

*Occasional Survey***Compliance of patients and physicians: experience and lessons from tuberculosis—II**

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Fully supervised intermittent chemotherapy

The already obvious clinical need to try to overcome the problems of self administration of medicaments,¹⁶ supported by a scientific basis,¹² led us to explore the efficacy and acceptability of intermittent regimens based on twice weekly or once weekly treatment with isoniazid and streptomycin in Madras.^{6, 7} Subsequently Mitchison and Dickinson¹³ showed that single pulses of bactericidal drugs could inhibit all division of bacilli for several days.

A key community study, which began in 1967 in the central Bohemian region of Czechoslovakia, surrounding Prague, compared in outpatients twice weekly streptomycin plus isoniazid and daily isoniazid plus PAS, both after an initial daily phase of three drugs in hospital. The supervised intermittent regimen proved to be as effective therapeutically as the widely used unsupervised daily regimen.⁴⁴⁻⁴⁶ This conclusion was confirmed in a controlled trial in Britain,⁴⁷ and in Singapore the intermittent regimen was rather better than the oral combination.⁴⁸ Supervised intermittent chemotherapy was therefore shown to be an effective alternative system to self administered oral regimens. Moreover, it improves the control of chemotherapy, reduces the risk of drug toxicity, and substantially lowers the cost of the drugs.⁴¹

An integral part of the organisation of the supervised intermittent regimens in Czechoslovakia was to make the arrangements as flexible as possible, our aim being to suit the convenience of the patients so that there would be as little disruption as possible of their normal lives.⁴⁴ Thus patients could choose to

attend a dispensary, general practitioner's surgery, health centre, or hospital near their home or place of work or en route to receive each dose under supervision. They could also choose to attend different facilities for each of the two weekly doses. Both the staff and the patients liked the intermittent regimen and the closer supervision it entailed, and the patients attended very regularly for their supervised medication, even though the great majority (91%) had selected a chest clinic or a general practitioner's surgery and had, in consequence, to travel substantial distances (9.7 and 4.8 km, respectively) and to spend over an hour doing so. Using the same organisational approach in the British controlled trial we found that nearly half the patients were given their chemotherapy at home visits by health visitors and 29% attended chest clinics, but only 9% attended a general practitioner's surgery.⁴⁷ Thus if a flexible approach is adopted the way supervised intermittent chemotherapy will be organised will vary from country to country.

In 1974 the ninth report⁴⁹ of the World Health Organisation Expert Committee on Tuberculosis endorsed the value of intermittent chemotherapy and the importance of flexibility in organisation and of decentralisation to reduce patients' travel. Many developing countries treat sputum smear positive patients in urban areas with streptomycin and isoniazid twice a week, as recommended by the WHO. Although intermittent chemotherapy was officially recommended in Czechoslovakia as long ago as 1972,⁵⁰ it is striking how few technically advanced countries have adopted it on any scale, although individual physicians have appreciated the importance of it in difficult patient groups, notably Sbabaro, who has used it since 1965 in a "skid-row" population in the United States of America.⁵¹

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THE USE OF INTERMITTENT REGIMENS IN BRITAIN

Precise measures of the extent to which fully intermittent chemotherapy has been used are available from the surveillance system in Scotland²⁶⁻²⁸ and the survey in England and Wales.⁴⁰

After the initial intensive phase the great majority of the patients entered the continuation phase, the stage when fully intermittent chemotherapy is used, but few patients had an intermittent regimen—namely, 1% for each of the three years in Scotland. In England and Wales only 26 (3%) out of 930 patients were given an intermittent regimen, and this was prescribed by only seven of the several hundred physicians. Thus hardly any physicians in the United Kingdom used intermittent treatment as a routine, which is not surprising. More surprising, however, is that it was not used more often for the common problem patients, such as alcoholics or elderly patients with failing memories, whose cooperation in self administered regimens is in doubt from the outset or has been found wanting in practice.

MODERN SHORT COURSE CHEMOTHERAPY

In 1970 we began to study short course chemotherapy. This was primarily because of the failure of regimens of standard duration (minimum of 12 or more months), both daily and intermittent, to achieve their potential, particularly in developing countries, because such regimens were beyond the organisational and financial resources of the health services of nearly all these countries.⁵²

Data from many studies now confirm that, as well as nine month regimens, there are also several equally effective six month regimens for treating extensive sputum smear positive pulmonary disease. Some are daily throughout, others intermittent throughout or intermittent in the continuation phase; some include streptomycin injections and others not.⁵³ Thus a choice of different types of regimen exists from which to select the most appropriate ones, whether for a service programme or the treatment of the individual patient.

The table shows, from amalgamated data of relevant studies, that there is a gradual decline in effectiveness as the duration of treatment is shortened below six months, but even with a regimen of three months' duration about 80% of patients will probably be cured. Even in the first three months the omission of

Degree of success of regimens of different durations in treating pulmonary tuberculosis in patients with smear-positive disease and drug-sensitive organisms. All the six month and shorter duration regimens contained streptomycin, isoniazid, rifampicin, and pyrazinamide initially. (Updated data from studies detailed by Fox⁵³)

Duration of regimen (months)	No of patients assessed	Bacteriological relapses		95% confidence limits
		No	%	
9	314	4	1	0.2-3
6	426	6	1	0.3-3
4½-5	589	25	4	3-6
4	364	43	12	9-16
3	359	57	16	12-20

some doses would probably not appreciably alter the success of the regimen. An even shorter duration might also well achieve a substantial rate of cure. Thus these modern short course regimens have strikingly reduced the compliance now required of the patients and the risk of therapeutic failure associated with failure to complete the course of treatment. Furthermore, if bacteriological relapse occurs it is almost invariably with fully drug sensitive organisms, facilitating successful retreatment. The regimens have other important advantages: they are highly effective in the presence of initial drug resistance to isoniazid or streptomycin, or both, and have low levels of toxicity.⁵³

THE USE OF SHORT DURATION CHEMOTHERAPY IN BRITAIN

A highly effective, well tolerated nine month regimen of rifampicin plus isoniazid supplemented by ethambutol for the first two months was recommended in November 1976⁵⁴ (and in

1980⁵⁵) by the British Thoracic Association as the treatment of choice for use in Britain. How widely has this been adopted?

Through the surveillance system in Scotland information has been obtained systematically on the outcome in patients 12 months after notification. Although the proportion of patients whose chemotherapy was completed as planned by 12 months is increasing, it was still only 46% for the patients notified in 1979, and 33% were continuing to take treatment regularly, so that physicians were still using long duration regimens on a wide scale beyond 1980. The categories "continuing on an irregular basis" (2%) and "not continuing, not completed" (7%) show that patient compliance remained an obvious problem. In a survey of patients who started treatment in 1976-8 in south and west Wales⁵⁶ only 20% has the above recommended regimen.

Two years after our national survey⁵⁴ in England and Wales of all notifications of tuberculosis in a six month period in 1978-9 we undertook a retrospective inquiry into the chemotherapy of the adults from the two main ethnic groups (white or from the Indian subcontinent) with newly diagnosed, previously untreated pulmonary tuberculosis and without complicating extrapulmonary disease or initial drug resistance. Of the total eligible patients 1261 (98%) were assessed; 35% of them did not complete their chemotherapy as planned, the main reasons being death, defaulting, or poor compliance, and modifications for toxicity. The remaining 821 (65%) who completed their planned treatment are of particular interest. Of these, only 468 (60%) were given the drug combination recommended by the British Thoracic Association—that is, rifampicin plus isoniazid, supplemented initially by ethambutol.

The recommendation of the British Thoracic Association is that the initial phase with this combination should last two months, but the median duration was in fact 2.5 months—that is, in half the patients the initial phase was longer than this, and only 42% had a two month duration (by definition 1½-2½ months); 10% had an initial phase of six or more months. Furthermore, although the total recommended duration was nine months, the median duration was 10.8 months and only 33% had a nine month duration; 42% were treated for 12 or more months. Some clinical colleagues have told me that they use the recommended nine month regimen and then, to be on the safe side, continue for a further three months, or six months, or even longer. This survey, documenting all the regimens used, will be reported in detail elsewhere.¹⁰

The current progressive dissolution of the chest service in the United Kingdom,⁵⁷ which was originally highly orientated towards treating tuberculosis, might well militate against rapid improvements in this disappointing situation. Nevertheless, it should be added that because there is an inevitable delay in a retrospective survey the position may well have changed subsequently, and it is clearly important to know whether this is the case.

Role of pyrazinamide in modern chemotherapy

In the 1950s pyrazinamide was relegated to the status of a reserve drug, but the Medical Research Council and our collaborating groups were responsible for reintroducing it into primary regimens. We included it in a regimen in our first short course study, the intake to which began in 1970,⁸ and have investigated it in 21 studies since. It is now established as an important drug in short course chemotherapy.⁵⁸ In brief, several studies have shown that it speeds the attainment of culture negativity and reduces the bacteriological relapse rate after the end of chemotherapy. It has a valuable sterilising role in the presence of initial resistance to isoniazid or streptomycin, or both,⁵⁹⁻⁶¹ and there are also widescale reports of its safety in currently accepted dosages in modern short course regimens for many countries and ethnic groups.⁶² Irrespective of what view individual physicians hold on the duration of chemotherapy, a very good case can be made for routine use of pyrazinamide in the early weeks of treatment in all

patients (except those with special contraindications), particularly if the disease is bacteriologically positive. This is because even if the patient proves to be non-compliant or to have initial drug resistance its use substantially enhances the chances of a rapid cure.

PHYSICIANS' USE OF PYRAZINAMIDE

In Scotland²⁸ only 3% of patients who started treatment in 1979 received regimens containing pyrazinamide and in England and Wales¹⁰ the proportion was 6%. I hope that these proportions will rapidly increase and that it will soon be (if it is not already) the exception rather than the rule for patients not to receive pyrazinamide. Clearly it is important, and also easy, to monitor this in surveys and in surveillance programmes.

Ways of influencing practising clinicians

In the light of these findings it is important to consider ways of influencing practising clinicians to bring and keep their management, particularly treatment, of patients up to date. My concern is not simply the dissemination of knowledge,^{63 64} the essential starting point, but how to ensure its implementation, and again I shall consider this primarily in the context of tuberculosis.

Dissemination of information

Clearly, publishing the findings of a study does not achieve dissemination. Even popular weekly journals have a circulation usually limited to a single country, and specialised journals have much smaller circulations, largely restricted to small professional groups. There may also be language barriers. Subsequent annotations will not necessarily disseminate the findings adequately, particularly in developing countries, yet improved dissemination is obviously an essential step. It should be possible, particularly for an international agency, to establish a world register of key journals that publish annotations and a mechanism for sending the editors copies of publications of major importance that are relevant to their country. Some journals are, in fact, prepared to reprint articles of major interest in full. For tuberculosis such arrangements have, for example, readily been negotiated between the editor of *Tubercle* and the editors of the *Indian Journal of Tuberculosis* and the *Bulletin of the International Union Against Tuberculosis* (which is published in English, French, and Spanish) and between the latter and the *British Journal of Diseases of the Chest*. In the United Kingdom the *Prescribers' Journal*, the *Drug and Therapeutics Bulletin*, and the *Adverse Drug Reactions Bulletin* are circulated free to all doctors in the National Health Service through the auspices of the Department of Health and Social Security. Furthermore, there are over 20 complementary privately financed journals and newspapers with a predominantly medical bias and wide circulations. Dissemination of information is therefore certainly widespread in the United Kingdom.

Government policies

For more direct attempts to change clinicians' practices, some countries issue governmental edicts that have much more force than mere recommendations. Thus in 1962 the Indians formulated a national programme, which is modified from time to time and which is widely followed within the major financial and operational constraints of that developing country. In 1980 Algeria formally adopted short course chemotherapy as the national policy,⁶⁵ making the necessary drugs available, and over two years such chemotherapy has spread to become the current national practice. In Holland governmental recommendations

including references to short course chemotherapy, were published in 1982.⁶⁶

Formal statements

In other countries learned societies make formal statements—for example, the American Thoracic Society (sometimes as a joint statement with the Centres for Disease Control⁶⁷) and the British Thoracic Association (now Society). It may have been a disadvantage that the recommendations of the British Thoracic Association on the use of short course chemotherapy in Britain were made in the discussions of the two reports of a study^{54 55} rather than being the subject of a formal statement about chemotherapy. Yet Sbarbaro,⁶⁸ too, has commented on the failure of clinicians in the United States of America to adopt modern practices in tuberculosis, despite statements from the American Thoracic Society.

WHO

The WHO Expert Committee on Tuberculosis (the WHO also has study groups) makes recommendations about all aspects of tuberculosis control, including patient supervision and regimens of chemotherapy, and the recommendations are widely adopted by developing countries, who, in general, base their policies and programmes on them. (The two most widely used regimens in developing countries with limited resources are still those recommended in the *Ninth Report*⁴⁹—namely, the inexpensive combination of thiacetazone plus isoniazid supplemented by streptomycin, and twice weekly streptomycin plus isoniazid, the latter being used widely in cities in many developing countries.) The technically advanced countries take much less notice of these expert committee reports. Indeed, in the past the average chest physician, unless in contact with the medical problems of the developing countries, was not even aware of the existence of these valuable WHO reports, much less their contents.

Educational activities

Individual clinicians may write authoritative updating reviews or give prestigious lectures at learned societies, which are subsequently published.

There are many postgraduate courses and an increasing interest in continuing postgraduate medical education and how best to provide it. This has become a growth industry, notably, but by no means exclusively, in the United States, with a proliferation of peer review organisations.^{69 70} Medical audit, usually at a hospital or district level,⁷¹ is increasingly widely used but is still regarded by many as a source of threat. The Royal College of Physicians' Medical Services Study Group is active in the field. Two Nuffield Provincial Trust publications contain much essential reading.^{72 73} The education of medical students is obviously important, but nowadays a student in Britain, as in many other technically advanced countries, may qualify without ever having seen a case of pulmonary tuberculosis and, even if he does see one, it is by no means certain that his teachers will necessarily practise or teach optimal treatment policies themselves.

The pharmaceutical industry clearly has a role, but there are commercial undertones that can create problems, particularly in the developing countries, where there are less well structured industries and controls.⁷⁴ The predominance of commercial rather than scientific sources of drug information has been reported in a study by Avorn *et al.*⁷⁵ The mass media too have an important role, and the general public and patients may hear of recent advances or problems as soon as their doctors, through the press or television. Benoxaprofen (Opren) was a striking example, and the entire United Kingdom is currently aware of and interested in asbestosis and its complications.

Research programmes

We have found that a research programme sustained over many years and based on multicentre controlled clinical trials inevitably influences routine practice in the area, since the service programme staff also undertake the research at a field level, and the directorates of medical services may make appropriate recommendations based on the study findings, which are directly relevant to their own patient population. This has happened, for example, in the countries of east Africa and in Hong Kong. This is in keeping with the suggestion that a two step process is involved, certain influential individuals hearing about a new approach and, because of their leadership and the respect of their local colleagues, influencing others to adopt the innovations, an important area of further research.⁷⁶⁻⁷⁷ An illustration of the need to sustain efforts aimed at modifying the clinical behaviour of physicians has been reported by Eisenberg.⁷⁸

National surveillance

Finally, national surveillance of actual practices is a most important measure in my specialty, and perhaps it will become the most important way of improving national standards. Broadly, the options are either continuous surveillance, as in Holland²⁵ and Scotland,²⁶⁻²⁸ or surveys at intervals, selecting the appropriate features to investigate at the time in question. This is a more flexible approach, and the one we have adopted as more relevant for England and Wales.⁴⁰ National surveillance, because it provides information for the whole country, produces findings of relevance to all concerned with the disease in question. The individual clinician has no reason to feel under inspection or to be anxious about the reasons for his selection, and anonymity is (and must be) fully protected. These are great advantages when compared with medical audit practised at a hospital or district level. An essential aspect of such surveillance, if it is to influence practice, is the publication of clearly presented results and the pertinent discussion of the findings and their implications and what improvements in management have been achieved or are still needed. Dollery's experience⁷⁹ in attempting to publish a valuable retrospective study of fatal malignant hypertension is a salutary example of a failure of journal assessors, at that time, to appreciate that much can be learnt from surveys as opposed to controlled clinical trials, essential as the latter are. It is, however, undeniable that experimental approaches offer important prospects⁷⁶⁻⁷⁷⁻⁷⁹ and must surely become an area for increased efforts. Computers have also offered many new opportunities.⁸⁰⁻⁸² Anderson and Jay⁸² have commented on their use to aid clinicians by providing, for example, a set of decision rules, but also on the less than enthusiastic acceptance of such computer applications.

Conclusion

I have been considering ways of influencing practising clinicians primarily from my own background and experience in tuberculosis. It is important that workers with experience in other disciplines should undertake similar reviews. As with patient compliance, it is by pooling experience from different disciplines and by combining experimental and observational approaches that we can best learn how to change the practices of clinicians rather than just informing the medical profession of recent developments and current thinking.

Addendum—The figures for patients notified in 1980 in Scotland have become available since this article was submitted for publication. They are practically unchanged from those quoted for 1979.

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A typist recently developed numbness of the distal phalanges of the middle three fingers but without loss of power. She made a full recovery after about 10 days. I have also seen a computer operator with a similar complaint. What is the diagnosis and how should the patient be treated?

This has to be a form of compression neuropathy. The most probable diagnosis is median nerve compression in the carpal tunnel. This can come on acutely during or after hand activity, probably because of swelling of the flexor tendon sheaths that also pass through the

tunnel. A prolonged spell at any sort of keyboard could do this, especially during a menstrual period. The tunnel has to be smaller than normal for the symptom to occur, and a relapse may be provoked by aggravating circumstances. Less likely diagnoses are a proximal compressive median nerve lesion, again related to activity but of a more strenuous sort, a multiple compression neuropathy of digital nerves due to carrying something very heavy by a thin handle, or a cervical rib. Treatment would only be needed for frequently recurring symptoms.—N J LEGG, consultant neurologist, London.