Occasional Survey

Compliance of patients and physicians: experience and lessons from tuberculosis—I

WALLACE FOX

For over 30 years I have been engaged in full time research into tuberculosis. Our major aims have been to improve chemotherapy, particularly of pulmonary tuberculosis, in a large series of controlled clinical trials and then to introduce the advances made into tuberculosis control programmes under routine service conditions. Over this long period a dominant and continuous factor influencing the direction of the Medical Research Council’s programme of research into pulmonary disease has been the problem of ensuring that patients take their medications regularly and for the prescribed period. World wide, poor patient compliance has been, and remains, the principal cause of treatment failure.

Among the major advances in the past 25 years resulting from controlled clinical trials was the demonstration that admission to hospital was not necessary to treat pulmonary tuberculosis effectively. This was already well documented in the early 1960s, particularly in the Madras study of patients and their family contacts.1 This development, however, highlighted the problem of patient compliance with outpatient self medication, which had already been recognised in the mid-1950s.3-4 A consequence was the development in the 1960s of regimens of intermittent, usually twice weekly, chemotherapy, every dose being given under full supervision.4-7 An alternative approach, developed in the 1970s, was to shorten the duration of chemotherapy. This became possible with the advent of rifampicin and the reintroduction of pyrazinamide into primary chemotherapy,8-11 and by the mid-1970s the effectiveness of both daily and intermittent short duration regimens was established.

My principal and recurring theme, however, is physician compliance, by which I mean the readiness of doctors to introduce into their practice clear cut advances established in well conducted controlled clinical trials and surveys—a widely overlooked issue.

History of patient compliance

The problem of patient compliance is old. Hippocrates wrote that the physician “should keep aware of the fact that patients often lie when they state that they have taken certain medicines.”12 In 1710 during an outbreak of plague a judicial edict was read from the pulpits in the Szabin district of east Prussia to the effect that “all those who would be regarded as suicides and their corpses would be publicly hanged who refused to take the prescribed medicines even if these proved to be of no avail.”13

Sackett and his colleagues from McMaster University put patient compliance on the map with the publication14,15 of two symposiums that they organised in 1974 and 1977. Sackett, however, gives the credit for the rediscovery, after Hippocrates, of the problem of patient compliance to the phthisiologists, and we were certainly fully aware of it in the 1950s.1,2 In 19584 and 196116 I reviewed the problem of compliance, particularly the difficulties we had encountered in our early controlled clinical trials of tuberculosis treatment in the Chemotherapy Centre, Madras, but also those already reported from other specialties. The difficulty of ensuring that diabetics took their insulin regularly and the problems with self administered diaminodiphenyl sulphone for leprosy were well recognised in the 1950s, as well as the problem with even a seven day course of oral penicillin for acute pharyngitis and otitis media due to streptococcal infections. Difficulties over compliance were also well recognised in the prophylaxis of rheumatic fever, malaria, and filariasis and in the early family planning campaigns in India and elsewhere.14

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Medical Research Council Tuberculosis and Chest Diseases Unit, Brompton Hospital, London SW3 6HP
WALLACE FOX, FRCP, FFPM, director
Methods of studying patient compliance

The main method of measuring compliance with self administered regimens is to document (a) the patients who default from treatment and are lost or who stop treatment prematurely, (b) the regularity with which those who continue attending collect their oral medicaments, and (c) the regularity with which the medicament actually is actually taken. This last is assessed by making surprise visits to the home to check the patient's stock of pills and to collect urine specimens to test for the prescribed drugs or their metabolites. When these urine tests are performed at the same time these investigations are particularly valuable. Moulding has for many years advocated the use of pill dispensers that incorporate a radioactive source and a strip of x ray film to check whether the medicament is removed regularly daily, although this is no proof that the patient has actually swallowed it. Even more elaborate devices have been used in research on patient behaviour.

Patient compliance is an important consideration when designing controlled clinical trials, as it may greatly influence the validity of comparisons of the efficacy and toxicity of alternative regimens of chemotherapy. It is important to study, analyse, and present compliance data from controlled trials with care and to appreciate their limitations. It is also important to obtain information in nationally representative sample surveys, as we did in 1964 and 1974 (and will repeat in 1984) for patients treated in Kenya, in Tanzania in 1969, in Scotland in 1968, and in England and Wales in 1978-9. (In my experience clinicians in Britain are uniquely cooperative in their willingness to participate in such national surveys.) An alternative is continuous surveillance of all new patients brought under treatment, which was introduced in Holland in 1973 and in Scotland by the Working Party on Pulmonary Tuberculosis from the middle of 1977. Representative surveys and surveillance have the advantage of a measure of performance for the whole country rather than of the best centres.

Findings in controlled clinical trials and surveys

Although we make every effort in our controlled trials to persuade patients with negative urine tests to take their medication more regularly, there may still be an association between an increasing proportion of negative urine specimens and an unfavourable response to treatment. For example, in a study in Hong Kong in patients taking self administered isoniazid plus sodium PAS (sodium para-aminosalicylate) for 12 to 18 months in the continuation phase of chemotherapy the proportion of patients with an unfavourable response rose as the number of tests negative for ingestion of isoniazid increased. On average about 15 tests were performed, and the proportion of patients with an unfavourable response increased from 4% among 279 patients with negative urine test results on fewer than four occasions to 29% among 85 patients with eight or more negative test results—a significant trend.

The value of documenting the chemotherapy administered in hospital or given to the patient at outpatient attendances during a year of treatment as a measure of countrywide failure of compliance was clearly demonstrated in the representative national survey in Kenya in 1964, when the standard duration of chemotherapy was up to 18 months. Ninety per cent of patients had a supply of medicament for three or more months, but only 28% had a supply for a full 12 months. In 1974 in the same districts depressingly similar results were recorded. In Tanzania a corresponding national sampling survey in 1969 yielded similar findings.

Furthermore, an association between the total chemotherapy administered or supplied and response to treatment at one year was shown in both the Kenyan and the Tanzanian surveys in patients who were initially culture positive and who could be assessed bacteriologically at one year. For example, in Tanzania the proportion of patients with negative cultures at one year increased from under 70% among the patients who had less than six months' supply to 96% for those who had nine to 12 months' supply of chemotherapy. These results reflect the therapeutic price paid for country wide non-compliance.

A comparison of the effectiveness of regimens based on oral thiacetazone and isoniazid in comparable groups of patients in Kenya treated in controlled clinical trials and in the service programme clearly showed the substantially much worse results of the service programme and their association with the amount of the oral combination received.

Pharmaceutical methods of improving compliance

Fixed dose combinations—Since the introduction of isoniazid in 1952 there has been widespread use of preparations in which two oral medicaments are combined in the same pharmaceutical formulation—fixed dose combinations. In the treatment of tuberculosis it is particularly important that the patients should have the right combination and in accepted dosages, so that monotherapy, or an inadequate quantity of one or other drug, which may cause therapeutic failure with the emergence of drug resistance, is avoided. Such combined preparations are simpler for the patient and reduce the number of pills to be swallowed. They also simplify dispensing and supervision through checks of pill stocks and urine testing, for the physician has only to test for one drug in the combined preparation. Tests for the metabolites of isoniazid, isonicotinic acid, and isonicotinyl glycine, are particularly satisfactory since these metabolites are stable in urine for many weeks and can be detected by a simple sensitive and specific colorimetric procedure, and isoniazid is a component of all antituberculosis regimens.

Special packs for medicament—So called “pill calendars,” which have a month’s supply of medicament, have been used in chemotherapy and chemoprophylaxis. They remind the patient and his family of the daily medication. Convenient and portable calendar packs, usually a week’s supply on a card or in a foil strip, are increasingly favoured pharmaceutical presentations.

Physicians’ use of urine tests and pill checks

Although the value of urine tests and pill counts is well established, to what extent have testing urine for antituberculosis drugs and checking pill stocks been routinely undertaken under programme conditions for a whole country? In Scotland we obtained information in a comprehensive survey of a 50% random sample of patients with pulmonary disease admitted to treatment in 1968, a year chosen because it was at the end of the era when nearly all patients received regimens containing PAS salts (usually sodium). PAS is an oral drug which is bulky, bitter, and unpleasant to take and often has side effects; because of this patients often failed to take it regularly. A total of 615 patients in 42 areas were prescribed PAS as outpatients (unpublished data from Heffernan et al 1976). In 30 areas (with 283 patients) no urine specimens at all were collected at clinic attendances to test for PAS, even though the ferric chloride test is very simple. In the remaining 12 areas some tests for PAS were done for 150 patients but none for 82 patients. Thus overall only 150 out of 615 patients prescribed regimens containing PAS had any urine tests for the drug. A further 59 patients in 22 of the areas were taking isoniazid regimens without PAS, but none of them had urine tests for isoniazid, although a simple one existed. In only one of the 42 areas were urine specimens collected at surprise visits to the home. Furthermore, there was no record that the stock of pills of any of the patients was ever checked during home visits. Thus at a time when there were good reasons for careful routine supervision of regimens containing PAS, little clinic urine testing was being done and there was virtually no domiciliary supervision of compliance.
Routine admission to hospital for tuberculosis

Ten controlled clinical trials (the world literature has produced no evidence that the sanatorium regimen of rest, good accommodation, good diet, nursing care, and airy surroundings is beneficial in the treatment of tuberculosis. The findings were particularly noteworthy in the Madras trial of treatment at home compared with treatment in a sanatorium. The very unfavourable home conditions were fully documented and every patient had smear-positive disease and was followed up for five years, with intensive bacteriological and regular radiological monitoring. We also found no greater transmission of infection (by tuberculin testing) and no more disease in the families of the patients treated at home than among the families of the patients isolated in a sanatorium. This important finding has been confirmed in several other studies. Clearly it is not necessary to admit patients to hospital unless there are special indications, such as complications.

Physicians’ approach to hospital admission

Because the admission of patients to hospital as a routine policy has clearly been shown to be unnecessary and is so much more expensive (currently above £70 a day in England) than outpatient treatment, clinical practice is of particular interest. Information is available for Scotland for all patients with pulmonary disease who were started on treatment in the second half of 1977 and the whole of 1978 and 1979, and for patients notified and brought under treatment in England and Wales in the last three months of 1978 and the first three of 1979. In both countries the proportion of the total number of patients with pulmonary disease admitted to hospital was high, ranging from 70% to 81%. In Scotland routine policy was reported to be ‘the main reason’ in 22%, 15%, and 15%, respectively, of the patients admitted in 1977, 1978, and 1979. In England and Wales, where the clinicians were asked to indicate one or more of a list of possible reasons, routine policy was one of the reasons in 23% of patients. Thus, many years after it had been well recognised that ‘routine policy’ was not in itself a reason for hospital admission, it was still a common practice in the United Kingdom.

Regimens of chemotherapy to improve patient compliance

The Madras study led directly to the development and introduction of fully supervised intermittent regimens, short duration regimens, and combinations of the two in attempts to overcome the problems of compliance during long term self administered daily regimens in outpatients.

This article will be continued next week. The references to both articles will appear at the end of the second article.

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**Personal Paper**

**Caesarean section under epidural: a personal account**

MONICA HARDWICK

In August 1982 I had an emergency caesarean section under epidural anaesthetic for the delivery of my first baby. I am an anaesthetist and had never had an operation during my adult life, so the experience made quite an impression on me.

I was 12 days overdue and had been threatened with induction, when at last the contractions started spontaneously. My husband, also a doctor, enthusiastically helped me to record the contractions for several hours before taking me to the maternity hospital, where we were disappointed to find that I was only 1.5 cm dilated and not even in established labour.

Eventually, the following morning, I was transferred to the delivery room, where the nursing officer performed the artificial rupture of membranes and the intravenous cannulation. The latter was definitely the most uncomfortable, and the Hartmann’s Solution produced a hot stinging sensation when first flushed through the vein. A fetal scalp electrode and intrauterine pressure manometer were introduced with little discomfort, and we settled down to watch the monitors. Several members of the medical staff, including the anaesthetist, called in to assess my progress and told me that I wanted an epidural. I replied to all of them that I was managing so far without, and persevered with the breathing exercises.

Several hours later, however, and still only 3 cm dilated, I had stopped coping with the increasing pain and was hanging on to the bed rails and groaning in a most undignified manner. The contractions would have been bearable but the constant severe backache was becoming intolerable, and I gratefully accepted the epidural.

Quick and pleasant relief

I was relieved to discover that I had been advising my obstetric patients correctly and that the insertion of an epidural catheter really is not painful. I flinched when the skin was infiltrated with lignocaine and could tell exactly what my colleague was doing, but there was no discomfort. The whole procedure was over remarkably quickly, and I realised that, despite the stories of doctors attracting complications, I had experienced an epidural without the dreaded dural tap. After 10 minutes warm waves of pleasant paraesthesia were lapping up both legs, the backache...