not be forthcoming from anywhere else. Politically it sometimes seems to be under a cloud because of doubtful ethics in the advertising and selling of their products. Sometimes there is criticism of the profits they make. Yet the industry is responsible for most of the major therapeutic advances in medicine. Certainly it makes advances available to a wide medical public by marketing.

Doctors are obviously needed in the industry in both laboratory and clinical work, and to maintain liaison with doctors in all fields of medicine. Doctors in the industry are also needed to assess medical publications and the worth of the ideas they contain to see if they might be exploited, for the benefit of the public and the firm. Moreover, these doctors carry a heavy responsibility in writing up drug information sheets for doctors who will prescribe their products and so in providing unbiased information in a commercial world. Doctors of high calibre are needed, and normally will be expected to hold higher degrees or diplomas. Advertisements for vacant posts appear regularly in the medical journals. Anyone who is interested might also write to the medical director of any of the major pharmaceutical companies for career advice.

Law and medicine

The law is intertwined with medicine in forensic medicine, forensic psychiatry, in the medical defence societies, and in the persons of coroners, police surgeons, and prison medical officers. The way into these careers is usually by general medical training, taking a higher diploma, and then entering the specialty. The first contact for information will usually be the postgraduate dean.

The person with a medical degree is fortunate in having a qualification which opens many doors, all of which lead into rooms of fascination and interest. You should have sampled the contents of many of the rooms as an undergraduate. After graduation you must decide which room you wish to enter finally. It ought not to be difficult because there must be something out there in the future that you will like, enjoy, and be happy in, and in which you will make a satisfying and useful career.

In the next few articles I shall discuss how to plan to take higher qualifications.

For Debate . . .

Asthma in New Zealand

IAN W B GRANT

In September 1982 I spent almost three weeks in New Zealand at the invitation of the Asthma Foundation. The main purpose of the visit was to provide a focus for the first medical educational exercise by the foundation, and to draw attention throughout New Zealand to the recently formed foundation together with the well established regional asthma societies. It was hoped that by exchanging views with physicians and general practitioners, and by addressing public meetings of asthma societies in most of the major centres of population, I could contribute to a better understanding of what was widely acknowledged to be a serious health problem in New Zealand.

Even before my tour was arranged I had read an article in the *Lancet* entitled "Has the change to beta-agonists combined with oral theophylline increased cases of fatal asthma?"[1] and although I did not agree with this hypothesis for reasons that I shall specify later, the authors' statement that 20 patients had died from asthma in Auckland between October 1980 and January 1982, a number considerably greater than the previous death rate, had obviously alarmed not only the medical profession but also the general public, who learnt about the article in the lay press. After I arrived in New Zealand I soon discovered that the recent increase in asthma mortality was not confined to Auckland. Until 1977 the number of deaths certified as having been due to bronchial asthma had fluctuated between 60 and 120 for the whole country (population 3·2m) but between 1977 and 1981 it had risen to almost 300. An article in the *BMJ*[2] that analysed death rates from asthma in New Zealand in the 5-34 age group until 1979 reported a similar trend. The authors put forward three possible explanations for this new "epidemic" of deaths from asthma, which has not been observed in any other country. Firstly, the prevalence of asthma in New Zealand might have increased and, secondly, asthmatic patients there might be developing a more severe form of the disease. Although neither of these two possibilities could be excluded, no population based studies of asthma morbidity were available to support them, and aetiological factors peculiar to New Zealand did not appear to have assumed greater importance recently. The third and most likely explanation was that the increased mortality was related to changes in the management of asthma.

In my discussions with respiratory physicians in New Zealand I concentrated on therapeutic management, and I shall now try to analyse in what respects their policy has recently diverged from that in the United Kingdom.

Hyposensitisation

Although a few physicians, most of whom practise outside hospitals, are enthusiastic advocates of hyposensitisation and other forms of immunotherapy, I did not get the impression that it was widely employed in New Zealand. Although there is a danger that patients so treated might be denied more effective forms of treatment at a stage when these were urgently

Respiratory Unit, Northern General Hospital, Edinburgh EH5 2DQ
IAN W B GRANT, MB, FRCPED, consultant physician and senior lecturer in medicine, University of Edinburgh

needed, it seems improbable that the use of hyposensitisation has contributed greatly to the increased death rate from asthma —for example, by causing anaphylactic reactions.

Sodium cromoglycate

Treatment with sodium cromoglycate, although widely used, is perhaps not as fully exploited in New Zealand as it is in the United Kingdom, particularly by general practitioners. This impression is to a large extent anecdotal and arose from conversations I had with the parents of asthmatic children at the end of asthma society meetings. Several children who, from the information I was able to obtain, would have been ideal candidates for this form of treatment had not been given it, even on a trial basis. Nevertheless, any such errors, while they may have exposed the children to unnecessary morbidity, are unlikely to have increased the risk of dying.

Sustained release theophylline preparations

Sustained release theophylline preparations were much more widely prescribed in New Zealand than in the United Kingdom, often in preference to sodium cromoglycate or corticosteroid aerosols as "maintenance" treatment. Sustained release theophylline preparations have, however, been available in New Zealand only since April 1980, and since the death rate from asthma had begun to increase appreciably at least two years earlier, they cannot have been primarily responsible for the rise in mortality. Nevertheless, the practice of administering a sufficiently high dose of drugs to produce "therapeutic" serum concentrations of theophylline, which often border on toxic concentrations, as advocated by American physicians, may be hazardous if a patient treated in this way is given a bolus injection of aminophylline for an acute attack of asthma, and this may have been responsible for a few deaths. On the other hand, I could not accept the fragile circumstantial evidence presented by Wilson and his colleagues[1] that combined treatment with oral theophylline and inhaled beta-agonists increased the risk of death from asthma. I expressed my reasons for opposing this view in a letter to the *Lancet*.[3] One of the points I made was that only two of the 16 patients in whom death or collapse was sudden and unexpected were being treated with oral corticosteroids, although there must have been some previous indication that they were "high risk" cases. A similar state of affairs was reported in a recent analysis of 90 deaths from asthma in two regions of England,[4] which showed that 32 patients already taking an oral corticosteroid preparation required a larger dose and that 11 who needed this form of treatment had not been given it. It thus seemed that undertreatment with corticosteroids was more likely to have been responsible for the deaths and near deaths from asthma in Auckland than combined treatment with oral theophylline and beta-agonists.

Corticosteroids

In the last section I mentioned the possibility that oral corticosteroids were being underused in New Zealand when asthma was severe and not responding to other measures. In general, however, I had the impression that most hospital consultants, certainly those in large centres, were well aware of the need for high doses of corticosteroids in such circumstances. Unfortunately, I did not have sufficient contact with general practitioners to discover whether most of them adopted the same policy. Corticosteroid aerosols, on the other hand, appeared to be extensively used in both general and hospital practice, although possibly too much was expected of this form of treatment when asthma became severe. It cannot be emphasised too strongly that corticosteroid aerosols are of value only in maintaining control of airflow obstruction and have little or no effect during acute phases of the disease.

Bronchodilators

Many doctors, including those in New Zealand, will recall the world wide epidemic of deaths from asthma in the 1960s.[5] This epidemic was initially attributed to the introduction of isoprenaline aerosols, which when overused were believed to cause death through the action of the drug on the myocardium. Recently, however, that hypothesis has been disputed, and the consensus of opinion now is that the cause of the increased number of deaths at that time was much more complex. The inhalation of an isoprenaline aerosol often dramatically relieved the symptoms of airflow obstruction, and with this apparent remedy literally in their own hands many patients derived a sense of false security from it—false because it did not correct, and might even have aggravated, the hypoxaemia produced by severe asthma, thus exposing the patient to the risk of hypoxic cardiac arrest, particularly if large doses of isoprenaline were inhaled over a short period. The warning eventually issued by medical authorities in the United Kingdom and elsewhere on the danger of isoprenaline inhalers, and the introduction of a regulation whereby these were supplied to patients only on medical prescription, was certainly followed by a reduction in the number of deaths from asthma. At the same time, however, the number of prescriptions issued for oral corticosteroids rose sharply as did the number of asthmatic patients admitted to hospital. It could thus be argued that better medical care in these respects contributed more to the subsequent reduction in the number of deaths from asthma than restrictions in the use of isoprenaline inhalers. Since 1970 the death rate from asthma has remained relatively static everywhere, and probably only errors of management, such as those disclosed in the recent British Thoracic Association survey,[4] have prevented it from falling well below the present still unacceptably high level. It is therefore a matter of grave concern that the death rate from asthma in New Zealand should have increased considerably during the past few years. Since this trend is peculiar to that country, and since no other change in drug prescribing appears to be implicated, we have to consider the possibility that it could be related to a change of policy in the administration of bronchodilator aerosols.

For many years it has been common practice in hospitals in the United Kingdom to use aqueous salbutamol or other beta-agonist aerosols, either inhaled from an oxygen driven nebuliser or delivered in oxygen by intermittent positive pressure breathing, to control severe attacks of asthma. In these circumstances large doses of salbutamol (5-10 mg) are used, and this treatment appears to be both effective and safe. In hospital, however, the partial pressures of oxygen and carbon dioxide in arterial blood can be regularly monitored and hypoxaemia corrected by continuous oxygen therapy. Respiratory physicians in the United Kingdom have so far adopted a much more cautious attitude towards providing electrically operated air compressor nebulisers for the self administration of large doses of aqueous salbutamol aerosols by patients in their homes. They fear that this form of treatment may reproduce all the hazards associated with the unbridled use of isoprenaline inhalers in the 1960s. Nebulisers are therefore supplied, usually on loan from hospitals, only to selected patients, mostly children, whose asthma cannot be controlled in any other way, and very strict precautions are taken to ensure that the treatment is carefully supervised.

The situation in New Zealand is radically different. In the past two years 6000 nebulisers have been purchased by asthmatic patients without necessarily having the approval of their

doctors, and salbutamol solution for use with these nebulisers may be obtained from a pharmacy without prescription. Up to 6000 patients may therefore be inhaling, at frequent intervals, 1-2 ml of 0·5% salbutamol solution, which is equivalent to 50-100 metered doses of 100 μg from a salbutamol inhaler. Most attacks of asthma in fact respond to two to four doses from that type of inhaler, and when airflow obstruction is so severe that massive doses from a nebuliser are required the patient ought to be in hospital. I had the impression, which was confirmed by most of the respiratory physicians I met in New Zealand, that the popularity of nebulisers was a fashion encouraged by pharmaceutical companies and the manufacturers of nebulisers which the medical profession had so far failed to counter. The Medical Advisory Panel of the Asthma Foundation has, however, recognised the potential risks of poorly supervised dosing through nebulisers, especially in severe asthma, and has published guidelines concerning the use of nebulisers in the home.[6]

There is no proof that the widespread use of nebulisers is the main cause of the recent increase in deaths from asthma in New Zealand. That will not be known until the completion of a two year nation wide investigation sponsored by the Medical Research Council and the asthma societies of all deaths certified as due to asthma from 1 August 1981 to 31 July 1983. Nevertheless, it is not inconceivable that we may already be witnessing in New Zealand the beginning of a "re-run" of the international epidemic of deaths from asthma in the 1960s. That may seem fanciful, but the parallels are too dangerous to ignore. Patients are now, as they were then, being given virtually uncontrolled access to a form of treatment from which they often derive undoubted subjective benefit but which on occasions may conceal the danger of the disease itself and cause them to underestimate the importance of seeking expert medical advice at times when their lives are potentially at risk. The popularity of nebulisers for administering large doses of bronchodilators is rapidly gaining momentum elsewhere in the world, and there may already be a prima facie case for restricting their direct sale to patients and for ensuring that salbutamol solution is available only on medical prescription.

Oxygen

Patients with severe asthma are always hypoxaemic, and most, if not all, sudden deaths from asthma are due to the effects of profound hypoxaemia on the myocardium causing asystolic cardiac arrest or, less often, ventricular fibrillation. The administration of oxygen is thus a potentially life saving measure in the treatment of severe attacks. It has been known since 1967 that bronchodilator drugs tend to increase the degree of hypoxaemia.[7 8] Thus to allow patients with severe asthma to use in their homes nebulisers capable of delivering large doses of salbutamol aerosol in air without at the same time providing them with oxygen may put them even more at risk. In an acute attack oxygen can, and should, be inhaled continuously before and after nebulised salbutamol, or indeed any rapidly acting bronchodilator drug, is administered. These views are widely accepted in the United Kingdom, and oxygen cylinders are available on National Health Service prescription to all patients with severe asthma. Although oxygen is also available free through hospitals to patients in New Zealand, nebulisers are apparently often used by patients with severe asthma in their homes without immediate access to a supply of oxygen. That alone could not account for the recent increase in the number of deaths from asthma, but some lives could almost certainly be saved if all patients with a history of severe attacks of asthma were provided with oxygen cylinders.

Use of peak flow meters

In the United Kingdom peak flow meters are supplied on loan, without charge, by hospitals to selected patients with unstable and life threatening asthma. As in New Zealand they are not available on the standard drug tariff in general practice, but on their doctors' advice patients may purchase them privately. It has been widely publicised in New Zealand that measurements of the peak expiratory flow rate before and after the inhalation of nebulised salbutamol provide a reliable indication of the response to that form of treatment.[6] Patients are told that if the peak expiratory flow rate does not increase considerably they must not repeat the treatment and should seek medical help immediately. These recommendations are entirely logical, and if followed should considerably reduce the potential hazard of inhaling large doses of air-nebulised salbutamol at home. Unfortunately, presumably for financial reasons, only 2000 peak flow meters were purchased in New Zealand during the same period in which 6000 nebulisers were sold. The failure of many patients to avail themselves of this potential safeguard could well be responsible for some avoidable deaths from asthma.

General management

The prescription of drugs is only one facet of the management of bronchial asthma. It would clearly be presumptuous of me as a visitor to criticise the general policy of medical care as it relates to the treatment of asthma in New Zealand, but I hope that I may be excused for drawing attention to several problems of which I became aware either through personal experience during my tour or from discussions I had with many medical colleagues. Before I try to identify these problems I must make it clear that hospital treatment of asthma in all the cities and large towns compares very favourably with that available at similar centres in the United Kingdom. Indeed, the teaching hospitals in Auckland, Wellington, Christchurch, and Dunedin provide facilities that those of us who have to work in old and decaying British hospitals would regard with envy. There did, however, seem to be inadequate communication, more apparent in some centres than in others, between hospital consultants and general practitioners.

Although it was flattering to have such large audiences, amounting in all to 2500, at the meetings of various asthma societies, this might have betrayed a certain lack of confidence, possibly completely unfounded, in the medical attention that asthmatic patients and the parents of asthmatic children were able to receive from their general practitioners. Being fully aware of the high standard of medical education in New Zealand, I did not believe for a moment that any such lack of confidence reflected on the competence or diligence of individual doctors. I wondered, however, if the method of payment by partially recoverable fees for each item of service might inhibit asthmatic patients from consulting their doctors as often as they should and perhaps create a disincentive to earlier referral to a hospital physician. Another undesirable consequence of the method of payment is that some hospital physicians supply drugs directly to asthmatic patients because they are afraid that some of them may not be prepared to incur the fee they would have to pay to a general practitioner to obtain a prescription. Although this practice ensures that patients receive the drugs they need without having to pay for consultations, it inevitably reduces the degree of liaison between hospital physicians and general practitioners, and this must have adverse effects on patient care.

Other observations

One of the major disappointments of my tour was that except in a few centres I could make very little contact with general practitioners; many of them were invited to my medical meetings but relatively few attended. I gathered from hospital physicians that they always had difficulty in attracting general

practitioners to clinical meetings, but perhaps their absence may be explained on the grounds that general practitioners in New Zealand are more individualistic than those in Britain, and that those who practise in rural areas have a natural dislike of travelling long distances during unsocial hours to attend meetings on topics in which they have no special interest. Nevertheless, it appears that there are gaps to be bridged in the relationship between general practitioners and hospital physicians, although I would not presume to suggest how this can best be achieved.

I was encouraged to describe and discuss the hospital self admission scheme we have in Edinburgh[9] for patients with life threatening attacks of asthma. The suggestion that such schemes should be introduced in major centres of population in New Zealand was welcomed by most of the respiratory physicians I met, but it cannot be implemented without the full support and cooperation of general practitioners. That will, I hope, be forthcoming in the near future because there is general agreement that the prompt admission to hospital of patients with severe acute asthma reduces the number of avoidable deaths.

I was most impressed by the energy and enthusiasm of the many regional asthma societies established throughout New Zealand. They fulfil a valuable role both in disseminating information about the nature of the disease and its treatment and in providing considerable material help and moral support to individual patients. The establishment of the Asthma Foundation will not interfere with the autonomy of asthma societies but will provide them with the additional funds needed to extend their activities. As a national body it will also be able to bring the problem of asthma in New Zealand to the attention of the general public and to provide funds for major research projects. All these objectives are of particular importance at a time when the death rate from asthma in New Zealand is increasing, and I sincerely hope that the foundation will receive wide support.

I should like to thank the chairman and council of the Asthma Foundation of New Zealand for funding my tour and for organising it so efficiently and the various asthma societies for their warm hospitality. I am also grateful to the many doctors I met for their advice and guidance. I am particularly indebted to Professor T V O'Donnell of the Wellington Clinical School of Medicine for his constant support and encouragement in what might otherwise have proved a difficult assignment. The views expressed in this report are, however, entirely my own, and I accept full responsibility for any misjudgments I may have made.

References

1 Wilson JD, Sutherland DC, Thomas AC. Has the change to beta-agonists combined with oral theophylline increased cases of fatal asthma? *Lancet* 1981;i:1235-7.
2 Jackson RT, Beaglehole R, Rea HH, Sutherland DC. Mortality from asthma: a new epidemic in New Zealand. *Br Med J* 1982;**285**:771-4.
3 Grant IWB. Has the change to beta-agonists combined with oral theophylline increased cases of fatal asthma? *Lancet* 1981;ii:36-7.
4 British Thoracic Association. Death from asthma in two regions of England. *Br Med J* 1982;**285**:1251-5.
5 Speizer FE, Doll R, Heaf P. Observations on recent increase in mortality from asthma. *Br Med J* 1968;i:335-9.
6 O'Donnell TV. Home nebulisers for asthmatics. *NZ Med J* 1982;**95**:637.
7 Rees HA, Millar JS, Donald KW. Adrenaline in bronchial asthma. *Lancet* 1967;ii:1164-7.
8 Rees HA, Borthwick RC, Millar JS, Donald KW. Aminophylline in bronchial asthma. *Lancet* 1967;ii:1167-9.
9 Crompton GK, Grant IWB, Bloomfield P. Edinburgh emergency asthma admission service: a report on 10 years' experience. *Br Med J* 1979;ii:1199-201.

(*Accepted 5 January 1983*)

MATERIA NON MEDICA

The blue period of Toulouse

Much to our surprise the late summer sky over the capital of Languedoc was grey and the day was cool and windy. "C'est exceptionnel," said Monsieur Bonrepos, the owner of the small hotel where we stayed. But it was a perfect weather for roaming through the narrow crooked streets of the oldest part of the town. We were glad to discover the splendid façades of the ancient houses and the hidden courtyards of imposing dwellings that escaped the disastrous fire of 1463. Richly ornamented gates, flamboyant windows, monumental staircases, elegant towers—most of it, alas, damaged, decrepit, and covered with a black patina of encrusted soot—bore testimony to the former opulence of local merchant princes of the XV and XVI centuries. Their wealth was so great that one of them, Jean de Bernuy, could pay a huge ransom for François I when the latter was captured at Pavia. And yet within a few decades after reaching the summit of its financial power, all this came to an end. The rise and fall of this mercantile society was due to ups and downs of the trade in two vegetable dyes: woad and indigo.

Woad (or "pastel" in French), a yellow-flowered herbal plant (*Isatis tinctoria*) of the family Cruciferae, was well known to ancient Britons, according to Strabo. It was also cultivated in Flanders, Picardy, Tuscany, but especially in the south of France, where it was known under the old name of "guède" or "vouède" (hence woad). Its flowers were used for the treatment of jaundice and fevers. The demand for French woad rose tremendously in the XV century when the permanent blue dye became widely used for clothing and the textile industry. The growers and producers of the French "pastel" used various little-known methods to obtain from the coarse leaves of the plant a dye varying in colour from bright blue to a deep greenish-blue tinge. In the region of Albi the leaves were ground, fermented in water, and shaped for export in the form of melon-sized balls called "cocans." They were loaded on ships in Bordeaux and the precious cargo went to Germany, Italy, Spain, and especially to England. It was from the name of these balls that the by-name of "pays de Cocagne" (land of plenty) came into the French language. Many of the richest merchants in Languedoc were of foreign origin, such as the Basque Cheverry or the Spaniard Bernuy and others. They built magnificent houses in Toulouse, intermarried with the local patrician families, and created a society of great cultural and political influence. The Hôtel d'Assezat, a splendid, palatial residence in Toulouse, was built by the merchant family of that name, made rich through trade in "pastel." It is said that the use of powdered woad, made into painting sticks (crayons), was introduced into Milan in 1499 by a French artist Jean Perréal.

However, in the mid XVI century an excessive production of this dye, together with other causes, led to a drastic fall in its value and many growers and producers were ruined. And then came another more serious event. An exotic plant *Indigofera tinctoria*, known for centuries in India, China, and elsewhere and yielding indigo, an equally permanent rich blue dye, was brought in large quantities into Europe and soon replaced the woad plant. The blue period of Toulouse came to an end.

Although the success of the indigo from the East lasted somewhat longer, it also came to an end after 1882, when the blue dye was synthesized in Germany and soon produced chemically in large quantities.—L J BRUCE-CHWATT, London.