"Type B" cardiology

Doctors make work, and work costs money. Costs can be counted; value is difficult to assess. The appointment of a new consultant is likely to be an expensive business, and Joy and Huggett (p 790) have now provided some data which show a district authority what to expect when it appoints for the first time a consultant with an interest in cardiology. To what extent the annual rates of 424 echocardiograms, 305 treadmill tests, and 275 24-hour electrocardiogram tape-recordings reported by Joy and Huggett are clinically useful cannot be judged; but—as they point out—the use of new tests expands to fill a department's capacity to do them, and specialists are bound to practise their art. In capital terms, however, the equipment for these tests is not particularly expensive, and much more important is the effect the appointment of such a consultant has on the local demand for invasive investigations and cardiac surgery.

Though the appointment of a new consultant always changes referral patterns—and this is particularly likely to be true in south-east England, where London is close at hand—there probably will be a real increase in the demand for these procedures. Joy and Huggett conclude that in their locality 270 open-heart operations per million population are needed each year, about the same rate as that suggested by the Joint Cardiology Committee of the Royal College of Physicians and Surgeons, and similar to that recently calculated as the requirement of the Trent region. Any district authority appointing a new consultant with an interest in cardiology should, therefore, satisfy itself that such a demand can be met by its regional cardiothoracic centre.

More important, this paper defines clearly the role of the "type B" cardiologist. Most medical specialties have grown in response to the development of techniques: for example, the growth of gastroenterology and the resurgence of chest medicine have followed the appearance of fibreoptic endoscopy. Type A cardiology appeared with cardiac catheterisation, and may be defined as the specialty practised by a physician in a regional centre who deals only with cardiac problems, and only with patients who have been selected by other physicians. Type A cardiologists need to be insulated from the hurly-burly of acute take-in, and from unselected referrals from general practitioners.

Type B cardiology has appeared with coronary care units, stress testing, echocardiography, and ambulatory monitoring. It is for the provision of these techniques and the interpretation of their results that other physicians look to the type B cardiologist. With rising standards of care in general practice many non-acute disorders that would 10 years ago have found their way to a general physician are now sorted and dealt with and referred to hospitals only when some fairly well-defined problem has been identified; this means that the outpatient work of the physician with an interest in cardiology is bound mainly to be cardiological. But 80-90% of the inpatient medical work in a district general hospital is unsorted and appears as an emergency, and any physician who shares an "on-take" rota still has to be a general physician first and foremost, even if his outpatient work gradually becomes more limited in scope. Conversely, since some of the most common disorders that lead to emergency hospital admissions are cardiovascular, students and junior doctors need a good education in cardiovascular disease—and all physicians in a district general hospital, whatever their special interest, must be competent cardiologists. The high proportion of cardiovascular problems among emergency patients makes nonsense of the suggestion that a cardiologist is someone who spends 40% of his time practising cardiology, but the paper by Joy and Huggett does not emphasise sufficiently that a type B cardiologist must spend a lot of his time on general medicine. Nevertheless, a district general hospital should have a physician with an interest in cardiology. The main tasks of the type B cardiologist, so far as cardiology is concerned, are the selection of patients for referral to the type A superspecialist and the follow-up of patients who have had surgery; there should be no need for type A cardiologists to run follow-up clinics except perhaps for complex congenital problems and for patients who need special techniques such as pacemaker checking.

Once the activities of the type A and B cardiologists have been clearly identified their training requirements may be specified. A senior registrar aiming at type A cardiology needs to spend the whole of his attachment in a regional centre. The career pyramid implies that few such senior registrars are needed, and some other way will have to be found for carrying out the main load of cardiac catheterisation: this might well form an attractive occupation for doctors working on a sessional basis with clinical assistant contracts. The aspiring type B cardiologist needs to do enough cardiac catheterisations under supervision to know what is entailed and to allow him sensibly to select patients and to interpret results; he does not need to acquire the dexterity of the type A. Non-invasive cardiological techniques are easy to learn and do not necessitate prolonged periods of training in specialist centres; the main emphasis of training for the type B cardiologist must be in general medicine. A distressing feature of current appointments committees is their expectation that applicants for senior registrar posts in all medical specialties should have had practical experience as a registrar that will allow them immediately to carry a heavy service load; this is seldom appropriate and never less so than for type B cardiology. If there are too many senior-registrar cardiologists it may be because over-rigid inspectors for the Joint Committee on Higher Medical Education have required too much formal (type A) cardiological training, and have blighted the senior registrar's prospects for a type B post.

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Serological tests for syphilis

Wassermann introduced his complement-fixation test for the serological diagnosis of syphilis in 1906. The original antigen was an extract of syphilitic tissue, but it was later shown that the active component in the extract was not *Treponema pallidum*, as had been thought, but a substance called cardiolipin, present not only in treponemes but in many mammalian tissues as well. Anticardiolipin antibodies are given the rather unsatisfactory name "reagin."

The Wassermann reaction and its later modifications held the field in serological testing for syphilis for many years, but when flocculation tests came in they were seen to be easier and more sensitive for detecting reagin. The Venereal Disease Research Laboratory test, introduced in 1946, is a flocculation test in which a mixture of cardiolipin, lecithin, and cholesterol is allowed to react with the patient's serum; the development

of flocculation indicates a positive reaction.[1] The rapid plasma reagin test is essentially the same test with technical modifications[2]; it may be used with autoanalyser equipment, when it is called the automated reagin test—very useful for screening large numbers of specimens.

Reagin tests can easily be quantified to provide a measure of the titre of anticardiolipin antibodies. They are sensitive, cheap, easy, and familiar. Unfortunately, reactions to reagin tests are found in some patients who do not have syphilis. These biological false-positive reactions may develop in immune disorders such as lupus erythematosus, in feverish and other conditions in which there is an increased destruction of cell nuclei, and sometimes in completely healthy people.[3] The problems created by biological false-positive reactions led to a search for other, better serological tests.

The first specific test for syphilis and allied diseases was the *T pallidum* immobilisation test, introduced in 1949. Live treponemes are added to inactivated serum in the presence of complement; a positive reaction is reported if half or more of the organisms are immobilised.[1] This test is highly specific, but it is expensive, potentially hazardous, and so technically demanding that it can be performed only in specialist centres. It dominated syphilis serology for many years, but is now obsolescent.

The fluorescent antibody (absorbed) test came into use in 1968. It is an indirect immunofluorescence procedure using *T pallidum* as the antigen. The test serum is first treated with an extract of Reiter treponemes to remove group-reactive antibodies, and the specificity of the test depends on the use of a really effective absorbent.[1] When this is available the test is highly sensitive and specific. False-positive reactions are rare, but they have been described in some patients with collagen disease. The fluorescent antibody (absorbed) test is expensive and tedious to perform and so is not usually used for screening, but it is useful as a confirmatory test. It can be modified by the use of monospecific fluorescein-labelled antihuman globulins to identify the immunoglobulin class of the antibody.

The *T pallidum* haemagglutination assay test was developed in 1966. Sheep or turkey erythrocytes coated with particles of *T pallidum* are mixed with inactivated serum, and specific immunoglobulins cause agglutination.[4] The test can be quantified and is highly specific. A cheaper microhaemagglutination assay is now usually used, and with automation large-scale screening is possible. The *T pallidum* haemagglutination assay test is the best of the specific tests available for the diagnosis of syphilis and related diseases.

How, then, is the clinician to use this array of serological tests? When a patient contracts the disease, the first serological test to become reactive is usually the fluorescent antibody (absorbed), followed by the reagin tests such as the Venereal Disease Research Laboratory or rapid plasma reagin. The *T pallidum* haemagglutination assay becomes positive next, and lastly the *T pallidum* immobilisation. Thus the fluorescent antibody (absorbed) test is of particular value in investigating patients with primary syphilis if dark-field microscopy is impracticable. In secondary syphilis all serological tests give positive results, and the titre of reagin is maximal. As the disease becomes latent the reagin titre slowly falls, though the specific tests remain positive. About three-quarters of patients with late syphilis show reagin tests which are positive, usually at low titre; the fluorescent antibody (absorbed) and *T pallidum* haemagglutination assay tests are positive, but in a small proportion the *T pallidum* immobilisation test is unreactive.

In most patients the results of reagin tests become negative one year after adequate treatment for primary syphilis and two years after treatment for secondary syphilis. The specific tests, however, may stay positive for many years, constituting a "scar in the blood"—an indication that the patient has had a treponemal infection at some time in his life. The IgM-fluorescent antibody (absorbed) test, which is constantly positive in untreated primary and secondary syphilis, usually becomes negative within nine months of successful treatment. Whether a persistently reactive IgM-fluorescent antibody (absorbed) test indicates the continuing presence of a syphilitic antigen is not yet clear. When patients are treated for latent or late syphilis reagin tests usually show a slow decline in titre and may eventually become negative. In a few patients the titre becomes stationary and is not affected by retreatment. The fluorescent antibody (absorbed) and *T pallidum* haemagglutination assay tests remain positive indefinitely.

No single serological test is completely satisfactory for the diagnosis of patients with syphilis and for their assessment after treatment. If a reagin test alone is used many patients with latent and late syphilis will escape serological diagnosis; conversely, patients with biological false-positive reactions may wrongly be diagnosed as having syphilis. The best combination is a reagin test with the *T pallidum* haemagglutination assay test. Ideally the reagin test should be quantitative, as this is useful as a determinant of recent or active infections and in assessing progress after treatment. Quantification of the *T pallidum* haemagglutination assay test may give some idea of the duration of the infection,[5] but on grounds of economy many laboratories prefer to quantify only one serological test—usually the Venereal Disease Research Laboratory or rapid plasma reagin. When reagin and *T pallidum* haemagglutination assay tests give contradictory results, a fluorescent antibody (absorbed) test should be performed. This test is also useful in the diagnosis of primary syphilis, when the results of both reagin and *T pallidum* haemagglutination (absorbed) tests may be negative. For evaluating progress after treatment quantitative reagin tests are of most use; specific tests are of little value.

There are two related problems which even modern techniques have not entirely solved. The first is the serological diagnosis of early syphilis in patients who have had syphilis before. These patients have positive specific tests from the previous infection. An unexpected rise in reagin titre (if the previous titre is known) may provide a clue, but this may also be due to a supervening biological false-positive reaction. An IgM-fluorescent antibody (absorbed) test might be considered in these circumstances, but even that may be unreliable. The detection of treponema-specific 19S (IgM) antibodies by immunofluorescence in serum fractions after gel filtration is a more reliable test,[6] but it is complex and available only in specialist laboratories. Sometimes the best course is for the patient to be kept under surveillance without treatment to see whether the reagin titre rises. The second problem is the interpretation of positive serological tests for syphilis in patients from areas where endemic treponematoses such as yaws and bejel are prevalent. In general, the serological reactions to syphilis and non-venereal treponematoses are identical. Thus patients who have had yaws in childhood show positive specific tests and have lipoidal antigen tests which are either negative or positive in low titre—a pattern identical with that in patients with latent or late syphilis, or with a previously treated infection. When a patient who has been treated for yaws develops syphilis his serological responses will resemble those shown by patients reinfected with syphilis.

Publications on serological tests for syphilis serology are littered with initials and acronyms, and there may be more to come. The enzyme-linked immunosorbent assay[7] (ELISA) has been shown in preliminary studies to be relatively quick and simple, equivalent in specificity to the fluorescent antibody (absorbed) test, but more work is needed before it can be brought into routine clinical practice. The same may be said of the solid-phase haemadsorption test for IgM antibodies, which has recently been developed.[8] Some workers have reported that the test is highly specific for IgM antibodies to *T pallidum*, easy to do, and inexpensive[9]; others have found that the test is unreliable in comparison with other tests for IgM antibodies.[6]

Reagin tests seem likely to continue to be generally used in the foreseeable future, with increased use being made of automated procedures for both reagin and specific tests. Nevertheless, it is as true today as it was in 1906 that the accurate diagnosis of syphilis, though greatly helped by laboratory aids, is ultimately based on a thorough history and clinical examination.

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Image and reality: drugs for the future

Pharmaceutical manufacturers share some of the characteristics of policemen and pawnbrokers; most people see them in black-and-white terms either as villains or as assets to our society. These polarised responses have become apparent recently in the public response to claims by the industry that new drugs cost so much to develop and take so long to test that innovation will soon no longer be cost effective. Certainly fewer new drugs are being marketed than 20 years ago—but might that not be simply because the drug explosion is over? Major innovations, such as H_2-receptor antagonists as treatments for peptic ulcer, can still make vast profits for the companies concerned. Does it really matter if the flow of new diuretics, tranquillisers, and hypotensive drugs is slowing?

These questions were examined at a conference last month in Oslo organised by the Association of Norwegian Representatives of Foreign Pharmaceutical Manufacturers. Speakers were quick to assert that the current generation of drugs were the results of 15 to 20 years' gestation and that without some change the pace of innovation would continue to slow.

The clear message from the research units was that there was no shortage of new, promising areas for development. The genetic manipulation of bacteria, though still in its early stages, had already produced human growth hormone and human insulin, so solving the problems of short supply that had threatened to become major anxieties for clinicians. Monoclonal antibodies were revolutionising diagnostic techniques in the laboratory. More antiviral drugs and antiviral vaccines were being developed with greater specificity and less toxicity. Whole topics of pharmacological research, such as the prostacyclin-thromboxane system, were just yielding their first products for clinical assessment.

Yet the pessimistic assessment of Professor William Wardell, of Rochester, United States, was that these research efforts would produce few new drugs by the year 2000. The possible exceptions were some cheap hormones made by genetic engineering and some modified interferons; the remainder of the research lines would, he thought, become delayed by the expense of laboratory and clinical testing. Certainly the companies based in the United States would produce fewer new clinical entities in the 1980s and 1990s than they had in the 1970s—despite the rapid recent advances in so many aspects of medical science.

This despondent assessment was not challenged by anyone at the conference. Critics of the pharmaceutical industry may point to its conspicuous affluence and its aggressive marketing techniques, but it is the only imaginable source of new drugs. Only half a dozen countries have an innovative pharmaceutical industry; the remainder are content to be free-riders. The poor image of the drug industry has encouraged several rich, technically advanced nations to legislate on costs, generics, and restricted formularies in such a way as to extinguish any possibility of their having a home-based industry.

Where does the future lie? The cost quoted to the conference of developing a single new drug is now approaching £100 million—a figure accounted for partly by the cost of the thousands of potential new drugs that failed somewhere along the line and partly by the extended programme of tests required by government drug-regulatory agencies. These costs could be reduced if the six to nine years of clinical testing could be simplified. Another substantial but sensible reform would be for more countries to follow the Scandinavian example of harmonising their regulatory requirements so that companies need not go through a complex exercise for each country in turn. With such changes the effective patent life of new drugs would be extended to about 10 years instead of seven years or less, as at present.

Substantial changes in legislation on drug safety will depend, however, on changes in public attitudes. The '60s and '70s were the decades of consumerism, when governments seemed to believe that the voices of the professional consumers should be given more attention than those of patients and their doctors. Drugs were portrayed by investigative journalists as expensive, dangerous, and largely unnecessary. Such a picture was based on examples such as the use of tranquillisers as treatment for discontent, and it ignores the reality: every outpatient department is thronged with patients with chronic diseases for which current drugs are ineffective or have serious side effects or both. Our society does need new drugs; only the pharmaceutical industry (warts and all) will provide them.

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