met said he had had no problems with patients, who had happily accepted him as one of the medical group. There was no question of his being used in a "service" capacity in practice. Indeed, he was given ample opportunity to pursue his own medical interests and was planning to sit for the M.R.C.P., for which he was being seconded to a hospital post in Edinburgh for two months. Trainees were encouraged to take diplomas, and, though during their hospital stage service commitments limited the amount of formal postgraduate training, the timetable in the general practice year was adaptable.

Administration and Finance

No fewer than six health authorities participate in the Livingston project, which is run by the joint advisory committee containing representatives from each, together with the Principal Medical Adviser—offspring of the Scottish medical superintendent genre—and his administrative staff. Even with this amount of co-ordination great goodwill has been needed on all sides to keep things moving forward. It was natural that the medical adviser should organize the vocational training course and his knowledge of the local medical scene has undoubtedly played a great part in the course's successful launching. He is readily available to the trainees and during the course takes considerable trouble to help and advise them. However, those I spoke to would have welcomed more frequent get-togethers of all those taking part in the course—consultants, general practitioners, and trainees.

The Livingston general practitioners were naturally enthusiastic about the scheme and had co-operated wholeheartedly, and the scheme has been strongly supported by several of the consultants, though not surprisingly they have differed in their approach to the course, reflecting the various views about the nature of the relationship between the general practitioner and the hospital. With the Scottish Home and Health Department providing the extra money required in addition to the salaries which the employing authorities were empowered to pay, the financial aspect of starting the scheme was less of a headache than might have been expected. The trainees I spoke to had no special comments to make either on pay or accommodation. Houses were available to rent in Livingston, though one or two of the hospital trainees lived in the Edinburgh area and commuted.

Looking Forward

While Livingston itself is well supplied with doctors, some of the surrounding areas are very short and it would not be surprising if adjacent executive councils and local medical committees cast occasional envious eyes on the facilities and apparently privileged medical position of the new town. However, in time the project should benefit a much wider population than the new town itself. Though so far the vocational training scheme has been filled on an informal basis it is shortly to be advertized nationally. In doing so perhaps the organizers should think about expanding the number of entrants despite the obvious problems involved. Understandably the scheme's primary objective has been to provide a supply of suitably trained family doctors for Livingston's expansion. However, it is also important to attract doctors to that part of Scotland as a whole, and an expanded vocational training scheme could well do this. Furthermore, in Britain a genuine experiment in health care is rare enough to merit a serious effort to give as many doctors as possible practical experience in it. So on this score too Livingston should aim as high as it can.

Today's Drugs

With the help of expert contributors we print in this section notes on drugs in common use

Antileprosy Drugs

Despite the great strides made by research bacteriologists in the cultivation of *Mycobacterium leprae* in laboratory animals during the past decade, ever since Shepard's discovery that the organism would multiply in the foot-pads of mice[1 2] no antileprosy drug has been found to displace sulphone from the position it has held since 1943 as the drug of choice for general use in treating leprosy. Rifampicin has been shown to be more effective, but its use in leprosy is severely restricted by its prohibitive cost.

Sulphone

The first publication of the use of a sulphone in leprosy was by Faget *et al.*,[3] who used glucosulfone sodium (Promin; Promanide), which had previously been shown to possess antitubercular activity in guinea-pigs.[4] This had to be administered intravenously, and the search for an oral sulphone led to the first reports on the use of dapsone (DDS, 4,4'- diaminodiphenyl sulphone).[5 6] This proved so toxic in the large doses used at that time that attempts were made to produce less toxic derivatives by altering the amino groups. Nevertheless, we now know that these disubstituted derivatives are less toxic because oral administration releases only small quantities of the active substance (dapsone) after hydrolysis in the stomach, the remainder being inert. Examples of such derivatives are sulfoxone sodium (Diasone) and solapsone (Sulphetrone).

Dapsone is, therefore, the sulphone in general use, and has the additional attribute of being very cheap. Until recently the usual adult dose was 600-700 mg/week, but this is now considered to be unnecessarily large, and dosage in the region of 100-200 mg/week is advocated at the present time, starting with 25 mg/week and slowly increasing. Controlled trials of even smaller doses are being carried out. For example, Leiker and Carling[7] found that 20 mg/week was as effective as 250 mg/week, but they warned that even though bacilli disappear from the skin there may be hidden foci of living bacilli which may become resistant to dapsone because of the small dosage used. Small doses of dapsone are indicated particularly in the management of those at risk from lepra reaction, and until recently it was difficult to treat such patients because a 50-mg tablet was the smallest available. This deficiency has been remedied in several countries, and in Britain it is now possible to obtain a wide range of tablets (1 mg to 100 mg).* As regards method of administration, dapsone can be given daily, twice a week, or once a week.

*Available from Thomas Marns and Co. Ltd., Brookside Avenue, Rustington, Sussex.

Parenteral Use

Under certain conditions it may be preferable to give dapsone treatment parenterally. Because of its insolubility in water it has been standard practice to give dapsone as a suspension in an oil such as arachis oil or chaulmoogra oil, injections being given intramuscularly every fortnight. Nevertheless, oily injections have the disadvantage of being painful and of sometimes causing sterile abscesses, and this has led to the production in recent years of non-oily preparations. A variety of these are available commercially; alternatively a preparation formulated by French[8] may be made in a hospital pharmacy. The formula is: dapsone 5 g, absolute alcohol 40 ml, benzyl alcohol 5 ml, propylene glycol to 100 ml. This produces a solution of dapsone containing 50 mg in 1 ml. A weekly injection is usual but possibly it could be equally effective given every two weeks or even longer.

Another preparation for intramuscular use is DADDS (4, 4'-diacetyldiaminodiphenyl sulphone). It is a repository sulphone which slowly releases dapsone or the monoacetylated derivative, and each injection is effective for over two months. Shepard *et al.*[9] gave 225 mg every 77 days to 10 patients who were matched with 10 other lepromatous patients given oral dapsone in a dosage of about 100 mg. daily, and found no difference in therapeutic effect. This method clearly has great possibilities in field work, but the results of further observations are needed before this compound can be recommended for general use in view of the possibility that the small quantities of dapsone released may encourage the emergence of resistant strains of *Myco. leprae*.

Sulphone Resistance

In recent years there have been several reports of sulphone resistance, but it is fortunately rare, occurring in roughly one in a thousand patients under treatment. There is no universal agreement about the length of treatment, but all would agree that it is better if in doubt to err on the generous side if relapses are to be avoided. In general, the recommendation is to base the decision on, firstly, the lepromin test carried out at the time of making the decision, or, secondly, the presence or absence of bacilli at the beginning of treatment (see Table).

Lepromin Reaction	Skin Smears	Length of Treatment
Strongly positive ..	Negative	5 years
Weakly positive	Few bacilli	10 years
Negative	Moderate or large numbers of bacilli	For life

Side effects of dapsone are rarely encountered by those who treat leprosy with doses of 700 mg/week or less, but they sometimes occur with higher dosage. Haemolytic anaemia heads the list; there does not appear to be any connexion between glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and haemolysis. Pengelly[10] has shown that the life-span of the red blood cells was reduced in four patients receiving dapsone for dermatitis herpetiformis to 29, 25, 46, and 48 days. Rarer side effects are methaemoglobinaemia, hepatitis, and various types of dermatitis. Psychosis is usually listed as a toxic effect, but it is doubtful if this can be accepted.[11] One case of agranulocytosis has been reported,[12] and one case of chronic nephritis in a patient treating himself with enormous doses of dapsone on the mistaken assumption that he had leprosy.[13] Dapsone may be given during pregnancy without any risk of a teratogenic effect. Lepra reaction is not a toxic effect of dapsone; it may be precipitated by other effective antileprosy drugs. One aspect of treatment, particularly of the lepromatous type, is the problem of getting rid of the enormous numbers of dead bacilli which remain in the tissues long after the disease has been brought under control, for these are important in the aetiology of the lepra reaction. We need a drug which will help the tissues dispose of them.

Thiourea Compounds

DISUBSTITUTED THIOUREAS

Thiambutosine (Ciba 1906; SU 1906; DPT) is the best known of the disubstituted thiourea compounds. Not only is it effective but it is virtually free of toxic effects, and its only disadvantage is that bacterial resistance is likely to develop after about two years. Optimum dosage is four tablets (2 g) daily. A parenteral compound is available for intramuscular injection once a week. Alternative compounds for oral use are thiocarlide (Isoxyl)[14] and dialide (Etoxid).[15 16] Both appear to be effective.

MONOSUBSTITUTED THIOUREAS

Thiacetazone (TBI: Conteben; Tibione; Amithiozone; p-acetaminobenzaldehyde thiosemicarbazone) is another established antileprosy drug, but has largely been displaced by the non-toxic thiambutosine. Optimum dosage is 150 mg/day, and as with thiambutosine there is a likelihood of bacterial resistance developing after about two years. Gastric effects may be troublesome, and can be reduced by taking the tablets with food. Other side effects are rare and include headache, vertigo, proteinuria, skin eruption, anaemia, agranulocytosis, and hepatitis. Probably leprosy bacilli becoming resistant to thiacetazone will be cross-resistant to thiambutosine, for this has been observed in experimental tuberculosis and in foot-pad infections in mice.

Clofazimine

This riminophenazine dye (Lamprene-Geigy; B663), synthesized by Barry *et al.*,[17] holds a unique position in leprosy therapy as it combines an antibacterial action, as effective as that of dapsone, with an anti-inflammatory action of proved value in suppressing the manifestations of lepra reaction complicating lepromatous leprosy (ENL reaction; Type 2 reaction.[11] As with the drugs described above, its action against *Myco. laprae* is bacteriostatic. It is a red crystalline substance which is put up in soft gelatin capsules containing the micronized active ingredient in suspension in an oil/wax basis. In the treatment of leprosy a minimum dosage of 1 capsule (100 mg) twice a week has been found effective,[18] but considerably larger doses are required to control the lepra reaction, usually in the region of 300-400 mg/day. Dosage may gradually be reduced once the reaction has been controlled. If the reaction breaks through while a patient is on clofazimine it is important that the dosage should be increased and *not* decreased (as would be normal practice with other antileprosy drugs).

Clofazimine is particularly valuable in treating patients with lepra reaction who have become steroid-dependent, for it enables the dosage of corticosteroid to be reduced progressively. There are no known contraindications to the drug, and bacterial resistance has not been encountered. The only side effect of any importance is discoloration of the skin and conjunctivae. The skin becomes red at first (as if it had been overexposed to sunlight) and later becomes mahogany brown, while the leprosy lesions darken and appear mauve, slate-grey, or black. These colour changes are most appreciable on the regions exposed to sunlight, and slowly disappear after stopping treatment. The conjunctivae show varying degrees

of red-brown discoloration, and a red tint may appear in the urine, sputum, and sweat. As would be expected, pigmentary changes are much less noticeable in those with dark skins. Nausea or diarrhoea, or both, occur rarely, and can usually be controlled by giving the capsules immediately after food. Skin irritation is even more rare.

Long-acting Sulphonamides

Long-acting sulphonamides have been given extensive trials and have been shown to be effective. Nevertheless, there is little likelihood that they will be used in preference to dapsone as they are more expensive, more toxic, and as liable to precipitate lepra reaction; moreover they are not more effective than dapsone, while they are ineffective in the treatment of dapsone-resistant leprosy.

Antibiotics

Several antibiotics have been used with success, such as cycloserine and terramycin, but the most effective appears to be rifampicin. Not only is it twice as effective as dapsone in treating infected mice, but Rees *et al.*[19] have shown its value in human leprosy. These workers found that all the bacilli in the skin were killed in five weeks as against five months in control cases on dapsone, and they found it effective against dapsone-resistant bacilli. They gave 600 mg daily in a single dose before breakfast, reducing the daily dose to 450 mg for patients weighing less than 35 kg. No toxic effects were met, and lepra reaction was only a minor problem.

Unlike all the other antileprosy drugs in current use rifampicin acts bactericidally (as it does in tuberculosis). It is put up in capsules of 150 and 300 mg, and the only side effects observed to date are nausea, abdominal discomfort, skin allergy, and an orange-red discoloration of the urine and sputum; in fact, its only real drawback is its high cost. It should always be given on an empty stomach.

Combined Therapy

Treatment with a combination of antileprosy drugs is not recommended, as there is no evidence that bacterial resistance can thereby be delayed or prevented. By giving two drugs such as thiambutosine and dapsone resistance to the former is likely to develop after two years (with cross-resistance to thiacetazone). Hence should resistance to dapsone develop later, the choice of alternative drugs will be seriously restricted.

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Conferences and Meetings

Freedom from Amphetamines

A conference on "Freedom from Amphetamines", organized by the Board of Science and Education, was held at B.M.A. House in London on 8 July. Professor Sir Ronald Tunbridge, Chairman of the Board of Science and Education, introduced Sir Keith Joseph, Secretary of State for Social Services, by reminding the audience that the B.M.A. had been interested in the abuse of alcohol, barbiturates, and also in amphetamines for the last ten years.

Sir Keith Joseph said that he was present to testify to the value the Government saw in the concern shown by the B.M.A. in the effects on the public of amphetamine abuse. Ministers were aware of the good done by doctors in the field of cigarette smoking, and valued the initiative of doctors such as Dr. F. O. Wells and his colleagues in Ipswich, who, Sir Keith thought, had been both right and persuasive. The government wished to indicate their admiration for what was being done to control amphetamine abuse.

Dr. Ronald Gibson, Chairman of Council, thanked Sir Keith for attending and pinpointing the importance of the problem. He said he hoped that a voluntary solution could be achieved and that this was most likely when all parties were able to work together.

Definitions

Dr. W. W. Fulton (Glasgow), taking the chair, was concerned to define exactly what "amphetamines" included—namely, compounds derived from phenethylamine with specific pharmacological properties. The world literature and experience with these compounds had been reviewed in the 1968 report of the B.M.A. Working Party on amphetamine preparations,* but Dr. Fulton thought that this had had too little impact. It had been written by doctors for doctors and was educational, but it had proved a useful blueprint on which to base action, so that in 1970 the Representative Body had advocated a voluntary ban on prescribing amphetamines. For the present conference 60 medium-sized towns had been invited to send representatives and 48 had responded.

The chairman then invited papers from three expert speakers before opening the meeting to the floor. The first was Dr. Denis A. Cahal (a Senior Principal Medical Officer, Department of Health), who emphasized that amphetamines in this context meant amphetamine racemate (rarely used), methyl-

* *British Medical Journal*, 1968, **4**, 572.