INFORMATION FOR MEMBERS
FROM THE
PARLIAMENTARY OFFICE OF SCIENCE AND TECHNOLOGY

BRIEFING NOTE 4
JULY 1989

IMPLICATIONS OF NEW TECHNOLOGIES IN CLINICAL TESTING

In the last fifteen years, there has been a revolution in our ability to test for a large and increasing range of diseases and indicators of human health. Simple tests which can be used in the laboratory, office or home have sprung from basic research in molecular biology and immunology, two areas in which the UK has been particularly active.

This technology has already had a major impact on the organisation of health services in some countries, though not yet in the UK. Screening for diseases or for susceptibility to disease is becoming possible. Some potential applications, however, raise ethical issues. These include the possible use of screening for workplace and insurance purposes, and issues associated with diagnosis of genetic disorders.

This Briefing Note describes the technologies concerned and their status in the UK, and highlights some of the issues which may be of interest to Parliamentarians.

NEW BIOLOGICAL DETECTION TECHNOLOGIES

What use are they?

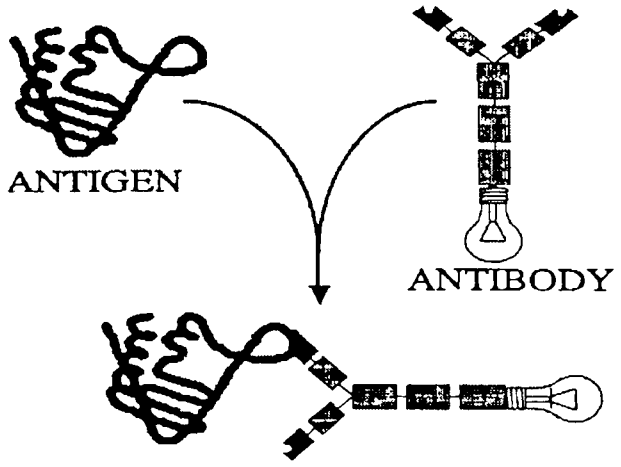
The examples below illustrate just some of the applications of the hundreds of test kits now available:

- Past methods of pregnancy testing have included regular witches' brews with urine extract injected into female toads and days or weeks of waiting for the results. Now a simple colour change on a stick in 3 minutes provides an answer only days after conception.
- Some cancers are not life-threatening if diagnosed early enough. New diagnostic tests detect the presence of cancerous cells before symptoms occur, improving survival rates.
- Traditionally, identification of organisms responsible for food poisoning took days or weeks - too slow to guide treatment. Diagnostic tests now track down contaminating organisms like *Listeria*, *Legionella*, *Salmonella* in hours.
- The AIDS-related virus HIV, like some other sexually transmitted diseases, does not show up in standard microbiological tests. Without these new technologies, testing for infection and screening the blood supply would be impossible.

How do they work?

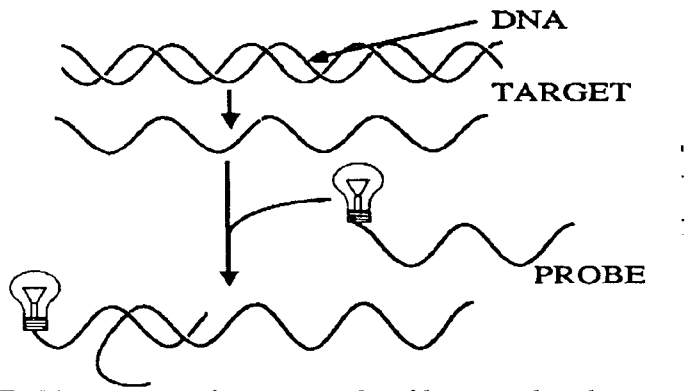
This note describes two main types of testing technology - **immunoassays** and **DNA-probes**. Both arose from the many breakthroughs which basic research in molecular biology has made since the structure of DNA (human genetic material) was discovered at Cambridge in 1956.

Immunoassays exploit our knowledge of the way our immune system works.This fights disease by making antibodies which are specifically designed to fit a unique characteristic of an invading bacterium or virus. Nobel prize winning work at the Laboratory of Molecular Biology at Cambridge in 1975 made it possible to produce large quantities of antibodies that will only react with specific disease organisms or other important health factors such as proteins and hormones. See Box below.



Microbes, viruses, proteins and other substances have external characteristics (antigens) which allow them to be recognised. Monoclonal antibodies can be produced which recognise a specific antigen and which bind strongly to it. Antibodies can be linked to a 'label' molecule (one that is radioactive or fluoresces under ultraviolet light), so that any antibody-antigen complexes which form can be detected.

DNA-Probes are a more recent development. They also detect bacteria or viruses, but through unique structures in the organism's DNA. Consequently they can detect some conditions inaccessible to antibody-based tests, and are able to differentiate disease-carrying and disease-resistant strains of bacteria and viruses from harmless ones. DNA-probes can also be used to find out if an individual's DNA contains genes (particular sequences of DNA) which are responsible for genetic diseases or predisposition to disease. See Box below.



DNA consists of two strands of long molecules entwined together, each one carrying the unique code of life for that individual. To find out if the sample contains the code for a gene that causes a disease, the two strands of DNA can be separated and broken up into shorter lengths. A DNA-probe is added consisting of the DNA sequence which corresponds to the target gene, linked to a labelling molecule (radioactive or fluorescent). If the sequence is present in the sample DNA, the probe itself entwines with the sample DNA and the combination can be detected by the label. Recent breakthroughs allow a **single strand** of DNA to be detected through a process known as the **polymerase chain reaction.**

ISSUES RAISED

Immunoassays and DNA-probes have two distinctive features. Many are quick and easy to use, which makes testing by non-specialist staff away from the laboratory possible. They are also capable of detecting many conditions that were hitherto undetectable. Their consequent potential for widespread use raises the following issues.

Point of Delivery of Health Care

Much clinical testing need no longer be limited to centralised hospital laboratories; routine tests can be carried out by non-specialist staff in doctors' offices - often on a while-you-wait basis. In the USA, over 25% of out-patient testing is now conducted in this way. In Europe, groups of doctors get together to set up their own local testing facilities. By contrast, testing in the UK is still the main preserve of the regional laboratories of the NHS.

Would it be desirable to encourage the same trends here? On the one hand, office testing may be more efficient, since it avoids the administrative and social costs of delays in sample collection, dispatch to lab and receipt of results. It may also make a second patient visit unnecessary, thereby reducing the demands on doctors' time. Where hospital stay is involved, a reduction may be possible in the number of beds occupied by patients waiting for results.

On the other hand, experience has shown that when local test facilities are available, more tests tend to be carried out. This leads to a short-term increase in costs, before the system can take advantage of the potential for savings elsewhere. Doctors may also be placed in a quandary over when and when not to test. Reimbursement practices and fear over liability have led to extensive testing in the USA and large increases in costs, leading insurance companies to tighten control over test fees. Studies have also shown that the accuracy of results can vary when tests are carried out at many different locations and by different operators. Special procedures may thus be required to check on the accuracy of local tests.

Changes to allow the expansion of testing by GPs were recommended by the Advisory Council on Applied Research and Development (ACARD) in 1986 and by the National Economic Development Office (NEDO) in 1987. This would require a mechanism for reimbursing doctors for the costs of local testing. The White Paper on the Health Service, which makes provision for local budgets, could allow GPs this flexibility.

Regulation

These tests are carried out on samples in the lab (*in vitro*), so patients are not exposed to test reagents. Since, however, proper medical treatment may depend on accurate and reliable test performance, some countries have decided to regulate. The US FDA (Food and Drugs Administration) has to approve all tests before sale. In Europe, a variety of mechanisms operate ranging from no control to formal registration requirements. The UK has no specific control over manufacture or marketing and *in vitro* diagnostic tests are not currently included in the Manufacturers Registration Scheme guiding NHS purchases. Though ACARD and NEDO recommended that DHSS extend the MRS to cover diagnostic tests, there are no plans to do so. The Department of Health prefers to encourage voluntary compliance with standards set by the International Standards Organisation (ISO 9000). Harmonisation of European regulations is being looked at by the relevant trade associations.

Commercial development

The UK has been among the leaders in the basic scientific research. How far has this led to wealth creation in the UK?

Clinical testing is big business. Its worth worldwide approached $10 000m in 1987. Antibody-based tests are the fastest growing sector, approaching $1 000m. The USA is the largest market with over 200 FDA-approved tests based on immunoassays or DNA-probes. Because of the size of its home market, and the large amounts of venture capital available for high-tech companies, hundreds of companies are active in the US and are well placed to export to other markets.

In the UK, only a few companies are active, and their turnovers are small in comparison to those of their foreign competitors. NEDO attributed this *inter alia* to:

- The small UK market (£100-150m) - the result of a low per capita spend and the policy of centralised testing. This makes it difficult to obtain backing for new ventures since manufacturers must export from day one, whereas in other countries significant income can be generated in the home market first.

- The in-house development, manufacture and distribution of diagnostic kits and chemicals by some hospital and public health laboratories. Although DHSS guidance on charging exists, manufacturers argue that such products are not fully costed and comprise a form of subsidised competition, restricting the home market even further. The recent Health Department initiative on generating income from the sale of NHS services may have an effect on this.

Though the NEDO and ACARD reviews made a number of recommendations to DHSS and DTI for actions to help the industry, the majority of these have not been taken up. The UK diagnostics industry continues, but the recent sale of two of the few UK diagnostic start-up companies to an overseas company may indicate continued difficulties. Some also believe that the limited UK market may have contributed to the decisions of a number of US diagnostics companies to set up their European subsidiaries outside the UK.

OTC testing

Many tests are simple enough to be sold over-the-counter (OTC), mainly by pharmacies. So far, tests for pregnancy, fertility, blood glucose levels (for diabetics), cholesterol blood levels and colonic cancer have been marketed. Tests for throat and urinary tract infections are future possibilities. Some tests (eg pregnancy) can be self-administered in the home; others are conducted by the pharmacist.

Advocates of OTC testing point to the benefits gained from an increase in health awareness and screening for potential illnesses which, when diagnosed early, are readily treated or even avoided. For example, early warning of elevated cholesterol levels could allow dietary control to be used to reduce the threat of heart attack. Pharmacists see OTC testing for indicators such as cholesterol as an extension of their role in illness prevention and health promotion.

Others are concerned over the potential for incorrect self-diagnosis and treatment in the absence of advice from the doctor. Tests alone rarely allow a conclusive diagnosis; some also produce a proportion of false positive and negative results. The implications of causing false alarm or complacency must therefore be considered. Regulatory bodies in the US are thus proceeding cautiously on OTC authorisation and have not approved proposals for self-testing for some sexually-transmitted diseases and for HIV, due to concern over possible mistakes in their use and over the results being interpreted and acted upon without medical advice and counselling.

In the UK there are no restrictions on tests for OTC sale other than those applying to all goods for sale.

Genetic testing

Limited genetic testing has been practised for some time (eg for Down's syndrome). However, the development of DNA-probes means that once a gene or genes responsible for a genetic disorder have been identified, a test may be developed. Table 1 lists genetic diseases which are expected to be capable of detection by commercially available DNA-probes within the next few years. In addition, progress is expected on understanding the genetic component of other common diseases such as Alzheimer's disease, diabetes and heart disease.

TABLE 1 : Some DNA-Probe tests for inherited diseases under commercial development

Adult polycystic kidney	Cystic fibrosis
Duchenne muscular dystrophy	Polyposis (familial)
Hypercholesterolemia (familial)	Neurofibromatosis
Huntington's chorea	Sickle cell anemia
Retinoblastoma	Thalassemia

Although such testing is still very much in its infancy and largely confined to specialist clinics and hospitals, certain ethical questions have already been raised, both in the press and by professional associations. It is only possible to touch on these briefly in this note; they include:

Diagnosis irrespective of treatment? Since many genetic diseases have no cure, some have argued that genetic tests should only be used when action can be taken on a positive result - either through medical treatment or changes to lifestyle. Alternative opinion holds that, with proper counselling, individuals should have the right to know with certainty what their future holds.

Pre-natal diagnosis. Current genetic testing relies on sampling the amniotic fluid, placental cells or fetal blood in mid-pregnancy. Identification of a serious genetic disorder may

lead to a decision to terminate the pregnancy. It is difficult to predict the effect that new genetic tests would have on the frequency with which parents consider termination of pregnancy. Some tests could provide precise genetic information to replace the probabilities (1 in 2, 1 in 4 chances) that parents must currently weigh, and reduce parental uncertainty accordingly. The opposite could occur if tests become widely available for genetic disorders which it has hitherto been impossible to quantify, thus extending the circumstances under which some parents could consider termination. In this respect, however, it is anticipated that pre-natal diagnosis would continue to be restricted to life-threatening or seriously disabling diseases.

Recent developments in test sensitivity and in handling the human fertilised eggs and pre-embryos *in vitro* hold out the possibility of screening for some genetic disorders only days after fertilisation when the egg has grown to only 8-16 cells. *In vitro* fertilisation techniques require the collection and fertilisation of several eggs; only 2-3 of these can be returned to the mother. It would be possible, therefore, to select and implant only those free of the serious genetic defect in the parents' genes. This procedure may be acceptable to some religions opposed in principle to abortion.

Confidentiality. Information on the genetic makeup of an individual would be very sensitive and there is concern over the potential for discrimination on the basis of a genetic defect. Safeguards on the use and transmission of such information must therefore be considered. It has been suggested that the results of genetic testing should initially only be available to the person undergoing the test.

Screening

As cheap tests become available, it becomes possible to consider widespread screening for particular health conditions. This could form part of a public health programme. In addition, tests could be used to assess risks in health or life insurance or in the workplace.

Public health screening could establish the frequency of infection by certain disease organisms (eg HIV), or allow detection of latent diseases or susceptibility to disease as part of a greater emphasis on preventative medicine.

Currently, applications in this field are limited by two factors. Firstly, most tests have limited predictive value in the absence of clinical symptoms (up until now, most have been used for making a diagnosis when disease is already indicated, and for monitoring the state of the disease during treatment). Secondly, most tests give a certain proportion of false positive and negative results. Even a small number of false positives can seriously reduce the usefulness of tests in screening low-risk populations.

The HIV test illustrates this point. Its specificity and sensitivity are good enough for use as a screening test to safeguard the blood transfusion supply and for establishing the extent of infection of high-risk groups. However, when it is used for screening large numbers of low-risk individuals, there are so few cases of true infection that the constant level of false positive results given by the test can swamp the true positive readings. Each screening test positive result needs to be followed by a more expensive and time-consuming confirmatory test. The cost of these confirmatory analyses, not to mention the emotional cost of being provisionally diagnosed as HIV-positive, makes screening low-risk populations very expensive. (OTA - the USA's Office of Technology Assessment - estimates that screening low-risk populations can generate ten false positives for every true case of infection, and can cost $50 000 per genuine positive result). In consequence, some states in the USA which introduced mandatory pre-marital HIV tests have rescinded the law.

Insurance and workplace testing could lead to results being used to refuse cover or employment to individuals most at risk from serious disease. This issue is particularly acute in the USA due to its dependence on private health insurance. Surveys in both the USA and UK suggest that companies do not at present regard screening tests as cost-effective. HIV tests are the exception and are extensively required for both health and life insurance policies. In the US, testing in the workplace has been mostly limited to indicators of drug abuse.

Although not a major issue at present, some US insurance companies are starting to fund biomedical research in this area. Improvements in test technology may thus lead to wider use of screening tests in the future, with the results cited as a reason to deny insurance cover to high-risk individuals. The seriousness of insurance denial in the USA has led to consideration of the following legal contols:

- Only tests cleared by a regulatory authority as reliable for screening should be used.
- Adequate quality control in testing labs must be ensured.
- The test subject should have the right to know the result and obtain a second opinion.
- Restrictions should be placed on the use/transfer of the information.

FURTHER INFORMATION

Additional details and background information are available from POST, 16, Great College Street, Westminster (222-7085).

The PARLIAMENTARY OFFICE OF SCIENCE AND TECHNOLOGY has been set up by the Parliamentary and Scientific Committee to inform Parliamentarians on scientific and technological matters underpinning current issues.