EDITORSIAL

DRUG THERAPY IN RHEUMATOID ARTHRITIS—A PERSPECTIVE

In an era of exploding biotechnology, which has had a profound impact on the treatment of other disorders, the management of rheumatoid arthritis (RA) has retained its familiarity even for the most mature cohort of clinical rheumatologists. With the goals of relieving pain and enhancing function, we employ various conservative measures and analgesic-anti-inflammatory drugs. These now include a vast array of new agents which may be more acceptable and better tolerated than traditional salicylate therapy but clearly much more expensive and not particularly more efficacious. Since the nonsteroidal anti-inflammatory drugs (NSAIDs) have been developed by screening likely candidates in animal and in vitro model systems, there should be little wonder that their clinical effects are similar. Hopefully, lipoxygenase inhibitors now in development will add a new dimension to the suppression of inflammation [1].

The other goal of treatment is to alter disease progression and outcome, using 'second-line' or disease-modifying antirheumatic drugs (DMARDs). In contrast to the NSAIDs, most of these agents have not been introduced by pharmaceutical companies for the purpose of treating RA, but have emerged from the clinical arena. Gold, D-penicillamine and antimalarials were originally used to treat other conditions and were redirected to RA because of serendipitous clinical or laboratory observations. The belief that an excessive activation and proliferation of immunocompetent cells plays an important pathogenetic role in RA led to the empirical use of agents developed for the treatment of malignancies. Although efficacy has been demonstrated for these cytotoxic drugs this seldom correlates with modification or suppression of a particular immune function or target cell activity. Indeed, despite all that has been learned about the pathogenesis of RA in recent years, its image as a therapeutic 'black box' has been slow to change, because each agent has several potentially relevant actions. However, progress has been made recently in highlighting critical actions of particular DMARDs [2], and perhaps this will lead eventually to the development of less hazardous agents with the same biological activity.

The concept of disease-modification or its ultimate extension, drug-induced remission, is an article of faith that eludes scientific verification. DMARD efficacy has been demonstrated in placebo-controlled trials, but their duration is generally a year or less, a period inadequate to apply radiographic assessment techniques [3]. In long-term open trials methodological problems and high dropout rates have confounded attempts to study the influence of DMARDs on the erosive process [4]. When the ARA criteria for clinical remission [5] are applied to groups of RA patients, those on DMARD therapy for less than a year seldom meet the criteria [4]. Less than one of five who continue treatment for longer periods achieve remission and these are usually transient [6]. Life-table analysis of treatment termination confirms the limited usefulness of available agents. Over a 5-year span only 10% of patients may remain on a single DMARD [4]. This may result in sequential treatment of refractory cases with several DMARDs, a policy which leads to considerable morbidity and expense, without supporting evidence for efficacy. A good deal of effort has been directed toward comparative studies of DMARDs, but significant advantages in therapeutic index of one over another are seldom demonstrable. The limited pool of available patients and the variability of our outcome measurements partially account for this, but the unavoidable lessons may be that none of these agents has an outstanding or lasting impact on the disease and that we have been unable to dissociate efficacy and toxicity.

All of these considerations point to the need to develop new agents and new approaches in the use of available DMARDs, such as simultaneous use of two or three drugs [7]. The latter must be supported by carefully controlled trials to demonstrate that gains in efficacy outweigh the expected cumulative toxicity. Such a study by Scott et al. [8] appears in this issue. Over a period of 1 year the concurrent use of hydroxychloroquine enhanced the efficacy of gold, but also increased withdrawals for adverse reac-
but it has the disadvantages of intravenous
tution, the toxicity of TP-5 appears to be minimal,
agranulocytosis. After several years of investiga-
levamisole, a drug with demonstrated efficacy in
immunomodulatory effects similar to those of
lated from bovine thymus. TP-5 has
glogically active segment of a larger peptide iso-
synthetic pentapeptide corresponding to a bio-

tions compared to baseline. The mechanism of
treatment groups, there was significant improve-
ment in several clinical and laboratory measure-
tions, particularly rashes. Since the components
administration and rather modest efficacy. Indeed,
laboratory indicators failed to improve and clinical measurements showed a tendency
toward early relapse. The association between
immunomodulatory and clinical effects was not
addressed in this study, but with levamisole
there was no close correlation, leaving us with-
out a clear understanding of its mechanism of
action [13]. The future success of this agent will
hinge upon ascertaining the optimal dose and
schedule of administration.

What is the future likely to bring in new
DMARD development? There seems to be no
weakening in our traditional behaviour of dis-
covering antirheumatic properties in available
drugs or of producing congeners of agents in
current use, hoping for some advantage in the
therapeutic index. With increasing frequency,
biological modifiers of inflammation and
immune function are being studied in RA,
including interferon, superoxide dismutase
and thymopentin [14]. In the future the field may
be broadened to include cytokine and protease
inhibitors, monoclonal antibodies to cell surface
receptors and idiotypes and other agents devel-
oped by biotechnology firms for multiple clinical
purposes, including malignant and infectious
diseases. Despite these modern wonders the
empirical approach will prevail in RA until we
can identify a critical point for therapeutic inter-
ception in its complex pathogenetic scheme.

Resurrection of ancient remedies has been a
recurrent theme in the treatment of RA. The
double-blind study by Larsen et al. [11] on the
use of a podophyllum derivative (CPH 82) is an
intriguing addition. The use of semisynthetic
glycosides rather than crude extracts of this
Himalayan herb reduced the frequency and
severity of adverse effects. Although the efficacy
of CPH 28 relative to placebo was not estab-
lished, probably due to the small size of the
treatment groups, there was significant improve-
ment in several clinical and laboratory measure-
ments compared to baseline. The mechanism of
action is unknown, but drugs of this class may
have antimitotic activity. The results of long-
term trials will be awaited with interest.

Kantharia et al. [12] have reported the results
of a controlled study of thymopentin (TP-5), a
synthetic pentapeptide corresponding to a bio-
logically active segment of a larger peptide iso-
lated from bovine thymus. TP-5 has
immunomodulatory effects similar to those of
levamisole, a drug with demonstrated efficacy in
RA but an unacceptable high frequency of
agranulocytosis. After several years of investiga-
tion, the toxicity of TP-5 appears to be minimal,
but it has the disadvantages of intravenous

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RHEUMATOLOGY EDUCATION IN THE LATE 20TH CENTURY

Education attempts to influence knowledge, skills and attitudes—and the greatest of these is attitudes. It has been increasingly recognized in the UK that rheumatology is a good model from which to learn. Unlike many other medical specialties, most rheumatic sufferers attending the out-patient department have physical signs. This is where much of the teaching should be done. Chronic rheumatic diseases also provide a valuable model for the assessment of disability, from which the skills in rehabilitating such patients can be taught. Rheumatologists have to teach some patients to accept disability, a difficult task which students must appreciate. Rheumatology also serves as a model for developing correct attitudes in the management of chronic disease and in the value of cooperation with members of the paramedical professions.

In 1979 only eight of 27 British medical schools had comprehensive clinical rheumatological teaching [1]. The situation has greatly improved, due largely to the efforts of the Arthritis and Rheumatism Council. This is an important change, since a survey of medical practitioners showed that rheumatology ranked 18th in the order of specialties in which postgraduate instruction had been received, only 19% having attended such a course [2]. Yet in our hospital one in four general medical consultations are for rheumatic diseases, and experience in general practice is similar. It may be that consultant rheumatologists are not teaching general practitioners what they want. To students we may say, 'You understand what is palatable, but not what is nutritious; therefore, you will eat what I decide', but the general practitioner can vote with his feet, as empty rows of chairs testify. Esoteric disorders of connective tissue may excite our interest, but general practitioners wish to know about backache and drug treatment [3]. This dilemma is worsened by our lack of understanding of the pathogenesis of most types of rheumatism, and is reflected in little research emphasis in this area, making teaching of these subjects unattractive.

As medical teachers we need to consider our methods, to evaluate our impact and to improve our skills. Last year in the USA the single theme which emerged as the most controversial and important in education of health professionals was evaluating competence [4]. The easiest facet to evaluate is knowledge, and modern technology makes this even simpler. Established computer-based programs in medical education include dynamic pathophysiological models and clinical simulations. These allow the testing of previously imparted knowledge in clinically relevant activities, with feedback and additional tutorial material [5, 6]. The inclusion of computer-based teaching in medical education (including rheumatology teaching) will not be received uncritically, but a recent conference on computers in medical education, sponsored by the Computers in Teaching Initiative Support Service, indicated a wide variety of projects already applied at preclinical and clinical levels. A number of general points can be made in relation to these introductions. Computer-based learning is good at reinforcing previously imparted factual information but not at provid-