also had to assist at tubal ligations, be present at caesarean sections, and assist in general surgery when the other student was away. It was a busy time, but it taught me a lot.

What I learnt

About medicine: I arrived knowing nothing about obstetrics. I left capable of conducting a normal delivery—in Arabic—and knowing the basic theory.

About the work of a missionary: It cannot be easy living in a compound within a strange culture. It's like living in a fish bowl. But the staff created an atmosphere of dedication to work, high standards, and good fun, and made their visitors very welcome.

About the Arab people: a friendly, volatile, dark-skinned race. They have one of the highest birth rates in the world—families of 10 or 12 children are not uncommon—and two or three times a week Nazareth would be filled with the sounds of a wedding party.

About the Jews: This was why I originally wanted to go to Israel, and in my five weeks at Nazareth any opportunity to talk with Israelis was cherished. For three weeks after finishing my elective I toured Israel and talked with many Jewish people. One

girl I talked to in Jerusalem, whose entire family with the exception of her parents had been wiped out in Nazi Germany, said that in every generation some group will rise up to persecute the Jews and that the maintenance of a Jewish State of Israel is the only way to give the Jews a refuge. After seeing Yad Vashem, the museum of the holocaust in Jerusalem, I can fully appreciate her point of view. This girl—Mia—is in the army and is prepared to die for Israel if need be. This feeling is shared by many Israelis.

Theirs is not an easy life. With inflation at at least 124% every year and three years' army service for men and two for women, with the prospect of future wars, it is a costly thing to emigrate to Israel these days. Many, particularly Americans, get disillusioned and leave, but many more share Mia's view and are prepared to come and live in remote settlements and work for Israel. While this spirit prevails vandalism and delinquency are minimal, and Israel is a challenging and exciting place to be.

On our journey out I told an American girl that I lived in Belfast and was on my way to Israel. She laughed and said that I had a fascination for war zones. Back home in the "safety" of one war zone, I listen with sympathy to news of that other one and hope and pray for courage for Israel's people and wisdom for her leaders, that her future may be good.

Today's Treatment

Clinical pharmacology

The Committee on Safety of Medicines and the prescribing doctor

JAMES CROOKS

To understand the role of the Committee on Safety of Medicines and how its work contributes to that of the prescribing doctor it is helpful to ask what the doctor requires of a new medicine. The first requirement is that the drug should be efficacious in patients for whom the drug is indicated. The second requirement is that the drug should be safe, not in absolute terms since this is rarely possible but rather that the adverse effects produced by the drug should be identified as early as possible together with an estimate of the frequency of their occurrence so that the prescriber can apply a benefit/risk assessment as a component of the therapeutic decision to prescribe. The last requirement is that the quality of the medicine in respect of its formulation, manufacture and physical properties, route of administration, etc, should be of an acceptable standard.

When considering the role of the committee it should be appreciated that it is a statutory committee of independent experts which *gives advice* to the Licensing Authority (Health and Agricultural Ministers) concerning the acceptability of a new medicine to undergo clinical trials or be granted a product licence that would allow it to be marketed. A pharmaceutical

company may appeal, under the Medicines Act of 1968, to the Medicines Commission against this advice.

Thus I have emphasised the advisory function of the committee, but how does it ensure that the prescribing doctor will have available new medicines that are efficacious, safe, and of acceptable quality? It does this in the following way. First of all it subjects a new drug to an assessment procedure before *recommending* that it is given a clinical trial certificate. It then takes into account all the information made available by the sponsoring company including the clinical trial results before *recommending* that it be given a product licence, which allows it to be marketed. Lastly the committee maintains its interest in ensuring that prescribers have safe and effective drugs at their disposal by organising postmarketing surveillance of new drugs in terms of adverse reactions, product manufacturing defects, advertising controls, and the provision of information to prescribing doctors about drug problems as they arise. The committee does much of this work helped by several expert subcommittees.

Clinical trial certificate

Before clinical trials may be performed with a new drug never before available or for a new indication for a drug already on the

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market a company must submit details of the drug to the Committee on Safety of Medicines. To grant a clinical trial certificate the committee must be satisfied that studies of the drug in animals and in human volunteers show adequate promise of therapeutic potential. Special attention is paid to the toxicity of the drug in both the animal and human studies. The former provides data on potential mutagenicity and carcinogenicity that are of particular importance when the chemical group to which the drug belongs, the indications for its use, and the type of drug regimen proposed suggest that there may be a problem. The pharmaceutical aspects of the formulation are also assessed to conform with agreed standards of purity in respect of the drug and other substances in the formulation.

The clinicians and centres carrying out the clinical trial have also to be acceptable to the committee, which has to try to achieve flexibility in its criteria for acceptable clinical trials to avoid inhibiting new drug development. It also has to try to ensure that the results of the trial will provide the scientific evidence that will allow it to reach a satisfactory decision on the allocation of a product licence.

Product licence

In granting a product licence the committee must be satisfied that the doctor can prescribe a drug secure in the knowledge that so far as is reasonably possible the drug has been shown to be both safe and effective as judged by animal studies and clinical trials and that all available evidence suggests that this will be maintained when the drug becomes generally available. It would be reasonable to say that the decision about the efficacy of the drug is usually resolved by the results of the clinical trials, provided the protocol has been satisfactory and the trial well executed.

The question of safety presents greater problems, and the committee goes to great lengths in making decisions over safety, particularly in respect of the extrapolation of toxicological studies in animals to man. Their concern over the problem was manifest by its sponsorship of an international conference on the validity of extrapolating to man the carcinogenic properties of drugs to produce breast cancer in beagle dogs. After consideration of a large amount of evidence the conclusion was reached that the extrapolation was not valid. The amount of effort expended by the committee on problems such as this must be reassuring to both the prescribing doctor and the patient.

Postmarketing surveillance

It has been appreciated in recent years that the price to be paid by the community for having effective drugs made available is that a few of these drugs may produce serious adverse effects, which, though rare, would require removal of the drug from the market—for instance, thalidomide and practolol. It is also clear that toxicological data derived from animal studies may not provide information to predict this and because of the rarity of the reactions conventional clinical trials cannot be expected to do so. It follows that the postmarketing period of drug development should be monitored to detect clinically important adverse effects. Through its adverse reactions subcommittee the committee attempts to do this by its "yellow card" system, in which the doctor is requested to report any suspected adverse reaction that is new or serious. The co-operation of prescribing doctors with the committee has resulted in the British system of voluntary reporting of adverse reactions being the most effective in the world. This view must be tempered by the fact that under 1% of serious previously unsuspected adverse effects are reported under this system—for instance, thromboembolism and the oral contraceptives—and to improve this voluntary reporting system prescribing doctors must recognise their responsibility to report

suspected adverse effects on the yellow cards if both they and the committee are to attain their mutual objective of increased safety of drugs for patients. It should be emphasised that, although summaries of the register of adverse reactions or excerpts from it are available to bona-fide inquiries, the name of the patient and the doctor concerned are always kept confidential. As well as the "yellow card" system the committee monitors adverse reaction reports from a variety of sources including the pharmaceutical industry, other countries through the World Health Organisation, and medical publications.

The committee can also *recommend* that a particular medicine should be given a product licence that will allow it to be marketed but on condition that the sponsoring company sets up a "monitored release" procedure. This means that the company must take special steps, using a method and time scale agreed by the committee, to monitor the use of the medicine in terms, for example, of adverse reactions and the appropriateness of the indications for use. Postmarketing surveillance of a new drug also includes continuing scrutiny of the manufacturing procedure by the licensing authority to ensure the maintenance of pharmaceutical quality.

The committee has also been considering the feasibility of developing new methods for postmarketing surveillance of drugs using, for example, the data provided by the prescription-pricing authority, but the choice of the most appropriate system is difficult because of the need to justify "cost effectiveness." Nevertheless, further developments can be expected on this aspect.

Communication between the committee and the prescribing doctor

An important part of the committee's work is directed towards providing the prescribing doctor with information that will allow him to identify problems that have been derived from "yellow card" reporting or other information sources. The methods of doing this depend on the type of problem and the urgency of finding a solution. For example, leaflets in the "Adverse Reactions Series" are issued to all doctors and dentists when it is necessary to give urgent warnings about an adverse reaction. For less urgent problems the committee chairman usually sends "Dear Doctor" letters, outlining the nature of the problem. When potential future problems in drug treatment are identified by the committee but where there is an absence of conclusive evidence that would allow appropriate advice to be given to prescribers the mechanism of communication used is the issue to doctors of a leaflet headed "Current Problems." The intention of this communication is to inform him of the nature of the problem (perhaps an adverse effect suspected but not conclusively) associated with the administration of a particular drug. It is hoped that the doctors' threshold for the detection of a possible association will change, although it should be emphasised that the interpretation of an increased number of reports after such a communication takes account of the changed circumstances.

The committee not infrequently uses other methods of informing doctors about drug problems—for instance, through the medical press and the manufacturers' publications. In the case of the latter the committee keeps under review the post-marketing performance of new licensed drugs, and if in their view the data sheet, which provides the information the pharmaceutical company must provide to doctors, requires amendment they *recommend* that this should be done. The committee also *advises* the Licensing Authority when, in their view, the promotion of the product, through advertising material, is not compatible with the claims made for the medicine in the data sheet that the committee have accepted as reasonable. The way in which the committee operates and its responsibilities to government, the medical profession, and the public needs to be understood by all three but especially by the prescribing doctor.