days, necessitating that carers in these outcome studies should be blind to such factors as whether conventional or laparoscopic surgery was conducted.[11] Indeed, the combination of epidurals, laparoscopic surgery, and a multimodal approach to aggressive postoperative rehabilitation may dramatically reduce hospital stay, as shown in nine elderly patients who stayed in hospital for only two to three days after colonic surgery, compared with the normal 10 days.[12] This was, however, an open investigation, and larger studies, necessary for proper evaluation of this multimodal approach, have not yet materialised.

Consideration of these studies raises the question of the adequacy of current outcome variables for evaluating recovery. Modern anaesthetic practice is inherently safe and differences in mortality between techniques may be difficult to detect, even in high-risk patients. Thus future postoperative outcome studies may need to focus on patients' own views of recovery, including their assessment of their overall well being and return to preoperative energy and activity levels.

Despite the evidence that use of epidural anaesthesia is associated with some improvements in postoperative outcome, it carries the risk of serious neurological complications. These are rare, but vigilance in the postoperative period is required to detect the triad of back pain, progressive motor weakness, and incontinence which may herald an epidural haematoma or abscess. Modern practice using dilute concentrations of local anaesthetics or opioids in epidural infusions (thereby reducing motor weakness) is helpful in aiding diagnosis of this potentially devastating complication. If suspected, immediate radiological investigation (with magnetic resonance imaging) and surgery are required to relieve spinal cord compression.

Thus, the balance of available evidence in the form of relatively few randomised trials and meta-analyses suggests that epidural anaesthesia and postoperative analgesia may facilitate earlier recovery and improved outcome by reducing the incidence of thromboembolic, pulmonary, and gastrointestinal complications after major surgery. A multidisciplinary approach to rehabilitation may help to capitalise on this improved postoperative physiological state, but further prospective evaluation is warranted.

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Hereditary haemochromatosis: to screen or not

Conditions for screening are not yet fulfilled

During the past several years hereditary haemochromatosis has risen from relative obscurity to become a topic of intense interest in the health community. Traditionally, hereditary haemochromatosis has been viewed as a rare inherited disorder, primarily of older men, that presents with life threatening complications such as "bronzed diabetes" (skin pigmentation, diabetes, and cirrhosis), primary liver cancer, or heart failure. Knowledge gained in the past 30 years, however, has shown that hereditary haemochromatosis occurs in as many as 5 in every 1000 white people of northern European heritage.[1] The classic "bronzed diabetes" presentation is actually rare because it represents only a small proportion of affected individuals, usually those in whom the diagnosis has been missed for many years.[2] This disorder more often presents in both men and women with non-specific medical complaints, such as abdominal pain, fatigue, sexual dysfunction, or joint pain, and hereditary haemochromatosis is often overlooked as a potential explanation.[1 2] As iron loading progresses many organs and tissues can be damaged, leading to hepatic fibrosis and cirrhosis, primary liver cancer, endocrine dysfunction, cardiomyopathy, or arthropathy.[1 2]

For over 10 years laboratory tests for assessing iron burden (transferrin saturation, serum ferritin) have been widely used in population screening, in conjunction with diagnostic protocols aimed at differentiating hereditary haemochromatosis from other acquired and inherited causes of iron overload. These trials identified 2-5 in 1000 people as having biochemical evidence of iron overload.[3] In 1996 a candidate gene for hereditary haemochromatosis, designated *HFE*, and two mutations (C282Y and H63D) were discovered.[4] In most white populations of northern European heritage about 85% of people with clinically diagnosed hereditary haemochromatosis are homozygous for the C282Y mutation.[5] The homozygous

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C282Y genotype is found in 4-5 per 1000 people in these populations, supporting earlier prevalence estimates.[5] Studies of medical records indicate that the rate of clinical diagnosis of hereditary haemochromatosis is consistently much lower than expected.[6] This discrepancy is probably explained by *(a)* lack of progression to serious clinical manifestations in a proportion of individuals with hereditary haemochromatosis and *(b)* underdiagnosis among those who are clinically affected.

Against this backdrop, some within both the medical community and patient support groups have been advocating population screening. An international consensus conference on hereditary haemochromatosis was held as part of the 1999 BioIron World Congress on Iron Metabolism to assess the feasibility of screening. One stumbling block was immediately apparent: the lack of good data for documenting the proportion of individuals with hereditary haemochromatosis who will develop serious clinical manifestations.

A relatively high proportion of relatives of clinically diagnosed individuals have typical early symptoms, but fewer have evidence of serious organ damage.[7] Studies of family members may overestimate the prevalence of symptoms because relatives may be more aware of, and likely to report, clinical manifestations. Also, those with health problems may be more likely to agree to be evaluated. Genetically predisposed relatives of diagnosed cases may even be more likely to become symptomatic.

By contrast, some population based trials, particularly those recruiting blood donors, have suffered from bias towards underestimating serious manifestations.[3] Not only are blood donors preselected as "healthy," but periodic blood donation would be effective treatment. Even in studies where biases have been avoided, the extent to which certain associated clinical manifestations, such as joint pain or diabetes, can be specifically attributed to hereditary haemochromatosis has not been documented.

What are the issues that need to be clarified before making a decision on screening? As discussed above, the most crucial question involves the extent of morbidity that can be attributed to hereditary haemochromatosis. Studies aimed at providing that information are now underway. If clinical consequences are found sufficiently serious to justify screening, then it will be necessary to determine the optimal time to screen, the most efficient screening strategy, and the appropriate target population(s).

Timing may differ for men and women, since men generally develop problems earlier in life.[1] Testing has been proposed in the newborn period, but this is not good screening practice, since no treatment would be advocated or clinical manifestations expected for at least two decades. Ideally, screening would be offered as near as possible to the expected time of onset of clinical problems, thus minimising the number of years of treatment and follow up needed. It would be necessary to determine whether the primary test should be biochemical iron status markers or *HFE* mutation analysis, and whether some combination might enhance effectiveness. It will also be important to determine the most appropriate target populations. Though common in places associated with Celtic migrations, hereditary haemochromatosis and the C282Y mutation are rare in Asia, the Middle East, and most of Africa.[8] A heritable, but non-*HFE*, form of iron overload occurs in some black populations, who may require an alternative screening approach.[9]

Those who have direct contact with clinically manifest hereditary haemochromatosis, whether as physicians, family, or patients, may question why the public health community is treating the issue of screening with such caution. Predisposition to iron loading due to hereditary haemochromatosis is, after all, common and can, at times, produce serious health consequences. Furthermore, an effective treatment (repeated phlebotomy) is readily available, low risk, and not overly costly.[10]

The answer is based on the balance between doing good and doing harm. If, for example, it were necessary to label 10 homozygous C282Y individuals with this diagnosis and commit them to lifelong medical management to prevent serious illness in one, then the benefit from screening might be judged insufficient, and another, more selective, strategy might need to be considered. At a more favourable ratio—say one individual benefiting for every two treated—the balance would almost certainly shift towards screening.

Between now and the time when the necessary data have been gathered to resolve this uncertainty, the health community should be alerted to the fact that hereditary haemochromatosis is quite common and may manifest in a variety of guises. This requires a heightened level of suspicion when unexplained, nonspecific complaints, such as fatigue or abdominal pain, and even more defined problems, such as liver disease or cardiac failure, are being evaluated.

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Zeneca Diagnostics has provided reagents for a study involving haemochromatosis in the authors' laboratory

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