of chronic disorders, including rheumatoid arthritis (not certainly attributable to erythropoietin deficiency),^{38,39} and neoplastic disease are possible candidates. Other more speculative uses include treatment of the anaemia of prematurity⁴⁰ and to replace the need for homologous transfusion after surgery or increase donations for autotransfusion⁴⁰; stimulation of production of fetal haemoglobin in sickle cell anaemia, thereby reducing the tendency to develop sickling crises⁴¹; and its administration (possibly combined with other colony stimulating factors) to provoke bone marrow regeneration in hypoplastic anaemias (whether primary or as a result of cytotoxic or other therapy).⁴²

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Safety and the therapeutic protein products made by genetic engineering

Recombinant DNA technology is now being used to produce large amounts of well known proteins, such as insulin, growth hormone, hepatitis vaccines, erythropoietin, and interferons, and also various novel substances, such as trace labelled monoclonal antibodies. Ensuring the safety of these products has presented new problems. Human insulin, the first product made by recombinant DNA technology to be licensed, is injected daily by millions of diabetics, and the criteria for its correct structure, purity, and safety are particularly exacting. In Britain good collaboration by the manufacturers, the National Institute for Biological Standards and Control, and the biological subcommittee of the Committee on Safety of Medicines helped to identify principles for the safe production and control of human insulin made by recombinant DNA technology, and in 1982 Britain was the first country to license the product. In 1983 the World Health Organisation then published guidelines for the quality control of biological substances produced by recombinant DNA technology¹; these depend on sound control during manufacture and independent scrutiny of successive batches, which in Britain is done at the National Institute for Biological Standards and Control.²⁻⁶

The production of these substances starts with the assembly of the necessary DNA sequence in a plasmid. The DNA includes coding for the intended polypeptide and "start," "stop," and "promoter" peptides and for antibiotic resistance and other characteristics designed for conditions of bulk culture. The assembled DNA sequence is inserted into host cells, usually *Escherichia coli*, a yeast, or a mammalian cell line. The cloned cells are then characterised in great detail and carefully preserved in ampoules as the primary seed pool. Samples of it are used to start each successive bulk culture, now carried out in thousands of litres. Although host cell mutations may occur rarely during bulk culture, any aberrant forms of the protein would almost certainly be detectable with present test methods. Purification of the protein product is much helped by the new methods of preparative chromatography. Steps to confirm the molecular identity and purity of the end product include tests for its immunological identity and for its physicochemical properties, using electrophoresis, isoelectric focusing, high performance liquid chromatography, mass spectrometry, peptide mapping, and other methods. Biological tests *in vivo* are essential to show if it has the same

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: