feeling frustrated at being told that results of investigations are negative but not receiving any convincing explanation of persistent distressing symptoms. Continuing unproductive investigation, multiple referral, and unnecessary drugs are all causes of further uncertainty.

Management should aim at avoiding the problems arising from prolonged and unproductive investigation followed by abrupt suggestions of a psychological explanation to a sceptical patient. Doctors should adopt a dual approach, whereby investigation is accompanied by the recognition and management of psychological factors. Patients should believe that, whatever the cause of their problem, their complaints and worries are being taken seriously.

All appropriate investigations should be undertaken at the outset, and further investigations should be done whenever specific clear indications arise. Psychological factors should be considered from the beginning and discussed in a way that is acceptable and convincing. Advice and information must take account of the patient's particular worries and beliefs.

Most patients with non-specific physical symptoms are satisfied by simple explanation, discussion, and reassurance. Much more difficult are patients whose symptoms persist despite this. Some remain convinced that their continuing symptoms must have a sinister cause; for them repeated reassurance is ineffective and may well exacerbate their problems and their demands on doctors.[14] Further detailed explanation, discussion, and simple behavioural advice (including advice on managing anxiety) in general practice or the outpatient clinic is often effective, but some patients require more specialist help. Unfortunately many psychiatrists have little experience of treating patients who present with somatic symptoms. They may need educating about the role and effectiveness of modern treatments and of the harm caused by their all too common response, once referral has eventually been achieved, of writing a letter concluding that "no psychiatric disorder is present."

Several well established psychiatric and psychological treatments may be useful.[9] Antidepressant drugs are effective in treating symptoms associated with a major depressive illness. They also have a wider role in pain syndromes, such as atypical facial pain.[15] Newer psychological treatments for anxiety disorders have an important role.[16] "Cognitive-behavioural" treatments aim at understanding and changing patients' erroneous beliefs about their symptoms and their causes. This cognitive component is combined with behavioural methods—such as techniques for managing anxiety (relaxation, distraction, and breathing exercises) and diary keeping—and a graded increase in activities. Clinical experience and research have shown that such methods are acceptable and are often effective when simple explanation has failed.[9,17]

The small group of patients who repeatedly present with chronic and multiple symptoms pose great problems for doctors,[8,9] as do patients attending pain clinics.[18] It is too late for prevention, and therapeutic aims may need to be modest—damage limitation rather than cure. A single doctor should take responsibility for consistent care for the patient and family, offering regularly scheduled appointments and limiting and controlling any other medical care.

Systematic management of persistent unexplained physical symptoms has been neglected. The numbers of patients and the extent and severity of their disability and of their demands on all forms of medical resources indicate the need for clearer and more effective clinical policies so that we can provide extra help to those who need it. Earlier this year the Royal College of Physicians and the Royal College of Psychiatrists held a successful joint meeting reviewing the aetiology and the management of the condition. It agreed the need for much greater collaboration in developing effective treatments, improving services, and in promoting changes in training. Research is urgently needed to develop and evaluate treatments and training. Clearly much could be achieved by simple and effective early treatment by general practitioners and physicians, but we also need greater specialist resources. Improved early care should be highly cost effective, saving much unnecessary investigation and ineffective and unsatisfying consultation.

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Testing for hepatitis C virus

Panels of antigens and antibodies are most practical

Blood banks in the United Kingdom began the routine testing of blood donors for antibodies to components of the hepatitis C virus this month. Doctors who want to make a firm diagnosis of hepatitis C virus infection, however, still lack a single laboratory test that is entirely satisfactory.

An assay to detect an antibody related to hepatitis C virus (C100-3 antibody) was published simultaneously with the cloning of a complementary DNA representing part of the viral genome.[1,2] C100-3 antibody recognises a composite polyprotein antigen (C100-3) within non-structural regions of the virus[2,3] and is a consistent marker of chronic parenteral non-A non-B infection.[1] In acute infections, however, this antibody is unreliable because of the delay (median 22 weeks) in seroconversion after exposure.[1]

Furthermore, the C100-3 antibody test lacks specificity for infection with hepatitis C virus, and there is no confirmatory test that is easy to use and widely available. C100-3 antibody reactivity is short lived in up to half the blood donors who initially test positive.[4] Reactivity also occurs in other diseases, especially those in which serum globulin concentrations are raised.[5]

The specificity of the C100-3 antibody test has been improved with modifications to the assays. In the neutralisation enzyme immunoassay recombinant hepatitis C virus antigen in solution forms immune complexes with any C100-3 antibody in the test serum and prevents binding to immobilised hepatitis C virus antigen also present. In the first generation recombinant immunoblot assay (RIBA-100) crossreacting controls as well as the recombinant C100-3 antigens are separately immobilised.[6] In a study of initially reactive blood donations fewer than half (45%) were considered to be specific for C100-3 antibody with the RIBA-100 test.[7] Because the antigen (C100-3) is the same these assays cannot be accepted as confirmatory tests and they do not improve detection in acute infection.

The second generation antibody tests, such as the RIBA-4 enzyme linked immunosorbent assay (ELISA)[8,9] and the hepatitis C virus 200 C-22 enzyme immunoassay,[10] include recombinant antigens and synthetic linear peptides representing structural antigens from the highly conserved core region of the virus as well as non-structural antigens. These additions seem to have resolved many of the previous difficulties with indeterminate and false negative results. Second generation antibody assays using ELISA will be used to screen blood donors in the first place. They can also provide a supplementary test for samples that give positive results in other tests.

The "gold standard" tests for assessing potential infectivity must depend on direct detection of virus either by its antigens or by genomic sequences. The pioneering studies of Bradley and coworkers showed that the causative agent(s) in chronic post-transfusion hepatitis are present in very low concentrations.[10]

The polymerase chain reaction technique has overcome the limitations of sensitivity. Even one molecule can be detected after several million amplifications. With this technique only 37% of blood donors who tested positive in the C100-3 ELISA had detectable viral genomic sequences (hepatitis C virus complementary DNA).[7] This correlation improved to 70% with the RIBA-100—but one third of the samples that gave negative results with this test had products detectable by the polymerase chain reaction.[7] To date, the second generation antibody tests show the best concordance between antibody reactivity and positivity on the polymerase chain reaction.[8,9] Furthermore, they seem to discriminate between potentially infectious and non-infectious blood donations that are positive for C100-3 antibody.[8,9] Indeed, overall, few donations that are positive for the antibody seem capable of transmitting hepatitis.

Unfortunately, current techniques using the polymerase chain reaction are too technically demanding for routine use. In blood banks these will be reserved as third line testing for samples giving indeterminate results in the second generation antibody tests. False positive results may be due to contamination and non-specific amplification of extraneous molecules. False negative results may occur if the RNA is destroyed by repeated freezing and thawing or by specific enzymes. Viraemias may be transient, and selected probes may fail to detect a few sequences in a variable region of the hepatitis C virus genome. Both the specificity and sensitivity of the polymerase chain reaction are, however, greatly improved by a second round of amplification using internal ("nested") primers.[11]

The reluctance to begin widespread testing of blood donors in the United Kingdom before the introduction of the second generation antibody tests seems justified in view of the poor correlation between C100-3 antibody positivity based on first generation antibody tests and results using second generation tests and the polymerase chain reaction.[6-9,12] Calculations based on a rate of C100-3 antibody reactivity among blood donors of 0·55-0·7%, and an annual total of 2·5 million donations show an unacceptable loss of around 10 000 units a year.[4,12] Hepatitis after transfusion is uncommon in Britain,[12] and blood products now are routinely heat treated.

The poor reputation of the antibody tests based on C100-3 antigen is likely to improve with the introduction of panels of antigens including those representing the core region of the hepatitis C virus genome.[13] The corresponding antibodies are more likely to be present and detected early after infection. Screening of blood donors, even with the newer antibody tests, will create ethical problems, such as counselling apparently seropositive people. There will also be practical problems of management even though confirmatory testing using the polymerase chain reaction will be available in reference centres.

The clinician will have to wait for these recombinant antigens and their corresponding antibodies to be "packaged" into the tidier, more familiar components of viral structure. Their importance in relation to the natural course of hepatitis C and their usefulness in diagnosing acute infections should become clearer with the newer, second generation antibody tests. Testing continues to be hampered by the apparently limited availability of some of the test kits and high costs of the reagents.[14] Detailed clinical studies will be needed to assess the usefulness of these tests for monitoring inflammatory activity of the liver disease and for assessing possible treatments of chronic hepatitis C as well as immunoprophylaxis. Such studies should extend beyond the blood bank to include non-parenteral non-A non-B hepatitis and non-C viruses and their corresponding liver diseases.

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