that previous blood transfusion enhanced graft survival, but it has now become abundantly clear that they were right.[4] Suggestions have also been made that the transmission of human immunodeficiency virus to haemophiliacs and other recipients of blood products is enhanced by an immunosuppressive factor in the blood.[5]

Everson and Cole in 1976 reviewed 176 well documented cases of spontaneous remission of cancer and suggested that blood transfusion was the trigger for the remission in some cases, particularly of melanoma.[6] On the other hand, Israel and others have claimed that removing plasma from patients with metastatic cancer may induce remissions.[7] The first report of an adverse effect of blood transfusion on survival came from Burrows and Tartter, who looked retrospectively at 122 patients who had undergone "curative" operations for colorectal cancer. Those who had not received a blood transfusion before, during, or after their operation survived longer without tumour recurrence.[8] Similar figures have been produced for carcinoma of the breast,[9] lung,[10] kidney,[11] and uterine cervix,[12] and for soft tissue sarcomas.[13] Other retrospective studies of colorectal cancer have confirmed the original observation,[14 15] but some have not.[16-20]

Now a report from Leicester suggests that an apparent survival advantage in patients with renal cell carcinoma who had not received a perioperative blood transfusion was due to differences in the stage of the tumour (p 537). That such an unperceived difference in stage might account for differences in survival in colorectal cancer is clearly an important concern and has been voiced by Taylor.[21] No matter how the figures are arranged, patients require blood transfusions not because of the whim of the surgeon or anaesthetist but because their tumour is more advanced or more difficult to remove or because of some other technical reason likely to worsen prognosis.

In an attempt to avoid these objections Blumberg and others have compared the survival of those patients with colorectal, cervical, and prostatic cancer who received perioperative transfusion of whole blood with those who received only packed red cells or nothing at all (p 530). The results show that those who were not transfused were less likely to have recurrent disease or to die from their tumour, but, surprisingly, that those who received three or fewer units of packed cells and no whole blood also had this advantage. The decision to use packed cells instead of whole blood was almost certainly made on grounds of local tradition or availability, and this result therefore suggests that there may be a factor in plasma which enhances metastatic spread.

Although we may be reluctant to think ill of an old friend, there is experimental support for this hypothesis. Francis and Shenton showed that rats inoculated with a chemically induced sarcoma had a faster rate of tumour growth if they had been transfused previously with compatible allogeneic blood.[22] Similar studies in Japan have shown that, though red cell transfusions had no effect, infusions of plasma accelerated tumour growth more than any other blood component.[23] Since this observation might explain the discrepancies between different retrospective studies, perhaps the time has come to examine the question in a prospectively randomised trial.

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Iron and the outcome of infection

Anything that retards microbial growth during the early phase of infection will favour resolution rather than overt disease. Though the host's immune system clearly plays a major part, another important factor is that the host's iron should not be available to the invading micro-organisms.

"Free" or ionic iron in the body hardly exists. Nearly all of it is found intracellularly in either haemoglobin or the iron storage protein ferritin, and the small but rapidly exchanging extracellular iron pool is bound to the serum glycoprotein transferrin. These various forms have several functions: they maintain iron in a soluble form, prevent potential toxic effects, and allow its use in metabolism. Nevertheless, their extremely high affinity for binding iron confronts invading micro-organisms with the problem of how to acquire enough of it to allow growth. Only lactobacilli can grow in the total absence of iron,[1] and many pathogenic bacteria need a substantial amount.

Successful pathogens must therefore possess some means of overcoming the problem of obtaining iron. Bacteria secrete a variety of low molecular weight compounds known as siderophores. Usually derivatives of either catechol or hydroxamiic acid, these can bind iron as strongly as the host iron binding proteins.[2] Once the siderphores have obtained iron the complexes are taken up by the micro-organisms through outer membrane receptor proteins,[3] and the iron is then released.

Siderophores and their membrane receptors are usually produced as a response to iron deprivation, and in some cases they are encoded by plasmids, whose presence correlates with increased virulence.[4 5] That siderphore mediated iron uptake is important in the establishment of pathogenic

micro-organisms is supported by reports that bacteria grown in animals[6,7] or isolated from the lungs of patients with cystic fibrosis[8] produce siderophores and the receptors. Moreover, antibodies to enterochelin, a siderophore produced by many enterobacteriaceae, can be detected in normal human sera,[9] and perhaps also in breast milk (J L Young and J H Brock, unpublished observations). These antibodies impede siderophore mediated iron uptake and act as a second line of defence against microbial iron acquisition in vivo.[10]

Some bacteria, notably the neisseria, may acquire iron differently, through a direct interaction between them and transferrin,[11] reminiscent of the receptor mediated process by which mammalian cells acquire transferrin bound iron. It will be interesting to see how widespread this mechanism is among bacteria, and to learn more about it.

It has generally been assumed that the source of iron scavenged by the siderophores produced by bacteria growing in vivo is almost certainly transferrin. The latter is normally only about 30% saturated with iron in man and has a key role in ensuring that the extracellular phase of bacterial multiplication occurs in an iron restricted environment. Lactoferrin, a related protein found in milk and other external secretions, may fulfil a similar role at secretory surfaces, and lactoferrin in breast milk is probably partly responsible for the increased resistance of breast fed infants to gastrointestinal infection.[12]

Nevertheless, iron transfer from transferrin to siderophores in vitro is slow unless an unphysiologically large excess of siderophore is present, or the rate is enhanced by non-physiological concentrations of anions such as citrate, pyrophosphate, or nitrilotriacetate.[13,14] Furthermore, desferrioxamine, a streptomyces siderophore which is used for removing excessive iron stores from patients with severe iron overload, scavenges intracellular hepatic iron rather than transferrin bound iron.[15] Of the different iron pools in the mammalian cell, one, which probably represents iron in transit,[16] is readily available to desferrioxamine. Hence possibly intracellular rather than transferrin bound iron is the major target for some microbial siderophores. Intracellular pathogens such as *Mycobacterium tuberculosis* presumably also utilise intracellular iron.

To what extent do the host's iron stores affect the outcome of infection? Iron overload is known to increase the susceptibility to infectious disease.[17] In severe cases, such as haemochromatosis and transfusional iron overload, the serum transferrin becomes fully saturated and a pool of iron bound non-specifically to other serum proteins appears,[18] which is more accessible to bacteria. The injudicious use of parenteral iron dextran to treat anaemia in infants may have a similar effect.[19,20]

Less severe iron overload, where the transferrin saturation is increased but is less than total, may still be associated with an increased susceptibility to infection. There is little evidence, however, to support the popular assumption that raised transferrin saturation is responsible for the increased availability of iron to bacteria, for other factors associated with iron overload, such as impaired phagocyte function,[21] may be more important. Another factor may be excessive intracellular iron. In two infants suffering from acute iron overload after accidental ingestion of oral iron the transferrin saturation never exceeded 40%. Both, however, developed infection with *Yersinia enterocolitica* after starting chelation treatment with desferrioxamine[22]; this scavenges intracellular iron and its iron complex can be utilised by this organism.[23]

Since iron overload favours microbial iron scavenging mechanisms, and hence infection, iron deficiency might be thought to be protective. Again, the decrease in transferrin bound iron occurring in response to infection or inflammation[24] might serve to reinforce the host's iron withholding mechanisms.[17] Nevertheless, does a modest change in the level of transferrin bound iron have much effect on its availability to scavenging siderophores? On the one hand, animal studies have shown that hypoferraemia induced by the injection of endotoxin has a protective effect against experimental infection[25]; on the other hand, the associated fever may reduce siderophore production,[26] and inflammation also changes the intracellular iron pools.[27] The reduced transferrin saturation might, however, affect those organisms such as neisseria which acquire iron by direct interaction with transferrin itself.

Finally, the effect of iron on the host's immune system must not be forgotten. Cell mediated responses in particular are susceptible to iron deficiency,[28] and the proliferation of lymphocytes requires acquisition of transferrin bound iron.[29] Experimental iron deficiency reduces the saturation of transferrin to a level below that required for optimal proliferation of T cells.[30] Thus while iron deficiency may increase the host's ability to withhold iron from bacteria, this advantage may be more than offset by impairment of the immune system.

Normal iron balance therefore seems to achieve a compromise in which iron is not readily accessible to invading micro-organisms yet is present in sufficient quantity to allow the host's immune system to function optimally. Transferrin plays a key part in both mechanisms, but the importance of changes in its iron saturation in affecting microbial growth in vivo has probably been overemphasised. Future studies should concentrate on how, and whence, pathogenic micro-organisms acquire iron in vivo. The results may lead us to a better understanding of how changes in the amount of iron in the body affect the clinical outcome of infection.

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Suing tobacco companies

Doctors do not like litigation, but few would argue that a manufacturer should get off scot free when its products kill one in four of their users and are the largest cause of premature death in developed countries. In the United States doctors, lawyers, and victims are joining forces to orchestrate legal action against the cigarette companies for tobacco induced disease. Last week in London British doctors, lawyers, and campaigners got together under the auspices of Action on Smoking and Health (ASH) to hear from Professor Richard Daynard, professor of law at North-eastern University in Boston and founder and cochairman of the American Tobacco Products Liability Project.

More than 100 cases are pending in the United States, with up to a dozen due to go to court next year. In Australia a dying lung cancer victim of 38 gave evidence last week from her hospital bed in an action against two tobacco companies. In Britain a 31 year old sufferer from Buerger's disease who risks losing a leg is taking legal and medical advice on the prospects of success in suing the manufacturer. His solicitors hope to get legal aid for his case or, if unsuccessful, to raise funds through ASH.

Product liability law exists to compel the manufacturer of a defective product to compensate his victim. But it can do much more. In the United States the relentless financial pressures of mass product liability litigation have driven products from the marketplace, even when the consensus view has been that the benefits outweigh the risks. Pertussis vaccine lawsuits, for example, have left only one manufacturer in the United States market, and the price of the vaccine has rocketed.

The battle against smoking is a public information and education battle. In Britain the battle is not going well, at any rate where it counts—among those under 16. Last year's results from the Office of Population Censuses and Surveys showed that 13% of teenagers under 16 regularly smoke 50 cigarettes or more a week; in 1982 it was 11%. Court cases make news. Teenagers have got the message that smoking may shorten their lives, but to a 15 year old 60 and 70 seem equally far away. Few imagine that smoking could lose them a leg, and the sight of a double amputee being wheeled out of court on an American television news programme must have been worth 100 antismoking lectures at school.

That victim of peripheral vascular disease is one of three whose cases have gone to court so far in the United States and been lost. The judge directed the jury to return a verdict in the tobacco company's favour on the basis that the health risks of smoking have been well known for many years. The defence of *volenti non fit injuria*—that the plaintiff has voluntarily assumed the risk—is a potential obstacle for plaintiffs on both sides of the Atlantic. But the concepts of assumption of risk and the plaintiff's own contributory negligence are not now uniformly accepted throughout the United States.

In Britain those concepts are well entrenched in law, and proving that tobacco caused the illness or death will be a problem. It was in the other two cases that have gone to a jury verdict in the United States—one a death from heart disease and the other a case of tongue cancer in a 19 year old user of oral snuff. But factors in the British legal system make it harder to mount ground breaking litigation. Judges, not juries, decide liability and the size of awards. British lawyers, unlike their American counterparts, cannot take on cases on a contingency fee basis. In Britain the losing party to litigation usually has to pay the costs of the winner as well as his own. No individual could contemplate such an action unaided; even for an organisation such as ASH raising the funds would be far from easy.

The legal aid authorities have been adventurous on occasion in backing untried litigation. Now that tobacco "teabags," widely used in the United States, are to be produced at a factory in Scotland built with the aid of a reputed £1m in public funds we face the piquant prospect of government funds, on the one hand, subsidising the manufacture of a product which the United Kingdom Co-ordinating Committee on Cancer Research considers incontrovertibly linked with oropharyngeal cancer, and, a few years down the road, financing litigation seeking redress for its victims.

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Correction

The lessons from the Savage inquiry

The leading article commenting on the Savage inquiry (2 August, p 285) stated: "What can be said—for the inquiry tribunal decided the issue as a matter of fact—is that Mrs Savage's academic chief Professor Jurgis Grudzinskas had determined shortly before taking up his appointment to 'change his senior lecturer.'"

We have been asked by Professor Grudzinskas to point out that that statement was incorrect. The inquiry tribunal found that shortly after his appointment he made a remark to another professor that one of his first tasks would be to change his senior lecturer (that is, Mrs Savage), although this is not accepted by Professor Grudzinskas. The tribunal also found, however, that the remark made by Professor Grudzinskas was to him merely an unimportant passing remark, made on a social occasion which left no impression on his memory and that although it did indicate that he had had negative feelings towards her work at that early stage it was not in itself an indicator that at that time he had any future intentions towards her.

We regret and apologise to Professor Grudzinskas for any offence and embarrassment caused by any inaccuracy in our leading article.