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 and found that previous blood transfusion enhanced graft survival, but in some cases, particularly of melanoma.8

Suggestions have also been made that there is a unperceived difference in some other cancers.9-12 From the evidence available, it seems that repeated transfusion of whole blood also had this effect, infusions of plasma having been shown to induce and maintain remission of carcinoma.
micro-organisms is supported by reports that bacteria grown in animals or isolated from the lungs of patients with cystic fibrosis produce siderophores and the receptors. Moreover, antibodies to enterochelin, a siderophore produced by many enterobacteriaceae, can be detected in normal human sera,1 and perhaps also in breast milk (J L Young and J H Brock, unpublished observations).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 nitritolriacetate.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; this scavenges intracellular iron and its iron complex can be utilised by this organism.22

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 inflammation23 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, animals have shown that hypoferraemia induced by the injection of endotoxin has a protective effect against experimental infection24; on the other hand, the associated fever may reduce siderophore production,25 and inflammation also changes the intracellular iron pools.26 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,4 27 and the proliferation of lymphocytes requires acquisition of transferrin bound iron.28 Experimental iron deficiency reduces the saturation of transferrin to a level below that required for optimal proliferation of T cells.29 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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1 Archibald PS. Lactobacillus plantarum, an organism not requiring iron. Federation of European Microbiological Societies Letter 1983;39:29-32.
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 Northeastern 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 Berger'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 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 volunti 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 Coordinating Committee on Cancer Research considers incontroversibly 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.