN IN RHEUMATOID ARTHRITIS

W. Eidsaunet, B.A.,¹ B. Borkje, M.D.,² S. Larsen, M.Sc.,¹
L. Sandvic, M.Sc.,¹ and K.L. Spongeen, M.D.³

¹Ciba-Geigy Pharma A/S, N-2011, Strommen

²Hatlestad Sykehus, N-5210 Kalandseidet, and

³Radhusgt., Oslo 1 Norway

ABSTRACT

Fifty-nine patients with rheumatoid arthritis were studied in a three-period cross-over comparison of diclofenac 50 mg b.i.d., naproxen 250 mg b.i.d. and placebo. Evaluation of various disease variables initially and after each 10-day period was carried out using 100 mm visual analogue scales. Diclofenac was significantly more effective than placebo in all variables and more effective than naproxen in two. Naproxen was significantly more effective than placebo in all variables except pain at rest. Physicians and patients preferred diclofenac significantly more often than naproxen and placebo. Diclofenac was rated as significantly more effective than naproxen regarding "overall efficacy". Thirty-two patients obtained good effect on diclofenac, 22 on naproxen and 39 on one or the other. Only 5 patients (10%) failed to respond at all to either drug. No typical characteristics for responders could be determined. Nine patients had unwanted effects on diclofenac, six on naproxen and three on placebo.

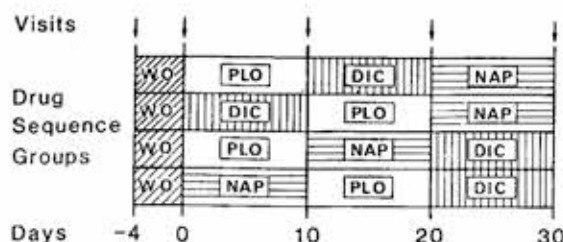
INTRODUCTION

Patients with rheumatoid arthritis react differently to the same drugs, some patients respond astonishingly well whereas others appear to gain little or no benefit from treatment with the same agent.^{1,2} This fact has been so widely recognized that one may in fact regard it as a "theorem" for NSAID use in rheumatoid arthritis (RA). We carried out a study of diclofenac, naproxen and placebo in order to elucidate this further. An additional purpose of the study was to estimate the efficacy of each drug and to compare them.

METHODS

The study was designed as a 3-period cross-over study using reduced orthogonal Latin squares in order to achieve a balanced design. After a washout period of four days minimum for patients previously on treatment, patients were randomly assigned to one of four treatment sequences (Fig. 1) with three 10-day treatment periods. Assessments were carried out on days 0, 10, 20 and 30 — i.e., before and after each treatment period. Naproxen was given in a dose of 250 mg b.i.d. and diclofenac 50 mg b.i.d. Blindness was maintained by means of a double-dummy technique. Paracetamol up to 1 gram q.i.d. was allowed as a rescue analgesic, the patients recording daily the number of tablets taken.

Figure 1 — Design of the cross-over study of Diclofenac (DIC), Naproxen (NAP) and Placebo (PLO)



Assessments methods

All assessments were based on subjective variables using 100 mm visual analogue scales (VAS). Patients assessed their pain at rest, pain on movement and status of disease (from very good to very poor), before and after each period. The physicians also assessed the patients' status of disease, and both assessed overall efficacy by the same method. The end points of the efficacy scale were defined as no effect and very good, best possible. In addition, patients recorded daily the duration of their morning stiffness. At each visit patients were asked about the presence of symptoms and complaints other than those caused by their rheumatic disease. If present, severity was assessed by means of VAS with end points not present and extremely severe, unbearable. Only symptoms that were not present before start, or, if they were present, increased in severity during treatment, were counted as unwanted effects.

At the end of the trial, patients and investigators indicated which of the three periods they preferred.

Laboratory examinations were carried out in accordance with each centre's normal routine. Haemoglobin and erythrocyte sedimentation rate (ESR) were the only laboratory tests reported at each visit. Initially the titre of rheumatoid factor was determined in addition.

Patients

Cooperative patients aged 18 or above with a diagnosis of "active" or classic rheumatoid arthritis according to the ARA criteria, who, after receiving written as well as oral information, consented to participate, were included. Patients with onset of disease before the age of 16 were excluded as were patients with severe hepatic or renal disease, peptic ulcers, severe infection, previous intolerance to either drug, salicylate sensitive asthma or who had surgery within the previous month. Patients who had no increase in pain during washout were not included. Concomitant treatment with gold or systemic

steroids up to 7.5 mg prednisone/day was permitted provided the patients were stabilized prior to entry. Altogether 61 patients were included. Demographic data are given in Table I and the diagnoses in Table II. Two patients discontinued for reasons not related to treatment (one suffered a leg fracture, one turned out to be uncooperative) and both were excluded from the analyses.

Table I — Patients characteristics. Data for the age and weight given as mean \pm SEM.

Drug sequence	Sex	Age (yrs)	Weight (kg)
Diclofenac, Placebo	8 M		
Naproxen	10 F	57.8 \pm 3.5	66.8 \pm 3.1
Placebo, Diclofenac	4 M		
Naproxen	10 F	56.1 \pm 3.6	61.5 \pm 2.4
Placebo, Naproxen	6 M		
Diclofenac	9 F	54.1 \pm 3.9	65.7 \pm 3.4
Naproxen, Placebo	4 M		
Diclofenac	8 F	54.7 \pm 2.7	66.8 \pm 2.9
Total	23 M		
	38 F	54.3 \pm 1.8	65.3 \pm 1.6

Table II — Diagnoses, duration of disease (mean \pm SEM) and concomitant treatment.

Drug sequence	Etiologic Rheumatoid Arthritis	Definite Rheumatoid Arthritis	Duration of disease (years)	Concomitant treatment Gold	Steroids	Chloroquine
Diclofenac, Placebo						
Naproxen	11	7	11.2 \pm 2.3	6	1	3
Placebo, Diclofenac						
Naproxen	10	4	12.4 \pm 2.0	3	3	1
Placebo, Naproxen						
Diclofenac	11	4	5.1 \pm 1.1	1	3	
Naproxen, Placebo						
Diclofenac	10	2	10.3 \pm 2.3	1	2	
Total	42	17	9.5 \pm 1.1	11	9	4

Four further patients discontinued prematurely due to treatment related reasons: One patient in period 1 (diclofenac) because of severe diarrhoea, one after two days in period 2 (placebo) due to lack of effect and two in period 3 (naproxen) for the same reason. These patients were included in the analyses.

Statistical analysis

Statistical analysis was based on one-tailed non-parametric tests.^{3,4} The Wilcoxon signed mid-rank test was used for testing of treatment effects and period effects. Initial analyses and treatment comparisons were based on the Wilcoxon mid-rank sum test. The theory of simple Bernoulli sequences was used for testing differences in period preference and frequency of unwanted effects. Kendall's τ was used as an index of correlation between two variables. A significance level of $\alpha=0.05$ was used.

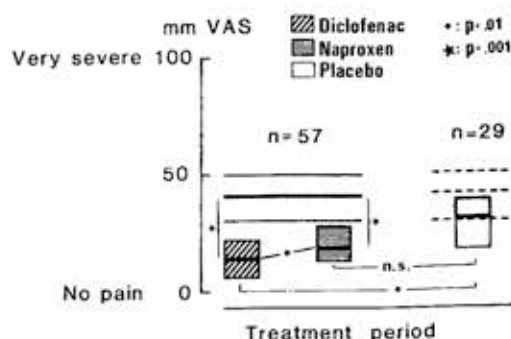
A significant period effect was detected for placebo, but not for the active drugs. Placebo was more effective when given in the first period than in the second. Due to the period effect for placebo, estimates for placebo effects were based on the 29 patients receiving placebo in the first period only.

Table III — Duration of morning stiffness (minutes)

	Initially	Naproxen	Diclofenac	Placebo
Mean	115 (142)	71	58	133
SEM	22 (39)	16	15	39
95% C.I.	32-118 (31-120)	10-60	9-42	25-120
p-value hrs/N/D/P		<0.001	<0.001	0.05
p-value P vs N/D		<0.001	<0.001	
N vs D			0.07	

Figures in () indicate initial values for 29 patients used to estimate the placebo effect.

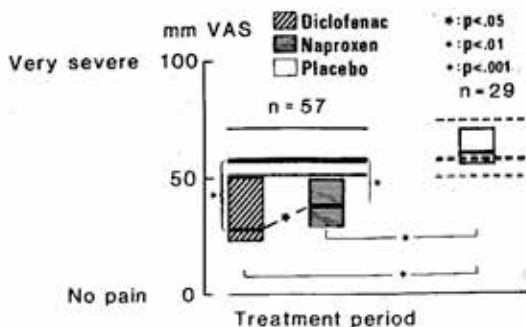
Figure 2 — Patients' assessment of pain at rest using 100 mm visual analogue scales. Shaded area indicates 95% confidence interval for initial scores, columns after each treatment period. Heavy lines indicate medians. Placebo effects are based on 29 patients receiving placebo as first treatment only.



RESULTS

The effect of placebo was significant only in two variables: duration of morning stiffness (Table III) and pain at rest. (Fig. 2) The effect of diclofenac was significantly better than placebo in all variables, and naproxen in all variables except pain at rest. (Figs. 2-6) Diclofenac was significantly better than naproxen in pain on movement and pain at rest (Figs. 2-3). There was a

Figure 3 — Patients' assessments of pain on movement using 100 mm VAS. (See Fig. 2 for explanation of details)



tendency in favour of diclofenac in morning stiffness (Table III) ($p=0.07$) and status of disease, (patient) (Fig. 4) ($p=0.06$). The two drugs were comparable with regard to status of disease evaluated by the physician. Overall efficacy scores were significantly higher on diclofenac than on naproxen and significantly higher on both drugs than on placebo (Fig. 6).

For 55 patients the period preference was stated at the end of the trial. Thirty-two patients (58%) preferred diclofenac, 15 preferred naproxen (27%), 5 placebo (9%) and 3 had no preference. Among the physicians, 29 considered the diclofenac period to be the best, 14 naproxen, 7 placebo and for 5 there was no preferred period. Diclofenac was preferred significantly more often than naproxen by patients ($p=0.01$) and physicians ($p=0.02$). Consumption of rescue analgesics were not significantly different on diclofenac, naproxen and placebo.

The correlation analysis using Kendall's τ test on data from 61 patients will yield coefficients significantly different from 0 (at a significance level of 0.01) if its numerical value is at least 0.23.

Figure 4 — Patients' assessments of status of disease using 100 mm VAS. (See Fig. 2 for explanation of details)

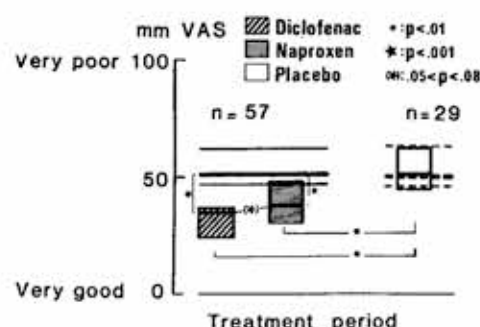
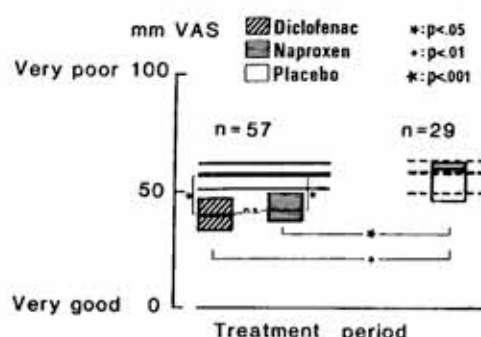
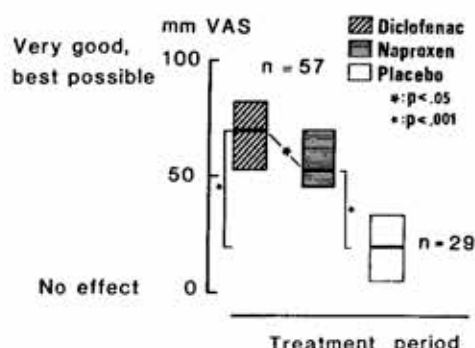


Figure 5 — Physicians' assessment of status of disease using 100 mm VAS. (See Fig. 2 for explanation of details)



In the present study all disease variables, with the exception of duration of morning stiffness, were significantly correlated. Status of disease evaluated by the patient was most strongly correlated to pain on movement, ($r = 0.58$) indicating that this is the dominant variable for evaluation of status of disease. There were no significant correlations between status and patient factors such as age, weight, or duration of disease.

Figure 6 — Patients' assessment of overall efficacy using 100 mm VAS. P-values given for comparison of each active drug and placebo and between active drugs.



There was a weak (not significant) correlation between status and ESR ($r = 0.18$) and a weak negative correlation between status and hemoglobin ($r = -0.18$) and a significant negative correlation between erythrocyte sedimentation rate and hemoglobin ($r = -0.31$) initially.

There were no significant correlations between overall efficacy and initial scores or patient factors for either drug.

Unwanted effects

Nine patients (15%) had unwanted effects — seven with gastrointestinal (GI) and two central nervous system (CNS) side effects on diclofenac (Table IV). Six patients (10%) reported unwanted effects — two with G.I., two with CNS and two with skin reactions — on naproxen (Table IV). Three patients (5%) reported unwanted effects on placebo. One patient was withdrawn from the trial because of severe diarrhoea while on diclofenac in period one, and in one case the final period was shortened because of ulcer-dyspepsia. The frequency of unwanted effects on naproxen was not significantly different from placebo ($p = 0.25$) or diclofenac ($p = 0.27$), whereas the frequency on diclofenac was significantly different from placebo ($p = 0.03$). Two patients reported unwanted effects on both active drugs, one of them also on placebo, and one patient reported unwanted effects both on placebo and diclofenac.

Table IV — Unwanted effects: No. of patients reporting each type of unwanted effects.

Category of unwanted effect	Severity	Treatment		
		Placebo	Naproxen	Diclofenac
Gastrointestinal	Mild	1	1	2
	Moderate			2
	Severe			3
Central Nervous System	Mild	1 s.s.s.	1	2
	Moderate			
	Severe			
Skin	Mild	1 s.s.s.	1	
	Moderate			
	Severe			
Total No. of Patients with Unwanted Effects		3	6	9

s.s.s.: severity not stated

Table V — Differences in response to diclofenac and naproxen based on VAS-scores for patients' evaluation of overall efficacy.

Diclofenac \ Naproxen	Little effect 0 - 3.3 cm	Moderate effect 3.4 - 6.6 cm	Good effect > 6.6 cm
Little effect 0 - 3.3 cm	5	2	6
Moderate effect 3.4 - 6.6 cm	3	6	11
Good effect > 6.6 cm	3	4	15

Twenty-six patients responded equally well, or failed to respond to both drugs (Table V). Eleven patients had little effect while on diclofenac and three of those (27%) had good effect while on naproxen. Thirteen patients had little effect while on naproxen and six of those (46%) had good effect while on diclofenac. Altogether 19 patients had higher efficacy scores on diclofenac than naproxen compared with 10 who had higher scores on naproxen.

DISCUSSION

It showed impossible to establish any correlation between patient factors or disease variables and response in this study. It is therefore not possible to characterize typical responders to either drug with the methods used. Nevertheless, our study appears to corroborate the contention that some patients respond better to one NSAID than to another. A close inspection of Table V reveals that 22 patients obtained good effect on naproxen alone at the dosage used — i.e., approximately 40% of the patients. On diclofenac this figure rose to 57% (32 patients), whereas, together 70% (39 patients) obtained a good effect on one or the other of the two drugs. Only 5 patients, i.e. less than 10 per cent, failed to respond at all to either drug.

The dosage used for the comparison of the two drugs was based on what was recommended as the normal or standard dosage at the time the trial was started — i.e. 2/3 of maximum daily dose. Subsequently, the maximum daily dose for naproxen has been increased, and a recent study⁶ indicated that the effect of naproxen is correlated with plasma levels, within the dose range studied, 250 to 1500 mg/day; i.e., a better effect is obtained with higher levels, and there appears to exist a threshold level. In this study⁶ 75% of patients whose serum levels were above 50 $\mu\text{g/ml}$ responded, and the threshold level was 18 $\mu\text{g/ml}$. Similar studies have not to our knowledge been carried out with diclofenac.

Our study indicates that diclofenac in a standard dose of 50 mg b.i.d. is more efficacious than naproxen in a standard dose of 250 mg b.i.d. The rate of good response increases from 40% on naproxen to 57% on diclofenac. There appear to be no particular patient or disease characteristics that determine which patient will respond to which drug. Non-responders may be patients who do not get sufficiently high serum levels, as has already been indicated by one study⁶ for naproxen. Similar studies should be carried out with diclofenac and other NSAIDs.

References:

1. Huskisson, E.C., Woolf, D.L., Balme, H.W., Scott, J., and Franklyn, S.: Four new anti-inflammatory drugs; responses and variations. *Brit. Med.* 1:1048-1949, 1976.
2. Huskisson, E.C.: Anti-inflammatory drugs. *Seminars in Arthritis and Rheumatism* 7:1-20, 1977.
3. Sverdrup, E.: Significance Testing in Multiple Statistical Inference. *Scand. J. Stat.* 3:73-78, 1976.
4. Lehmann, E.L.: *Non-parametrics; Statistical Methods Based on Ranks*. San Francisco: Holden-Day Inc. 1975.
5. Kendall, M.: *Rank Correlation Methods*. London, Charles Griffin & Co. Ltd., 1975.
6. Day, R.O., Furst, D.E., Dromgoole, S.H., Kamm, B., Roe, R., and Paulus, H.E.: Relationship of serum naproxen concentration to efficacy in rheumatoid arthritis. *Clin. Pharmacol. Ther.* 31:6,733-740, 1982.

□ □ □

OUT FOR A DUCK

Numerous enquiries were received about the "patient assessment machine" shown in the last Bulletin. Most were from insurance companies wishing to introduce automation into their busy compensation rejection departments. One was from a member with a large practice wishing to purchase a machine to improve patient handling by his accounts staff. Unfortunately, all were to be disappointed: one could almost say caught out (for a duck).

The apparatus shown is in fact some of the modern hydrotherapy equipment installed at the Illawarra Rehabilitation Centre. An article about the Centre, and the comprehensive range of services it provides, will appear in the next Bulletin.



PRODUCT REVIEW

Orion 660-01 TENS Unit

Transcutaneous electrical nerve stimulation is now widely recognised as an effective means of relieving pain. It provides a satisfactory alternative to analgesic medication and especially to the long-term use of drugs with a potential for addiction. It is particularly useful for the control of pain of musculoskeletal origin.

Administration of TENS requires a suitable pulse generator and this must be chosen from the large number of machines now available. These range from the very basic to the very sophisticated and differ greatly in price, features and effectiveness. Cheaper units with few features and limited effectiveness are often sold direct to the public or by mail order. Lack of professional supervision further limits their practical usefulness. Patients who have tried TENS in this way may have a misguided opinion of what it can achieve. The more sophisticated units, from better-known manufacturers, are a great deal more versatile and effective. They are generally supplied by reputable medical equipment companies under ethical arrangements which encourage professional supervision for proper use of the apparatus and better patient care.

The Orion TENS unit is certainly of the latter variety. Manufactured by the American firm Neuromedics, it is a sophisticated instrument with a large number of features allowing great versatility.

It is a dual channel machine, which means that either two or four electrodes can be used simultaneously according to the number of sites to be treated. Having two channels is of obvious benefit if stimulation of more than one site is required and TENS is to be employed continuously or almost so.

The characteristics of the stimulating pulse are variable within a wide range of parameters to suit individual patient needs. Such variability is most important, as the effectiveness of TENS for the individual patient seems largely a matter of empirical trial.

Each channel of the Orion has an amplitude control allowing variation of output current from 0 to 150 milliamperes with a pulse width of 20 microseconds. Maximum current density at the electrodes is rated at 72 microamperes per square millimetre. The rate (frequency) of the pulse stimulus is controlled separately and is variable from 3 to 100 hertz; in addition, a 2 hertz low rate bursting mode can be selected on the rate control. Another control provides what Neuromedics term "ramped modulation". This is a rhythmic rise and fall of amplitude and frequency to create a pattern of stimulus sometimes more comfortable than a regularly repeated pulse. The ramped modulation control is an on/off switch, allowing the use of this pattern of stimulus with any selected maximal amplitude and in any of the high

rate, low rate or low rate burst frequency modes. The resultant variability of stimulus characteristics offers a very wide choice in the commonly effective ranges of all parameters.

Another feature of the Orion unit is constancy of power output. This means that for a given setting of the controls the output stimulus is maintained irrespective of battery condition. Automatic compensation within the machine obviates the need for the constant adjustment of controls which is a significant problem with some other units.

Two types of power source can be employed, either disposable AAA alkaline batteries or rechargeable nickel cadmium battery modules. Each rechargeable module will supply current for approximately 24 hours and they are supplied in pairs, so that one may be charging whilst the other is in use. The charger supplied with them also acts as a tester of the unit itself, a useful facility for demonstrating the machine to patients and for checking its functions. The rechargeable battery packs are designed to tolerate being left in the charger for long periods of time: this enables the user to have one battery module always fully charged when the other is depleted. It also obviates the problem of battery damage sometimes encountered when rechargeable batteries are inadvertently left charging for long periods.

The unit is compact (only 10.5 cm. long, 4.5 cm. wide and 1.7 cm. thick) and light (only 117.5 grams). It is fitted with a belt clip which rotates through three hundred and sixty degrees, with ninety degree stops, allowing the unit to be worn in a variety of ways.

The carbon silicon electrodes are available with either pin or snap connections. Micropore paper fixing patches are provided with them and for those sensitive to tapes, plastic fixing patches and self-adhesive disposable electrodes provide two other options. Leads are provided in a standard length of 1 metre with 1.5 metre lengths also available.

Overall, the Orion unit impresses as a compact, well designed, state of the art TENS machine with a wide range of stimulus variability to suit patients' needs. It is supplied in Australia by the well-known firm CIG-Medishield and can either be purchased for a retail price of approximately \$350 or hired from the company for about \$32 per month. The hiring option is particularly useful for patients with a short-term need or those wishing to evaluate TENS before actually purchasing a machine. The company requires a letter from a doctor or a physiotherapist before supplying a unit, thus encouraging professional supervision of the way it is used and the purpose for which it is employed. This adds a nice ethical touch to a treatment system which has a great deal to offer for the patient with chronic pain.

Orion

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an alternative to
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you're looking at the answer in Orion.™

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powered TENS unit. It offers a
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alternative in the control and
relief of acute and
chronic pain.

The Orion is the
first device to integrate the
most desirable TENS features.

Flexibility

The Orion is a dual channel, battery powered stimulator
capable of conventional, high rate, low rate, and low rate
burst TENS.

Ramped Modulation

A gradual rise and decline in amplitude and frequency
that is designed to prevent the stimulated nerve from
accommodating to stimulation. Modulation can be
accomplished in high rate, low rate and low rate burst TENS.

The effect of a modulated waveform on your patient is
demonstrated or explained as a rhythmic sensation. The
perception is one of comfort rather than the more tingling
sensations associated with unmodulated stimulation. Greater
comfort results in greater patient compliance.

Modulation can be achieved easily with a turn of one
knob. This makes it simple to explain and simple to use.

Hybrid Integrated Circuitry

Orion is among the most sophisticated TENS devices on
the market today through the utilization of hybrid integrated
circuits. The benefits of this design show up as reliability,
quality of performance, and a smaller size.

Reliability With thousands of Orions being utilized by
customers, the reliability has been demonstrated to be over
99%. It's the type of dependability and performance
demanded by clinicians and patients.

Lifetime Warranty This performance has allowed
Neuromedics to offer a Limited Lifetime Warranty, one of the
most liberal warranties in the industry.

Variable Power System The Orion technology
automatically adjusts output as batteries deplete so that once
set, the unit does not have to be constantly readjusted.

Convenience of Use All adjustments are made with the
convenience of turning a knob. Individual amplitude knobs are
available for each channel, a frequency knob for both
channels and a modulation control. Easy to explain, easy for
the patient to use. A choice of AAA alkaline or Nicad
rechargeable battery packs are available.

Belt Clip The Orion clip is specifically designed with
ease of use in mind. The belt clip rotates 360° and can clip into
a lock position at 90° intervals making the Orion easy to wear.

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Perth
387 6011

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**TREAT
YOUR
OWN
NECK**

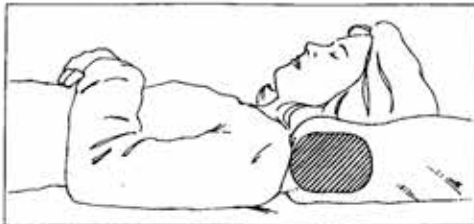
THE ORIGINAL McKENZIE CERVICAL ROLL

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CERVICAL ROLL DESIGNED
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- This roll have been developed over many years and is designed, when used correctly, to prevent the onset of pain. It must be used with a pillow containing feathers, kapok, rubber chips or foam chips. Moulded rubber or foam pillows should never be used if you have neck problems.
- Place the roll between the pillow and the pillow case, so that it will be in a position to give added support to your neck. This position is usually found where the edge of the pillow comes in contact with your shoulder. (See Illustration.)
- Initially the roll may feel a little uncomfortable and you may have to adjust your position slightly. After two or three nights use you should be accustomed to the roll and will feel uncomfortable without the extra support.



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BOOK REVIEW

Aspects of Manipulative Therapy

edited by E.F. Glasgow, L.T. Twomey, et al.
Churchill Livingstone, Melbourne, 1985

This book is actually a revised, second edition of a collection of papers first published as the result of a conference held in Melbourne in 1979. This conference was a little unusual in that it brought together people from different disciplines, with medical, paramedical and non-medical backgrounds and a diversity of qualifications and attitudes, to discuss their common interest in musculoskeletal disorders and manipulative therapy. Speakers included academics, scientists, teachers and practitioners from Australia and overseas, many with international reputations in their special fields.

A number of papers were published after the conference as a record of the proceedings. The information they contained was considered of sufficient significance as to warrant their revision and republication as an updated review of the subject. The new book is much more comprehensive than the original proceedings. Some papers have been partially re-written, some have been expanded considerably to include additional concepts and the results of more recent work and some totally new papers have been added. There are twenty-seven papers in the new edition, each able to stand on its own as a treatise on one aspect of the subject, but group under five headings, entitled Biomechanical Aspects, Neurological Aspects, Techniques and Rationales, Pain Tolerance and Assessment and Assessment of Disorders.

The first section is on biomechanics. It contains seven papers, contributed by a bioengineer, a biochemist, two radiologists, an anatomist and three practising physiotherapists. Factors affecting joint function, at rest and in motion and in health and disease, are presented and discussed, with emphasis on morphological, mechanical and biochemical aspects. The section includes a review of the more established concepts, such as the work of MacConaill, with some recent experimental findings on the effects of mechanical stresses and disease states on articular and peri-articular structures.

The second section, on neurological aspects, contains four papers by academic neurologists actively involved with research. All four ought to be required reading for any practitioner treating musculoskeletal disorders. They are Lewis's paper on muscle spindles and their functions, Bradley's paper on the posterior primary rami of spinal nerves, Korr's work on neurochemical and neurotrophic consequences of nerve deformation and Wyke's paper on articular neurology and manipulative therapy.

The third section of the book is entitled "Techniques and Rationales". It contains six papers on theoretical and practical aspects of manipulative treatment techniques and two on clinical research. The papers on techniques are by practitioners and they reflect the different attitudes of the disciplines to which the authors adhere. The

emphasis is on general principles rather than a comprehensive description of individual manoeuvres. Those new to the subject will not find detailed descriptions of how to perform techniques (that would not be appropriate in any case). However, they will find useful information about treatment principles and practitioners familiar with manipulative techniques will find valuable insights into aspects of their application. The papers on clinical research are included in this section, no doubt as the "rationales". That by Winer discusses the principles and particular problems of such trials and goes on to review ten controlled trials already published. It is a useful summary of material that ought to be evaluated by all with a serious interest in manipulation as a scientifically-based treatment modality. The other research paper describes an uncontrolled study comparing two treatment programmes. It is a survey rather than a trial but it does raise important points about the value of research.

The fourth section is headed "Pain Tolerance and Assessment". Four papers are included, all by academics involved in research and teaching. The topics are a neurological approach to neck pain, by Bogduk, a differential diagnosis of neck pain with emphasis on the soft tissues, by Cailliet, a broad approach to pain in the locomotor system, by Janda and cultural determinants of pain perception by Polgar. All contribute significantly to the understanding of pain mechanisms and the evaluation of the most important musculoskeletal symptom.

The fifth section is entitled "Assessment of Disorders" and contains four papers. The first, on prevention of complications from spinal manipulative therapy, again reflect the diversity of attitudes represented in this book. Some points raised may be seen as controversial, depending upon the reader's point of view. For instance, the assertion that radiological examination is a necessary prerequisite for manipulative therapy would be treated with reservation by many, as it is plainly at variance with the common practices of many competent manipulators. The second paper in the section describes an experimental method of quantitative assessment of musculoskeletal function. It is really more an interesting research project than a practical diagnostic technique. The third paper is on computerised tomography and is a most useful treatise on a diagnostic tool of great importance. The fourth paper is on pictography, a system of recording and describing the results of patient assessment and treatment.

This book is not the definitive work on manipulative therapy: that will never be written. Nor is it authoritative in its approach but rather a reflection of a diversity of views. It is nonetheless, a most useful reference on many aspects of the subject and as such deserves a place on members' bookshelves.

BAMM ABSTRACTS (1)

Cloag, Daphne:

"Rehabilitation in Rheumatic Diseases"

British Medical Journal. Vol. 290. 12 January 1985

As many as 42% of arthritics in a study done in the early 1970s could have been helped by specialist advice and treatment had it been offered at an earlier stage; the position is not thought to be greatly altered today.

Some 20 million people a year are suffering from some sort of rheumatic complaint and over 8 million consult their doctor; more than one million are impaired by one of these diseases and over 200,000 severely disabled.

Rehabilitation in rheumatic diseases is concerned as in any chronic disabling condition, with the total situation. The battle is won and lost in the mind of the patient, who must cooperate with professional help and believe in the rehabilitation process.

With the total care approach and early referral, falls in the proportion of near complete cripples from 25% to 5% in rheumatoid arthritis, and from 15% to 1% in ankylosing spondylitis, have been reported.

The Arthritis and Rheumatism Council's excellent series of booklets for patients should be stocked by doctors and other workers: booklets produced by the Disabled Living Foundation and the Directory for the Disabled and 'Coping with Disability' are also relevant. Some 7,000 aids and appliances are available. The only way to make intelligent use of them is to visit an aids centre or study publications on aids. The increasing number of elderly people with degenerative joint disease can be seen at home by health visitors who assess their needs. Advice about good and bad positions for the joints and posture, with thought about furniture and kitchen arrangements is given by physiotherapists and occupational therapists.

Exercises are to help joint mobility, prevent deformity and strengthen the muscles around the joints, so lessening the stress on affected joints as well as improving strength, and they need to be individually tailored. They are divided broadly into isometric exercises to build up mus-

BAMM ABSTRACTS (2)

Lewit, K. and Simons, D.G.:

"Myofascial Pain: Relief by Post-Isometric Relaxation"

Arch. Phys. Med. Rehabil. 65:452-456, 1984

The principle, involving manually-resisted isometric contraction followed by relaxation to increase restricted range of movement, was originally described in a paper "Proprioceptive Neuromuscular Facilitation" by Knott & Voss, (New York 1968) but its application more specifically to Manual Medicine was pioneered by Fred L. Mitchell Sr. and described by F.L. Mitchell Jr. (Evaluation & Treatment Manual of Osteopathic Muscle Energy Procedures. Valley Park, MO, Mitchell, Moran & Pruzzo Associates 1979).

Later, a systematic search was made for tender pain points in muscles at joints that showed restricted range of motion and post-isometric relaxation to the muscles was applied. The term "maximale schmerzpunkte" is synonymous with this "trigger-point" phenomenon.

Post-isometric relaxation has also been found to facilitate manipulation carried out in the relaxation phase.

NEWSLETTER

cles, active or passive exercises to maintain or improve a range of movement, and possibly activity to promote general fitness, especially in younger patients. Simple measures can make a striking difference. An important example is quadriceps exercises, which (together with weight reduction if needed) might mean that someone with arthritis of the knees can get up from a chair instead of becoming chairbound. A sheet of exercises to follow is not enough. Home exercises are doomed to failure unless patients know that they are going to be assessed at a follow up visit, and have a diary for recording progress. For acutely inflamed joints, exercise must not overshadow the healing potential of rest.

Hydrotherapy is often enjoyed and found helpful but is not widely enough available. A pool in a district general hospital may be threatened with closure for lack of money. The best rehabilitation for some is surgery. The snag is the long waiting time for joint replacement, often several years.

The way forward lies in finding a method of helping the primary care team as well as a more explicit pinpointing of the immediate aims in each case, so that all members of the team and also the patient, his family, and others concerned can have a clear contribution to make.

This article is part of an extensive coverage of needs and opportunities in rehabilitation. Many expert views have been gathered and well listed, but there is insufficient emphasis on the prevention of avoidable disability. Hip replacement cannot be the only way of tackling osteoarthritis of the hip. Correct exercises, taught in schools, have a constructive part to play in health maintenance and preventing disease progression.

The aim of the specialist in manual medicine is to integrate the technique of palpatory diagnosis and manipulative therapy into the comprehensive medical practice of diagnosis, treatment and rehabilitation. Rehabilitation cannot claim to be holistic if it fails to acknowledge the first class skills of manipulative medicine.

Lewit and Simons selected 244 patients who showed the following:

1. Pain points in a muscle and/or its insertion.
2. Increased muscle tension during stretch.
3. Tension-shortening not secondary to joint dysfunction.

351 muscles or muscle-groups were treated

Technique 2 pairs of photographs in the article illustrate the principle:

A patient's head and shoulders are shown; the head over the end of a couch with the neck moderately hyper-extended and rotated to the right, displaying the sternal head of the L sternocleidomastoid in near maximal stretch but in isometric contraction checked by the therapist's hand on the L cheek. In the next photograph the patient's own hand supplies counterpressure. Therapy is here directed specifically to the sternal head, the complaint being of tenderness at the sternal end of the clavicle. Rotation to the right ensures that contraction and subsequent stretch are exactly parallel to the line of the muscle fibres involved, and, as this point was found to

be essential, the technique must accommodate complex pennate muscles also. Best results were obtained when the patient added to the number of sessions with further autotherapy.

In the next pair of photographs radial epicondylitis is treated: the left elbow, wrist and fingers are held in near full flexion to stretch the extensors of wrist and fingers; therapist, then patient supplying counter pressure as before.

Each session begins with passive stretching proceeding to just short of pain or to the onset of resistance. Now a gentle isometric contraction against minimal resistance continues for about ten seconds, or longer in difficult cases. Relaxation follows, and when complete the patient inhales then exhales completely. During exhalation gentle passive stretching of the muscle is attempted. The whole procedure is repeated from the point of any increased length gained. The muscle is always allowed to lengthen in its own time. Lengthening was often not achieved until the second or third attempt. Three to five cycles is regarded as constituting one session.

The study revealed the following relationships of practical therapeutic value:

1. Where tender periosteal points were muscle insertions.
2. A painful posterior arch of atlas and suboccipital muscles.
3. Levator scapular spine (although the muscle is attached to neither point).
4. Humeral lateral epicondyle and supinator, extensors of the wrist and fingers and/or involvement of biceps.
5. Painful sacroiliac and iliolumbar ligaments with (possibly) tensor fasciae latae.
6. Coccyx and Gluteus Maximus. Therapy here also relieved levator and tenderness.

7. Calcaneal spur and muscles attached to plantar aponeurosis.
8. A trigger point in soleus and heel pain.

Certain reflex relationships were also found, as follows: post-isometric relaxation of suboccipital muscles induced relaxation of sternocleidomastoids and vice versa; similarly with the thoracolumbar portion of erector spinae and iliopsoas; likewise therapy of sternocleidomastoids and of scalenes reduced tension in the pectoral muscles.

Variations on the technique, ie "contract-relax" and "rhythmic stabilization" are displayed in graphs in the original article. Contract-relax (CR) is similar to post-isometric relaxation (PIR) except that the cycles of PIR proceed more slowly and much less force is exerted than during CR. Following relaxation, the increased range is obtained actively in CR and passively in PIR. In both, co-contraction of agonists and antagonists is avoided. In Rhythmic Stabilizers (RS) co-contraction is specifically sought in some descriptions but not mentioned in others.

CR and RS increase range of motion to some extent via the neurophysiological mechanism of reciprocal inhibition; ie, voluntary contraction of the shortened agonist receiving therapy inhibits its antagonist and vice versa. However this mechanism is unlikely in PIR where contraction of the antagonist is avoided. More likely the stretch equalizes the length of the sarcomeres in each involved fibre so harmonizing contractile length throughout the muscle.

Electromyographic monitoring demonstrated increased range of hamstring stretch in most cases counterpressure and passive stretch, for isometric and relaxation phases respectively, with, finally, a full inhalation then exhalation as slowly as possible to obtain a last stretch increment.

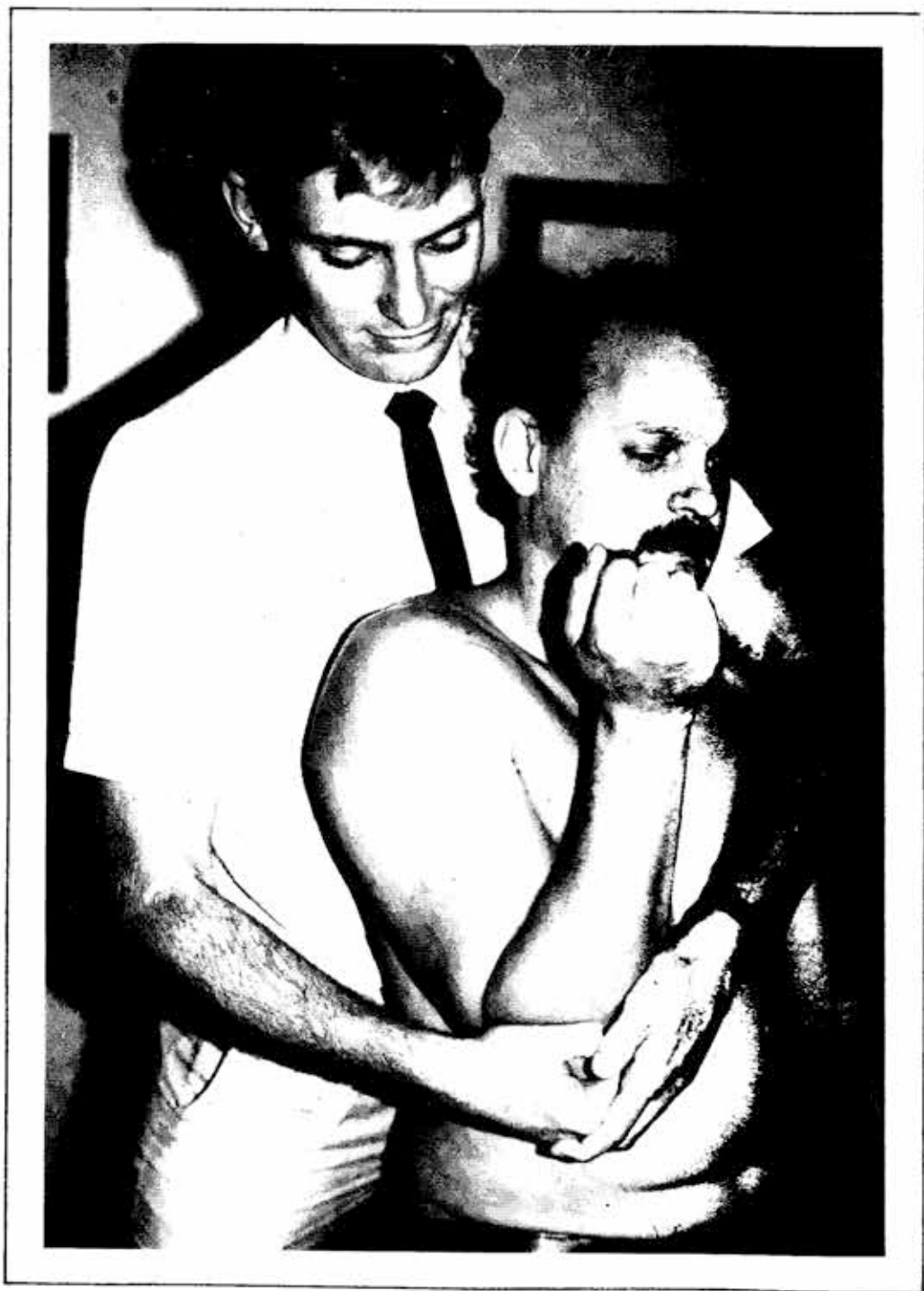
Relief of Pain or Tenderness by the Post-isometric Relaxation Technique
(Associated Nonmuscular Structures in Parentheses)

Muscles stretched	Total treated	Relief of pain number	%	Relief of tenderness only number	%	No effect number	%
Upper trapezius	7	7	100				
Wrist & finger flexors (Medial epicondyle, arm)	5	5	100				
Iliopsoas	2	2	100				
Quadratus lumborum	1	1	100				
Lateral epicondyle (arm)*	20	19	95	1	5	0	0
Suboccipital	23	21	91	0	0	2	9
Soleus (achilles tendon)	6	5	83	1	17	0	0
Sternocleidomastoideus	9	7	78	2	22	0	0
Pelvic muscles (ligaments)	29	22	76	4	14	3	10
Hamstrings (Ischial tuby.)	8	5	63	2	25	1	12
Oblique abdominals (lower ribs)	5	3	60	0	0	2	40
Gluteus maximus (coccyx)	27	15	56	9	33	3	11
Levator scapulae	19	10	53	7	37	2	10
Piriformis	21	11	52	6	29	4	19
Pectoralis	4	2	50	1	25	1	25
Infraspinatus	2	1	50	1	50	0	0
Erector spinae	28	13	46	12	43	3	11
Deep paraspinal (adjacent spinous process)	15	7	46	5	33	3	20
Upper pectoralis major (Upper ribs)	22	10	46	5	22	7	32
Biceps Femoris (fibular head)	18	8	45	6	33	4	22
Adductors (pes anserinus)	7	2	29	0	0	5	71
Gluteus medius (gr troch.)	2	0	0	2	100	0	0
Calcaneal spur (plantar aponeuritis)	1	0	0	0	0	1	100
Scaleni	1	0	0	1	100	0	0
Total group	284	177	63	66	23	41	14

*Spinator, wrist and finger extensors, and or biceps brachii.

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Picture Quiz



What are these men doing? Would they be permitted to do it in Queensland, even if they were consenting adults and did it only in private? Could you make your living like this? Does being given the cold shoulder repeatedly result in that shoulder becoming frozen?

If you don't know the answers to these important questions, don't miss the special feature on shoulder problems in the next issue of the Bulletin.

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There is space on this list for many other companies with interests in the field of musculoskeletal medicine. The Bulletin welcomes advertisements for any products or services considered worthy of members' attention. Advertising managers are invited to contact the editor.



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