within 12 months of a thromboembolic event one year survival was 38% compared with 47% in the controls. The study concludes that patients with cancer diagnosed at or around the time of a thromboembolic event have a significantly worse prognosis than those patients without such an association.

So would screening for cancer in patients who present with a venous thromboembolic event be an effective use of resources? In the absence of an obvious risk factor for thrombosis there is a clear increase in the incidence of an underlying carcinoma in these patients. Estimates range from 7.3% to 19% at the time of presentation. Assuming an incidence of perhaps around 10%, screening for cancer becomes a reasonable option. On the basis of current evidence, however, intensive investigation cannot be recommended.

Firstly, cancers associated with venous thrombosis seem to have a relatively poor prognosis, and early diagnosis of many of these cancers has not been shown to improve survival. Secondly, we should not underestimate the potential harm to patients, both psychological and physical, associated with any kind of screening programme, as increasingly invasive investigations may be used to follow up abnormal screening tests for what may turn out to be benign or untreatable disease.

A practical approach would be always to consider the possibility of an underlying cancer in patients presenting with a venous thrombosis, particularly if they have no underlying risk factor for the thrombosis. We should take a careful history and make a thorough examination and do the simple routine blood tests—full blood count, liver function tests, urea and electrolytes—and a chest radiograph. This simple screen will lead us to the diagnosis in most patients with an underlying cancer. Further investigations would depend on the results of these tests. Before recommending more intensive investigations we need the results of a large randomised prospective study to assess whether incorporating investigations such as tumour markers, faecal occult blood, and computed tomography into a screening protocol will lead to improved outcome for those patients found to have an underlying cancer.

Tony Fennerty *consultant in general and respiratory medicine*

Harrogate District Hospital, Harrogate HG2 7SX
(Anthony.Fennerty@hhc-tr.northy.nhs.uk)

1 Trousseau A. Phlegmasia alba dolens. *Lectures on clinical medicine, delivered at the Hotel Dieu de Paris*. London: New Sydenham Society, 1872:281-95.
2 Sproul EE. Carcinoma and venous thrombosis: the frequency of association of carcinoma in the body or tail of the pancreas with multiple venous thrombosis. *Am J Cancer* 1938;34:566-85.
3 Nordström M, Lindblad B, Anderson H, Begquist D, Kjellström T. Deep venous thrombosis and occult malignancy: an epidemiological study. *BMJ* 1994;308:891-4.
4 Baron JA, Gridley G, Weiderpass E, Nyren O, Linet M. Venous thromboembolism and cancer. *Lancet* 1998;351:1077-80.
5 Sørenson HT, Mellemkjaer L, Steffensen FH, Olsen JH, Nielsen GL. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. *N Engl J Med* 1998;338:1169-73.
6 Prandoni P, Lensing AWA, Büller HR, Cogo A, Prins MH, Cattelan AM, et al. Deep vein thrombosis and the incidence of subsequent symptomatic cancer. *N Engl J Med* 1992;327:1128-33.
7 Cornuz J, Pearson SD, Creager MA, Cook EF, Goldman L. Importance of findings on the initial evaluation for cancer in patients with symptomatic idiopathic deep venous thrombosis. *Ann Intern Med* 1996;125:785-93.
8 Hettiarachchi RJK, Lok J, Prins MH, Büller HR, Prandoni P. Undiagnosed malignancy in patients with deep vein thrombosis. *Cancer* 1998;83:180-5.
9 Monreal M, Lafoz E, Casals A, Inaraja L, Montserrat E, Callejas JM, et al. Occult cancer in patients with deep venous thrombosis. *Cancer* 1991;67:541-5.
10 Bastounis EA, Karayiannakis AJ, Makri GG, Alexiou D, Papalambros EL. The incidence of occult cancer in patients with deep venous thrombosis: a prospective study. *J Intern Med* 1996;239:153-6.
11 Sørensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med* 2000;343: 1846-50.

Wrong biochemistry results

Interference in immunoassays is insidious and could adversely affect patient care

The success of analytical methods in clinical chemistry has led to a sense of security in the value of laboratory results. This is largely justified, as evidenced by the quality of laboratory performance assessed by external assurance schemes. Nevertheless, it is not widely recognised among clinicians that some biochemical tests are more prone to interference from unusual serum constituents than others—and that quality assurance schemes can do little about this.

An important example of this is tests carried out by immunoassays based on the recognition of molecules by antibodies. The antibodies are largely derived from animal sources and are typically used for measuring hormones, tumour markers, cardiac troponins, and therapeutic drugs and for viral serology.

The design of assays has evolved enormously since the discovery of immunoassay by Berson et al in 1956,[1] and it is now a major analytical tool in clinical laboratories worldwide, allowing relatively minute (picomole (10^{-12})) amounts of analytes to be measured with unrivalled precision.

Interference in immunoassays by antibodies is a recognised phenomenon. For example, endogenous antithyroglobulin antibodies invalidate thyroglobulin measurements, and exogenously administered antibodies used to treat digoxin toxicity prevent measurement of plasma digoxin. However, there is more insidious interference due to the presence of unsuspected abnormal binding protein(s) in the patient.[2–4] These mainly include heterophilic antibodies such as rheumatoid factor, anti-animal antibodies (anti-mouse, anti-rabbit, anti-sheep, etc), and anti-idiotypic antibodies (antibodies elicited by an idiotope on another antibody molecule during the course of an immune response). In some cases these antibodies in patients' sera may interfere with the analytical reaction between the analyte being measured and the antibodies used in the immunoassay's cocktail. The exact effect of such interference will depend on the site

BMJ 2001;323:705–6

where they interfere with the reaction, leading to falsely raised or lowered measurements. These interferences are specific to each patient, so only that patient's data will be affected, while quality assurance criteria for the assay will have been passed.

Examples of this type of interference that has had serious clinical consequences include human chorionic gonadotrophin assays.[5] As a result of wrongly interpreted results six young non-pregnant women were aggressively treated with chemotherapy and surgery for non-existent "occult" trophoblastic disease.[6] In our experience at a national reference steroid laboratory, samples with consistent and substantial increases in steroids using routine direct immunoassays have raised the possibility of disease but have subsequently been found to be normal after reassay using more robust techniques involving extraction procedures. In one case a raised oestradiol value led to a patient having a hysterectomy and bilateral oophorectomy, and only when no fall in oestradiol was seen postoperatively was the sample further analysed and the original result found to be wrong because of immunoassay interference. Similar problems are also noted in other steroid assays, such as testosterone in women.[7] False positive interference in troponin assays in patients with chest pain due to acute coronary syndrome has led to prolonged inpatient stays and invasive investigation.[8 9] False negative results are equally important in that they lead to underinvestigation.[10]

The presence of interfering antibodies is surprisingly common, affecting 30-40% of the population.[3] They probably arise from mundane activities such as keeping pets, ingesting animal antigens, vaccination, infection, or even blood transfusion. Most analytical assays currently in use can neutralise and block low concentrations of these interfering proteins (µg to mg/l) with no or minimum impact on analytical accuracy. Larger amounts of interfering proteins, which may be as high as grams per litre, or proteins with high binding affinity can, however, overwhelm the analytical system, leading to assay interference and erroneous results. The number of these extreme cases is not known, though specific types of interference, such as heterophilic and anti-murine antibodies, in the order of 0.05% have been reported.[4 11] Our experience suggests that interfering antibodies of various types affect about 0.5% immunoassays (A Ismail, J Barth, unpublished data), though others have reported higher percentages.[12] Even the lowest prevalence quoted should be seen in the context of the total number of immunoassays—many millions a year in British hospital laboratories alone. Thus many thousands of patients in the United Kingdom might be affected. Furthermore, this problem is likely to worsen owing to the wider use of biotechnologies such as monoclonal antibodies and T cells for diagnostic and therapeutic purposes.[13]

Since these interferences are relatively uncommon, clinicians need to be aware of them and alert to the mismatch of clinical and biochemical data. They should not discard clinical evidence in favour of a numerical value. Moreover, this form of interference is not specific to a single analyte and may affect other immunoassays performed on the same patient in a different clinical setting. Thus patients who have such interference detected should have this fact documented in their clinical records, so that the results of future immunoassays can be viewed with caution.

Adel AA Ismail *consultant biochemist*

(dr.ismail@panp-tr.northy.nhs.uk)

Julian H Barth *director*

Leeds Supraregional Assay Service, Steroid Centre, General Infirmary, Leeds LS1 3EX (j.h.barth@leeds.ac.uk)

1 Berson SA, Yalow R, Bauman MA, Newerly K. I^{131} insulin metabolism in human subjects: demonstration of insulin binding globulin in the circulation of insulin-treated subjects. *J Clin Invest* 1956;35:170-90.
2 Kricka LJ. Interference in immunoassays—still a threat. *Clin Chem* 2000;46:1037-8.
3 Selby C. Interference in immunoassays. *Ann Clin Biochem* 1999;36: 704-21.
4 Ward G, McKinnon, Badrick T, Hickman PE. Heterophilic antibodies remain a problem for the immunoassay laboratory. *Am J Clin Pathol* 1997;108:417-21.
5 Cole LA, Rinne KM, Shahabi S, Omrani A. False-positive hCG assay results leading to unnecessary surgery and chemotherapy and needless occurrences of diabetes and coma. *Clin Chem* 1999;45:313-4.
6 Rotmensch S, Cole LA. False diagnosis and needless therapy of presumed malignant disease in women with false-positive human chorionic gonadotrophin concentrations. *Lancet* 2000;355:712-5.
7 Torjesen PA, Bjøro T. Antibodies against I^{125} testosterone in patient's serum: A problem for the laboratory and the patient. *Clin Chem* 1996;43:2047-8.
8 Cavinsky M, Laterza O, Pfeifer JD, Farkas ST, Scott MG. IgM antibody to Escherichia coli produces false positive results in multiple immunometric assays. *Clin Chem* 2000;46:1157-61.
9 Krahn J, Parry DM, Laroux M, Dalton J. High percentage of false positive cardiac troponin I results in patients with rheumatoid factor. *Clin Biochem* 1999;32:477-80.
10 Bohner J, von Pape KW, Hannes W, Stegmann T. False-negative immunoassay results for cardiac troponin I probably due to circulating troponin I autoantibodies. *Clin Chem* 1996;42:2046-7.
11 Norden AGW, Jackson RA, Norden LE, Griffin AJ, Barnes MA, Little JA. Misleading results for immunoassays of serum free thyroxine in the presence of rheumatoid factor. *Clin Chem* 1997;43:957-62.
12 Kuroki M, Matsumoto Y, Arakawa F, Haruno M, Murakami M, Kuwahara M, et al. Reducing interference from heterophilic antibodies in a two-site immunoassay for carcinoembryonic antigen (CEA) by using human-mouse chimeric antibody to CEA as the tracer. *J Immunol Methods* 1995;180:81-91.
13 Weber TH, Kapyaho KI, Tanner P. Endogenous interference in immunoassays in clinical chemistry. A review. *Scan J Clin Lab Invest* 1990;50(suppl 201):77-82.

Monitoring the safety of over the counter drugs

We need a better way than spontaneous reports

Last year the Food and Drug Administration in the United States recommended that phenylpropanolamine be removed from non-prescription and prescription medicines and that pharmaceutical companies voluntarily discontinue products containing phenylpropanolamine. This was in response to a case-control study by the Yale haemorrhagic stroke project investigators designed to determine the risk of haemorrhagic stroke in people exposed to phenylpropanolamine.[1] Though this action was not followed in the United Kingdom, because the market conditions for phenylpropanolamine are

BMJ 2001;323:706–7