For Debate . . .

Compensation and drug trials

The Association of the British Pharmaceutical Industry has last month circulated to member companies guidelines on compensation to patients for injuries incurred in clinical trials of drugs. We publish below the text of these guidelines together; on the next two pages is a commentary on the guidelines by Professors A L Diamond and D R Laurence.

Guidelines: Clinical trials—compensation for medicine induced injury

It is becoming common practice for ethical committees to expect assurance that patients participating in clinical trials will be appropriately compensated, by a simple procedure, should they be adversely affected by reason of their involvement in the trial. While such adverse effects are very uncommon, the Association of the British Pharmaceutical Industry (ABPI) accepts this as a guiding principle and has noted that quite different considerations apply to medicines undergoing clinical trial compared with medicines generally available on prescription. Consequently, in cases where injury is attributable to a medicine in clinical trial, the ABPI recommends to its member companies that the following guidelines should be accepted without legal commitment on the part of the member companies.

(*a*) The company should favourably consider the provision of compensation for personal injury, including death, in accordance with these guidelines but without the requirement for negligence to be proved against the company.

(*b*) Compensation should only be paid when there is a balance of probabilities that the injury (including exacerbation of an existing condition) was attributable to the company's medicine under trial.

(*c*) Compensation should only be paid for the more serious injury of an enduring and disabling character, and not for temporary pain or discomfort or less serious or curable complaints such as skin rashes.

(*d*) These guidelines only apply to injuries to patients involved in clinical trials, conventionally known as phase II or phase III trials, that is to say, patients under treatment and surveillance (usually in hospital) and suffering from the ailment which the medicine under trial is intended to treat. These guidelines do not apply to injuries arising from studies on healthy volunteers (phase I), whether or not they are in hospital, for which separate guidelines for compensation already exist. These guidelines also do not apply to injuries arising from clinical trials on marketed products, except when the trial is on a marketed medicinal product being tested for a prospective indication not yet authorised by inclusion in a product licence.

(*e*) These guidelines apply to an injury whether or not the adverse reaction causing the injury was foreseeable or predictable although compensation may be abated or excluded in the light of the factors mentioned in paragraph (j) below.

(*f*) Compensation should not be payable (or should be abated, as the case may be) (i) when there has been a significant departure from the agreed protocol, (ii) where the injury was attributable to the wrongful act or default of a third party, including a doctor's failure to deal adequately with an adverse reaction, or (iii) when there has been contributory negligence by a patient.

(*g*) Compensation should only be payable to patients receiving the medicine under trial and therefore not to control patients not receiving the trial medicine or to patients receiving placebos, or to patients receiving other non-trial drugs or medicines for the purpose of comparison with the medicine under trial.

(*h*) The giving of consents to participate in a clinical trial, whether in writing or otherwise, should not exclude a patient from the benefits of compensation or in any way prejudice his position under the guidelines, although compensation may be abated or excluded in the light of the factors mentioned in paragraph (*j*) below.

(*i*) No compensation should be paid for the failure of a medicine to have its intended effect or to provide any other benefit to the patient. This includes the failure of any vaccine or other preparation to provide the preventive or prophylactic effect for which it is under trial and the failure of any contraceptive preparation or device to prevent pregnancy.

(*j*) The amount of any compensation paid by the company should be appropriate to the nature, severity and persistence of the injury. However such compensation may be abated, or in certain circumstances excluded, in the light of the following factors (on which will depend the kind of risk the patient should be expected to accept): (i) the seriousness of the disease being treated, the degree of probability that adverse reactions will occur and any warnings given; (ii) the hazards of established treatments relative to those known or suspected of the trial medicine; and (iii) the availability and relative efficacy of alternative treatments that the patient could have had if he had not volunteered for the trial.

Note: This guideline assumes that the level of any compensation paid will depend upon the circumstances in the light of the factors mentioned above. As an extreme example, there may be a patient suffering from serious or mortal disease such as cancer who is warned of a certain defined risk of adverse reaction. Participation in the trial is then based on an expectation that the benefit:risk ratio associated with participation is better than that associated with alternative treatment. It is, therefore, reasonable that the patient accepts the high risk and should not expect compensation for the occurrence of the adverse reaction of which he or she was told.

ASSOCIATION OF THE BRITISH PHARMACEUTICAL INDUSTRY

Commentary

We welcome the public acceptance by the Association of the British Pharmaceutical Industry (ABPI) of the "*guiding principle*" that member companies should accept responsibility to compensate patients adversely affected by involvement in clinical trials of medicines before marketing and in trials of marketed products for new indications. The above guidelines should render easier the work of ethics committees in fulfilling their function of protecting patients. But our experience as members of an ethics committee[1] leads us to think that it will be useful if we attempt to clarify several points in these guidelines.

Need for the guidelines

Small though the risk is, the possibility of adverse effects resulting from participation in a trial cannot be ignored. The present law gives a patient the right to compensation only if someone has been negligent—has failed to take reasonable care. Since all practicable precautions are likely to have been taken, a patient who suffers from a trial is probably without any legal remedy. Generally the pharmaceutical company's insurance policy will not help, because that normally covers only legal liability—that is, negligence.

Ethics committees have been troubled by this, and some have sought assurances from pharmaceutical companies that patients adversely affected should be adequately compensated. It is unfair that this random risk should fall on an unfortunate individual when the trial is conducted for the benefit of all. Our experience in the clinical research ethics committee of University College Hospital and University College London has been that major companies have accepted their responsibility for the welfare of subjects in the trials they sponsor. These guidelines now reflect the acceptance of the pharmaceutical industry as a whole of this attitude, thus mitigating the inadequacy of existing legal provisions.

Without legal commitment

Given this inadequacy, and in the absence of special legislation, the only way a legally enforceable commitment to individual subjects could be entered into would be by a contract with each patient. The complexities of the law of contract are such that most members of the medical profession would regard such a cumbersome procedure—from which most patients, suffering no harm, would not ultimately benefit—as inadvisable and unworkable. The guidelines do not therefore rely on legal enforcement but represent a genuine commitment to researcher and institution to compensate patients as necessary.

Favourably consider

Guideline *a*—"The company should favourably consider"—taken with "without legal commitment," might be thought at first sight to offer nothing. But the choice of words is important. The deliberate use of "favourably," taken with the acceptance of the guiding principle that patients should be appropriately compensated, clearly denotes an intention that compensation should be provided.

Without requiring negligence to be proved

Guideline *a* requires the provision of compensation "without the requirement for negligence to be proved against the company." This does *not* mean that compensation depends on the existence of negligence, and that the concession is merely to dispense with proof. The legal background (see "Need for the guidelines" above) makes it abundantly clear that compensation is to be awarded whether or not there has been negligence. Proof of causation (see "A balance of probabilities" below) will be sufficient. This meaning is reinforced by guideline *e*, because foreseeability or predictability would be relevant to the existence of negligence but are expressly excluded as factors determining the obligation to compensate.

A balance of probabilities

Guideline *b* simply means that the clinical trial must be the cause of the injury. Proof of causation on "a balance of probabilities" is the ordinary criterion used in the civil courts in this country. There is no presumption that because something happens to a subject participating in the trial, it must have been caused by it. Causation depends on the inference to be drawn from all the circumstances of the particular case. There is, however, the important question of how the "balance of probabilities" is to be decided.

A simple procedure

The introductory words of the ABPI statement accept that as part of its "guiding principle" there should be "a simple procedure" for determining appropriate compensation. The courts of law are not a simple procedure, and the absence of legal enforceability effectively excludes recourse to the courts anyway.

The contract recommended by the ABPI for healthy volunteers (see "Healthy volunteers" below) does contain a simple procedure in which, in the event of dispute, the president of one of the royal colleges appoints an arbitrator on the medical aspects with power to consult a barrister of 10 years' standing on the amount of compensation. Given the fundamental legal principle that "no man shall be a judge in his own cause" there can be no doubt that the ABPI intends this or something close to it for any disagreement on the operation of these guidelines.

The medicine under trial

Guideline *b* speaks of a balance of probabilities that the injury "was attributable to the company's medicine under trial." We hope this is intended to refer to the whole of the trial procedure, for an attempt to limit responsibility to proved action of the medicine alone would not only introduce a legalistic interpretation inconsistent with the non-legal nature of the statement; it would also appear to be inconsistent with the "guiding principle" of compensation of patients "adversely affected by reason of their involvement in the trial." For example, injury can occur from special investigations used to monitor the patient's progress without any negligence on the part of the medical or nursing staff, investigations that would not have been carried out but for participation in the trial. We feel justified in assuming that the broader interpretation is the one that would be used in the event of such injury, despite the title of the guidelines and especially in the light of the contract for healthy volunteers (see "Healthy volunteers" below).

Guideline *g* would exclude from the scheme patients who do not receive the medicine under trial. We do not think it is fair to deny compensation to any patients who could be shown to have suffered injury by reason of the withholding of treatment as a consequence of participation in the trial, whether or not they are given a placebo. Despite the wording of guideline *g*, we cannot believe that it is the intention of ABPI to exclude such cases. We do not suggest that the scheme should cover injury caused by standard treatment used for evaluation of comparative efficacy.

Healthy volunteers

Guideline *d* excludes healthy volunteers from these guidelines. They are already covered by the ABPI recommendations published in June 1970 relating to staff volunteers employed by

the companies themselves. We understand that the ABPI considers that those recommendations should (pending their revision) apply to all healthy volunteers, including those in the investigating institutions. For healthy volunteers a separate contract with each volunteer is feasible, and the draft contract recommended in 1970 is admirable. It rightly provides for compensation for injury "caused by my participation in the experiment/trial/test," with no restriction to injury caused by the drug alone (see "The medicine under trial" above).

Negligence of others

Guideline *f* excludes or reduces the right to compensation where the injury was caused by the negligence of medical, nursing, or supporting staff not in the company's employ. It is not appropriate that companies should cover the responsibility of these others, and the patient will have legal remedies against them if they have been negligent. The suspicious may argue that *f*ii, by adding to wrongful act or default—that is, negligence—the phrase "including a doctor's failure to deal adequately with an adverse reaction," is attempting to refer to cases where the doctor has not been negligent, but we do not believe this to be the intention; we think this is merely to ensure that a doctor's negligent failure to deal with an adverse reaction is included in the concept of wrongful act or default.

Therapeutic failure

Guideline *i* excludes compensation where, in a trial, there is "failure of a medicine to have its intended effect. . . ." This is generally acceptable, for exploration of a new medicine unavoidably carries the possibility of therapeutic failure as well as of injury. Generally, comparative efficacy—that is, efficacy in relation to other drugs (see "Abatement or exclusion of compensation" below, in reference to guideline *j*iii)—takes years to establish at all precisely and in practice there are unlikely to be serious problems in this area. But failure of a contraceptive is singled out for special mention in the guidelines. Where a woman agrees to use a new contraceptive she is agreeing to forgo a treatment that is nearly 100% effective when properly used, and failure will affect the rest of her life. We feel uneasy that she should be deprived of any possibility of compensation for failure of efficacy by application of a blanket rule. This is plainly a difficult area and one where understanding consent is particularly important.

Since a woman participating in a clinical trial of a new contraceptive is not suffering from any ailment (see guideline *d*), we think that the procedure used for healthy volunteers is more appropriate; in other words, this is one situation where it would be right to negotiate an individual contract between each trial subject and the pharmaceutical company.

Amount of compensation

Although guideline *j* does not expressly say so, we think it can be taken that the amount of compensation should be in line with the amounts awarded for similar injuries in the civil courts. This is why we think it would be right to consult an independent lawyer if there is any disagreement with regard to the amount (see "A simple procedure" above).

Abatement or exclusion of compensation

Guideline *j* goes on to suggest that the compensation may be abated (or in certain circumstances excluded) in the light of three factors, together to be taken into account. This again is a difficult area, and since the criteria plainly require the application of delicate judgment here is an added reason why the "simple procedure" should include provision for arbitration.

The note at the end of guideline *j* clearly covers all three factors. Although it is said to be an extreme example, it may well be the only example of consequence. Certainly one would not expect the relative efficacy of alternative treatments (subparagraph iii) by itself to lead to a reduction in the amount of compensation for injury.

Conclusion

We have been aware for several years of the need for a general policy on industry sponsored trials of new drugs and of old drugs for new uses. The ABPI guidelines contain some uncertainties that must be of concern to ethics committees. We have therefore sought to interpret the intentions in the light of the "guiding principle" and our previous experience in dealing with members of ABPI in a way that will be helpful to committees reviewing proposals for clinical trials. If our interpretations are correct, we consider that in the present state of the law ethics committees can be satisfied that they are providing properly for the welfare of patients if a sponsoring company is able to answer "Yes" to the question "Does your company accept the ABPI guidelines *Clinical Trials—Compensation for Medicine Induced Injury?*"

A L DIAMOND

Professor of Law,
Institute of Advanced Legal Studies,
University of London,
London WC1B 5DR

D R LAURENCE

Professor of Pharmacology and Therapeutics,
School of Medicine,
University College,
London WC1E 6JJ

[1] Ethical Committee, University College Hospital. Experience at a clinical research ethical review committee. *Br Med J* 1981;**283**:1312-4.

(*Accepted 24 August 1983*)

What is the difference in the action of prednisone and prednisolone in the treatment of acute bronchial asthma attack and in rheumatic conditions such as myalgia rheumatica?

Corticosteroids such as prednisone and prednisolone inhibit the inflammatory response without affecting the underlying disease process in both bronchial asthma and the rheumatic diseases. The precise mechanism by which they produce their anti-inflammatory effects is incompletely understood but, among other actions, they inhibit the production of arachidonic acid from membrane phospholipids and thus inhibit formation of inflammatory prostaglandins and leukotrienes.[1] In the rheumatic diseases their beneficial effect is probably due to inhibition of both the early phenomena of the inflammatory process such as oedema, vascular permeability, fibrin deposition, and leucocyte migration and the later manifestations such as fibroblast proliferation and deposition of collagen. The mode of action of corticosteroids in bronchial asthma is not fully understood. Suppression of the acute inflammatory response reduces bronchial mucosal swelling but there may also be other factors. For example, prostaglandins and leukotrienes are generated during contraction of bronchial smooth muscle in response to histamine and immunological challenge; and prostaglandin $F_{2\alpha}$ and some leukotrienes are bronchoconstrictors. In addition, corticosteroids potentiate the effect of adrenergic stimulation on bronchial smooth muscle, and there is some evidence that they can restore catecholamine responsiveness in asthmatic patients with beta-adrenoceptor agonist induced desensitisation.[2]—LINDA BEELEY, consultant clinical pharmacologist, Birmingham.

[1] Black AK, Greaves MW, Hensby CN. The effect of systemic prednisolone on arachidonic acid, and prostaglandin E_2 and $F_2\alpha$ levels in human cutaneous inflammation. *Br J Clin Pharmacol* 1982;**14**:391-4.
[2] Hui KKP, Conolly ME, Tashkin D. Reversal of human lymphocyte β-adrenoceptor desensitisation by glucocorticoids. *Clin Pharm Ther* 1982;**32**:566-71.