metabolic fate and direct and indirect biological properties as those of the intended protein. Many such tests depend on comparisons with reference preparations.⁷ Tests are also made for undesirable impurities, which may include residual proteins from the host organism, pyrogens, contaminating viruses, and residual DNA.

The first host organism used to produce human insulin by recombinant DNA technology was *E. coli*. In this organism the protein is not folded with the correct s-s bonding and is retained within the bacteria, so it requires extensive and costly purification from a mass of dead bacteria. Yeast cells secrete proteins (making purification simpler), but inadvertent polymannose glycosylation may occur, giving rise to strongly antigenic impurities; purification must be scrupulous, and the product yield is less. Mammalian cell lines can make natural human proteins with the correct s-s folding and glycoproteins, but their use requires exacting culture conditions. The cells must be free from pathogenic viruses; and scientists have been gravely concerned about the possible hazard of traces of residual DNA that might be oncogenic. This last issue was tackled definitively in a report from the World Health Organisation, which describes the reasoning and calculations whereby a limit of 100 pg of DNA per dose may be regarded as safe⁸ (current products contain less than 10 pg for each dose).

Many medically valuable substances—such as gonadotrophins—are glycoproteins. Animal cells can make glycoproteins that are similar but probably not identical to human glycoproteins. Their detailed molecular structure is too complex for routine analysis with present methods, and evidence for their identity relies heavily on comparison tests with reference materials. Clinical experience with erythropoietin made in Chinese hamster cells suggests, however, that it is scarcely immunogenic.^{9,10}

The toxicology of products made by recombinant DNA technology also presents new problems. Proteins identical to normal human components whose actions are well known—for example, insulin—require little toxicological study. Substances hitherto in short supply—such as human growth hormone—may need further study to understand their natural effects, especially as they are coming to be used for more and different indications. Novel substances, including modified natural proteins and monoclonal antibodies, need fuller toxicological study. The design and interpretation of tests must take into account that human proteins are antigenic in laboratory animals; suitable transgenic animals that tolerate human proteins may be useful for long term tests. The toxicology of cytokines—such as interferons and interleukins—presents special problems since natural ones are produced and act locally in cells and tissues, and it may be misleading to study the effects of testing such products after they have been given systemically.

All these aspects—the newest methods of synthesis, production, purification, characterisation, safety, and control—were excellently reviewed at a Banbury conference on therapeutic peptides at Cold Spring Harbor in 1987 and are due for publication this spring. Various national and international guidelines are being drafted, all based on similar principles.¹¹ Ultimately the safety of the products depends on good science, common sense, and adaptability for this exciting, fast developing methodology.

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Lateral thinking in gynaecology

As students we are taught how to examine patients, and during the early postgraduate years our techniques of clinical examination are refined and reinforced by regular use. Soon our methods become fixed, personal to each doctor and almost immune from criticism. The more basic a clinical skill the less likely it is to be objectively reviewed. Obstetricians and gynaecologists, however, are now accustomed—almost addicted—to self assessment, and a recent survey by Amias has looked at a fundamental aspect of gynaecology: the position of the patient during pelvic examination.¹

Fifty years ago English textbooks stated that “in this country it is customary to make vaginal examinations with the patient lying in the left lateral position,”² though parts of the examination were carried out with the patient lying on her back³ or in the lithotomy position.² Nowadays, according to Amias, 45% of British gynaecologists never use the lateral position for bimanual or speculum examination. Another 29% use it in some circumstances, particularly for examining vaginal prolapse, but their first choice is the dorsal position. Of the remaining 26% who prefer the lateral position, half use it for both bimanual and speculum examination and half for speculum examination only. After more than a century of use Sims's speculum is preferred by only a minority, and about 85% of British consultants use a bivalve speculum in all circumstances.

These variations seem to be related not to open minded experimentation but to geography and the age of the gynaecologist. In Scotland the lateral position is hardly ever used,¹ and the dorsal position is generally preferred in Scottish textbooks.^{4,5} In England the lateral position tends to be preferred by older consultants and those practising in the Liverpool region and the south.¹ Although this distribution may be chance, Amias suggests that it probably reflects the influence of the local university. English textbooks now describe several positions for pelvic examination, commenting that “each has its advantages and disadvantages”⁶ and “strict adherence to one position is limiting.”⁷

British gynaecologists have always agreed that patients are embarrassed by the lithotomy position, which is routinely used for examining unanaesthetised women in Europe and America.^{2,6,8} Nevertheless, both “dorsalists” and “lateralists” claim that their preferred position is less upsetting for the patient. It has been suggested that the dorsal position is particularly embarrassing at a teaching clinic,⁷ but pelvic examination should now be taught “on a 1:1:1 (doctor:

student:patient) basis.”¹ The dorsal position allows eye contact between doctor and patient, and most gynaecologists think that this reassures women rather than increasing their embarrassment. Nevertheless, the lateral position may be more acceptable for shy or nervous women, young girls, older unmarried women, and women from some ethnic minorities.¹ Although the teaching of pelvic examination to students has been studied,^{9,10} there is surprisingly little objective information about its effect on patients.

Bimanual palpation is easier in the dorsal position,¹¹ but the lateral position is useful for assessing prolapse and for examining patients with limited hip abduction or with cardiac or respiratory disease.¹ Examination in both positions should continue to be taught to undergraduates and particularly to postgraduates. Doctors preparing for higher qualifications in gynaecology should know that they may encounter an examiner who thinks that examination in the lateral position is a skill that must not be allowed to disappear.

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Second opinions

In Britain the request for a second opinion comes sometimes from a general practitioner but more often from patients or their relatives. In the United States it is often the patient's insurer who asks for a second opinion, and a recent study has suggested that second opinions on the need for coronary artery bypass operations could reduce operations from 200 000 to 175 000 annually with a saving of more than \$500m.¹ Are second opinions thus to be encouraged, and will we see more of them in Britain?

Second opinions are sought for many reasons. The patient or the patient's relatives may be so concerned at the diagnosis and its potential prognosis that the first opinion is unacceptable or not fully comprehended unless confirmed by another expert—preferably “well known” or “recognised.” The proposed treatment may be perceived as too radical or wrong considering the patient's age or physical state; some alternative, less threatening, measures are hoped for. Interpersonal difficulties may be the reason for the second opinion or patients may think that the first consultant did not give enough time for full discussion of their symptoms. The physical examination may be deemed insufficiently exhaustive. The consultant may appear not to have understood the problem fully or to have paid too scant attention to the investigations already done by the general practitioner.

In rare instances the patient and the consultant simply do not “get on” for reasons that are often undefinable without psychological delving. Another common reason for seeking a second opinion is that the prescribed treatment has failed or the degree of improvement has fallen short of the patient's expectations. On the rare occasions when family practitioners suggest a second opinion they do so either because they sense the patient's dissatisfaction or have strong opinions of their own at variance with those of the consultant.

There are no rules about first or subsequent opinions, but over the years the profession has evolved conventions of etiquette, which for the good of the patient and the profession should not lightly be disregarded.² Only for exceptional reasons should a consultant see a patient without formal referral from the general practitioner, although this is difficult to ensure with foreigners. It has been claimed that to ignore this convention offers a convenient escape route for British patients who feel dissatisfied with their general practitioner or local hospital,³ but such action may lead to problems. If medication is necessary this will have to be prescribed by the general practitioner; if the patient is medically insured and expects to be reimbursed for a private consultation the insurance company will insist that the referral is initiated by the general practitioner. Without proper referral the consultant may be incorrectly informed about the patient's previous illnesses, medication, or investigations. The second opinion must always be communicated to the patient's general practitioner and in most instances to the giver of the first opinion.

Older consultants usually give more second opinions than younger ones, and for some senior consultants 10% of their consultations may be second opinions. Dermatologists, because of the unpredictable response of skin disease, orthopaedic surgeons, mainly in relation to back pain or osteoarthritic hips, and oncologists may see many patients seeking a second opinion on treatment, while physicians are more likely to be consulted when the diagnosis is in doubt.

How are the benefits of a second opinion assessed—from the patient's peace of mind, the outcome in terms of quantity or quality of life, or savings in the financial cost of the treatment advised? A more precise answer to one of these questions is beginning to come from the United States, where health insurance companies have observed wide differences among communities in the incidence of, for example, hysterectomies and coronary artery bypass operations. To reduce the cost of “unnecessary” operations in cases where the indications are controversial the insurer will pay for a second opinion, which the patient may or may not accept.

In a recent study in Boston 88 patients—all of whom had had coronary arteriograms and had been advised to have bypass operations—sought a second opinion.⁴ Continuation of medical treatment with certain adjustments was advised in 74. Sixty of the 74 accepted this advice, which was assumed correct because there were no deaths during a mean follow up of 28 months. At the end of the follow up over two thirds of these patients were actively and fully employed, although two had developed new myocardial infarcts. Of those in whom the need for an operation was endorsed a tenth had died and a fifth had had new infarcts at the end of the follow up; only just under half were actively and fully employed.

This example emphasises some of the ethical and practical difficulties inherent in giving a second opinion. Although technically complicated indications apply to coronary artery bypass operations, every disease in any patient has its special and unique features. How is the patient to choose between