118. P. Vittorelli, T. Winkler, H-J. Hansen, H. Schmid, *ibid.* **51**, 1457 (1968).
119. R. K. Hill, R. Soman, S. Sawada, *J. Org. Chem.* **37**, 3737 (1972). Because of a typographical error, the (*R*)-acid is shown in the paper of Hill *et al.* We thank a referee of our article here for bringing this to our attention.
120. W. Sucrow, B. Schubert, W. Richter, M. Slopianka, *Chem. Ber.* **104**, 3689 (1971); W. Sucrow and W. Richter, *ibid.*, p. 3679; W. Sucrow and B. Girgensohn, *ibid.* **103**, 750 (1970); W. Sucrow, P. P. Caldeira, M. Slopianka, *ibid.* **106**, 2236 (1973); W. Sucrow and P. Polyzou, *Tetrahedron Lett.* (1971), p. 1833.
121. B. M. Trost and R. F. Hammen, *J. Am. Chem. Soc.* **95**, 963 (1973).
122. Because of the ability of the sulfonium salt to racemize by inversion, it is possible to convert all of the material to one optically pure salt.
123. B. M. Trost and W. G. Biddlecom, *J. Org. Chem.* **38**, 3438 (1973).
124. J. E. Baldwin and J. E. Patrick, *J. Am. Chem. Soc.* **93**, 3556 (1971).
125. Y. Yamamoto, J. Oda, Y. Inouye, *Chem. Commun.* (1973), p. 848.
126. M. Moriwaki, S. Sawada, Y. Inouye, *ibid.* (1970), p. 419.
127. S. Braverman, *Int. J. Sulfur Chem. Part C* **6**, 149 (1971).
128. O. Achmatowicz, Jr., and B. Szechner, *J. Org. Chem.* **37**, 964 (1972).
129. L. N. Mander and J. V. Turner, *ibid.* **38**, 2915 (1973).
130. P. M. McCurry, Jr., and R. K. Singh, *Tetrahedron Lett.* (1973), p. 3325.
131. The transfer of asymmetry for a structure closely related to **106** has been demonstrated: R. K. Hill and N. W. Gilman, *ibid.* (1967), p. 1421.

Iron and Susceptibility to Infectious Disease

In the resolution of the contest between invader and host, iron may be the critical determinant.

Eugene D. Weinberg

Precisely three decades have elapsed since Schade and Caroline described evidence for the presence of strong iron binding proteins in egg white and plasma, and suggested that the ligands might function to withhold the metal from bacterial invaders (*1*). At that time, it was known that a prompt and consistent host response to bacterial invasion is a reduction in the amount of iron in the blood plasma. The reduction is now understood to be brought about by suppression of intestinal assimilation of iron (*2*) and by an increase in the quantity of the metal stored in the liver (*3*). Inasmuch as successful invaders obviously obtain the iron that is essential for their growth from living tissues, the microbes must either have a mechanism that enables them to destroy host ligands or else have the potential to produce their own powerful iron binding compounds. No evidence exists for the former mechanism; but in 1952, Neilands and his students began to describe microbial metabolites that can vigorously extract iron from a variety of environments (*4*), and several laboratories have subsequently participated in the development of this field [for a review, see (*5*)].

Thus, by 1960, enough information was available for studies to be made of the confrontations between the iron chelators of hosts and those of microbial invaders. In the earliest study (*6*), on pasteurellosis, several principles were recognized that remain valid. Parenterally administered iron, which enhances the infectious process, has no effect on (i) mobilization or activity of phagocytic cells, (ii) antibody production or activity of complement, or (iii) toxicity of dead organisms. Within the past decade, numerous reports on the competition for iron between hosts and invaders have appeared (*7*, *8*), and there is general agreement that excess iron simply functions as a microbial nutrilite. The ability of the host to withhold iron from microbes is called "nutritional immunity" (*9*).

In this article, I review (i) the microbial need for and acquisition of iron, (ii) the offensive advantage provided to the invaders by hyperferremia and hypotransferrinemia, and (iii) the defensive advantage provided to hosts by hypoferremia. I conclude by discussing the extent to which nutritional immunity might have general applicability in host-parasite interactions.

The author is a professor in the Department of Microbiology, Indiana University, and in the medical sciences program at the School of Medicine, Indiana University, Bloomington 47401.

Microbial Acquisition of Iron

Similar quantities of iron are required for the growth of plant, animal, and microbial cells (*10*). Green algae, mouse L cells, and gram-negative bacteria need from 0.3 to 1.8 micromolar concentrations of iron; most gram-positive bacteria and fungi need from 0.4 to 4.0 μM iron. Minimal synthetic culture mediums contain from 0.5 to 3.0 μM iron, usually as a contaminant of the sugar and the phosphate salts; commonly used complex culture mediums contain 3.0 to 12.0 μM iron. Thus laboratory mediums generally need not be enriched with additional iron to support growth.

Nevertheless, because of the extreme insolubility of ferric iron at neutral *p*H, aerobic and facultative microbial cells must synthesize phenolates or hydroxamates to solubilize and assimilate the metal; compounds with these functions are called siderophores (*11*). Although anaerobic bacteria do not need to produce ferric iron binding compounds (because the metal is in the reduced valence state in their growth environments), they probably form transport ligands that have a selective affinity for ferrous iron (*11*). Those aerobic and facultative strains that are unable to synthesize siderophores (that is, are anautosequesteric) must, of course, be supplied with preformed phenolates or hydroxamates in addition to iron.

Although the production of siderophores is repressed by quantities of iron greater than those needed for growth, the repression is by no means absolute in iron-rich environments. The quantity of the nonrepressible residue of siderophores is actually much greater than that needed for growth of anautosequesteric mutants (*11*). In systems in vitro, it has been observed that autosequesterism is restricted by elevated temperatures (*12*); it is possible that the ability of invaders to synthesize iron ligands in the host is suppressed by fever (*13*).

However, information is not yet available on the rate and quantity of siderophore production in various tissues of infected hosts.

The quantity of iron in host fluids, such as milk and plasma, is more than sufficient for microbial growth. Depending on the species, milk of normal individuals contains between 10 and 30 μM, and plasma between 10 and 65 μM iron. However, proteins such as lactoferrin and transferrin in healthy human hosts are present in sufficient quantity to bind the iron (two atoms per molecule); the normal iron saturation level of transferrin is 20 to 30 percent. Since the association constant of transferrin for the metal is about 10^{30}, the amount of free ionic iron in equilibrium with a 25 percent saturated complex is approximately 6×10^{-9} μM. This amount is at least 10^8-fold less than that required for microbial growth.

Not surprisingly, microbial siderophores likewise have association constants for iron of 10^{30} or more, and at least some of these are equal to the task of withdrawing the metal from 30 percent saturated transferrin. For example, in tests in vitro, at a mycobactin to transferrin molar ratio of 1 : 100, the microbial metabolite transferred sufficient iron from the 30 percent saturated protein to tubercle bacilli to permit growth of the bacteria. With 100 percent iron-saturated transferrin, a molar ratio of as little as 1 : 50,000 was sufficient to achieve bacterial growth (*9*). Siderophores of gram-negative bacteria such as 2,3-dihydroxy-*N*-benzoyl-L-serine and its trimer, enterochelin, likewise can remove the metal from iron-transferrin complexes (*14*).

As is true for extracellular host fluids, the iron within host cells also is not readily available for microbial growth. Ligands such as ferritin and lactoferrin provide nutritional immunity in intracellular environments. However, if either mycobactin or additional iron is supplied to the host cells, intracellular growth of mycobacteria is enhanced considerably (*15*).

Microbial siderophores are not always advantageous to microorganisms. If contained in the diet of mice, enterochelin (enterobactin; pacifarin), a cyclic trimer of 2,3-dihydroxy-*N*-benzoyl-L-serine, causes injected virulent salmonella bacteria to be suppressed, provided that an avirulent salmonella strain is injected 1 to 2 days earlier (*16*). Some actinomycetes produce iron-chelating antibiotics, which are termed sideromycins. These contain the entire structure necessary for siderophore function, but owe their antagonistic nature to an attached side chain. The structural resemblance of part of the sideromycin molecule to a siderophore probably serves the purpose of facilitating entry of the molecule into the cell. Inside the cell, the antibiotic action is caused entirely by the pendant group (*5*). In contrast to this type of antimicrobial antagonism, there is evidence that microorganisms can use each others' iron chelators to obtain the growth-essential metal. For example, mutants of *Salmonella typhimurium* that cannot synthesize their natural siderophore are able to grow in culture when supplied ligands formed by other bacteria or fungi (*17*).

Although bacteria grow well throughout a range of concentrations of iron of 2.0 to 2000 μM, their ability to form secondary metabolites (such as exotoxins) is restricted to a rather narrow segment of this range. Generally, formation of such metabolites is stimulated or inhibited by iron concentrations between 3.0 and 30 μM. It is postulated that the metal acts in association with either a transcriptional or translational event required for the formation of the secondary substances (*18*).

Secondary metabolites consist of a wide diversity of thousands of natural products, each narrowly restricted to one or a few species, that are synthesized for a brief time by microbial cells that have stopped dividing. Presumably, the substances serve as disposal packages of primary metabolites that have accumulated in cells no longer able to divide. Successful completion of the packaging process yields cells with long-term viability, whereas interruption or distortion of the process results in early death of the microorganisms. A very small minority of secondary metabolites are, probably by accident, pharmacologically potent against cells either of other microbial groups (that is, they are antibiotics) or of plants or animals (that is, they are toxins) (*18*). As with the range of iron concentrations within which secondary metabolites can be formed, the range of temperatures that permit secondary metabolism is considerably narrower than that which allows cell growth (*13*).

Manipulation of iron concentration and temperature is widely used in industry to control the amount of toxin and antibiotic formation in fermentation processes; but it has not yet been possible to control toxigenesis in infected hosts in this manner. As I will show, addition of iron to hosts so strongly stimulates microbial growth, and deletion of the metal so strongly retards growth of the invaders, that it is difficult, and perhaps unnecessary, to observe a specific effect on toxin formation in vivo. Nor is it yet known to what extent host alterations of iron metabolism and body temperature might suppress toxigenesis while still permitting a limited amount of microbial growth.

Hyperferremia; Hypotransferrinemia

From the preceding section, it might be supposed that a critical determinant of virulence is simply the ability to produce a siderophore that can withdraw growth-essential iron from host protein ligands. Yet the actual situation is considerably more subtle. For example, nonvirulent tubercle bacilli synthesize as much mycobactin as do virulent strains but the lesser content of surface lipids of the former facilitates extraction of the siderophore by such nonionic surfactants as lecithin (*19*). And even virulent mycobacteria have difficulty in withdrawing iron from transferrin whose metal saturation is less than 70 to 80 percent unless a large quantity of mycobactin is available to the organisms (*9*). Antibodies to *Escherichia coli* depressed siderophore synthesis in a coliform strain of low virulence but not in a more virulent strain. However, when preformed siderophores were supplied, each strain could obtain iron from transferrin that was 43 percent saturated with the metal (*20*).

Nevertheless, a very consistent finding is that the intricate checks and balances between the iron chelators of microbes and of hosts are readily and markedly upset by changes in the environmental concentration of iron. If the metal is added, microbial growth is enhanced; if the metal is deleted, host defense is strengthened. This situation obtains not only in experimental systems in vitro and in vivo but also in clinical disease situations.

The ability of iron to neutralize the microbiostatic action of mammalian serums contained in culture mediums has been observed with a wide spectrum of fungi and bacteria (*9, 21*). Organisms tested include species of *Candida, Clostridium, Escherichia, Mycobacterium, Pasteurella, Shigella,* and *Staphylococcus.* Generally, sufficient exogenous iron to achieve at least 60 to 80 percent saturation of serum transferrin

Table 1. Correlation of level of iron saturation of transferrin (Tr) with bacterial growth in mammalian serums in vitro. Bacterial growth is expressed as the number of generations of tubercle bacilli in 14 days. Data modified from Kochan (*9*).

Source of serums	Number of samples	Fe concentration in serum (μM)*	Saturation of Tr (%)*	Bacterial growth	
				No added Fe	36 μM added Fe
Human	10	17	30.0	0–1	10–14
Bovine	4	34	39.0	0–1	10–14
Mouse	10	41	60.2	1–5	9–15
Rabbit	8	36	64.3	1–5	10–15
Guinea pig	20	49	84.4	9–14	9–14

* Individual variations fell within 10 percent of the mean values listed.

is necessary. With *Cl. perfringens*, for example, horse serum containing transferrin saturated 18 percent with iron prevented bacterial multiplication. Addition of 10 μM ferric iron resulted in 83 percent saturation and permitted growth. With the BCG strain of *M. tuberculosis*, 36 μM iron neutralized the bacteriostatic activity of transferrin in human, bovine, mouse, and rabbit serums. However, exogenous metal was not needed in tests with guinea pig serum because of the guinea pig's normally high level of iron saturation of transferrin (Table 1) (*9*).

As could be predicted from these studies in vitro, the parenteral administration of iron compounds to experimental animals reduces the size of the inoculum (number of microorganisms) needed to produce disease or death, and permits a greater amount of multiplication of microorganisms in invaded tissues. For example, the number of cells of strains of *Pseudomonas aeruginosa, S. typhimurium, Listeria monocytogenes*, or *E. coli* needed to kill 50 percent of test rats or mice, compared with controls, was lowered by 3, 3, 4, or 5 log units, respectively, simply by concurrent intraperitoneal or intravenous injection of 1.0 to 5.0 milligrams of iron per kilogram of body weight (*7*). The number of cells of *Cl. perfringens* in guinea pig muscle was increased 6000-fold; of *E. coli* in rat kidney, 1000-fold; and of *M. fortuitum* in mouse kidney, 33-fold, in animals stressed by injection with iron, compared with control animals (*22*). Even coagulase-negative staphylococci, that were harmless in control rats, were able to cause renal abscesses in iron-stressed animals; and an attenuated strain of *Pasteurella pestis*, that caused no deaths in control hosts, killed 100 percent of iron-stressed mice (*22*).

To be effective, the metal must be able to diffuse to the site of invasion; thus for systemic diseases, intravenous, intraperitoneal, and intramuscular routes of injection generally are effective whereas oral administration is not. Active forms of iron include ferric and ferrous salts; organic compounds of low molecular weight, such as iron sorbitol citrate; and products of host origin such as heme, hemin, hemoglobin, and ferritin. Such exogenous high molecular weight polymers as iron dextran and iron dextrin cannot pass the renal glomerulus and thus, when injected intraperitoneally, were not able to enhance bacterial kidney infections (*22*). Iron compounds are active when administered during the early portion of the incubation phase of experimental infections as well as when given concurrently with the inoculation of microorganisms.

As could be predicted from these studies in vivo, persons exposed to infection who are undergoing hyperferremic episodes have greater susceptibility to bacterial and fungal pathogens than in periods when their plasma iron is within the normal range. Also, such persons are more susceptible than non-hyperferremic members of their families or communities when exposed to identical kinds and quantities of potential pathogens (*23*). Hyperferremic episodes occur in persons suffering from (i) destruction of liver cells containing ferritin (as in viral hepatitis or louse-borne relapsing fever), (ii) silent or overt hemolytic anemia (as in malaria, bartonellosis, sickle cell disease, leukemias, lymphomas, or Hodgkin's disease), or (iii) an overload of iron from exogenous sources (as when neonates are born with excess iron that had been obtained from maternal plasma, or when excess dietary iron causes hemochromatosis).

Human beings in the acute phases of the conditions listed above in (i) or (ii) generally have plasma iron concentrations greater than 35 μM (compared with normal values of 17 to 23 μM) and, because the amount of transferrin does not appreciably increase, the saturation of the protein is often greater than 60 percent. In some cases of leukemias, and in persons with thalassemia major who have had a splenectomy, saturation values of 100 percent have been reported (*24*). In the neonatal condition listed in (iii), mean iron concentrations in the plasma of normal infants aged 6 to 12 days were found to be 27 μM; this is only a moderate elevation but, because such infants have insufficient transferrin, saturation values are approximately 75 percent (*23*). A deficiency of transferrin is observed also in older children suffering from kwashiorkor. Although children dying of this condition are actually hypoferremic (mean iron concentration in plasma, 11 μM), their transferrin concentration of only 3.5 μM results in a saturation value of greater than 100 percent (*25*).

Patients stressed by these various hyperferremic or hypotransferrinemic states have far more infection during such episodes than when their transferrin iron saturation values return to normal, or than their nonstressed neighbors (*23*). Systemic salmonellosis, for example, is so common in persons with either bartonellosis or viral hepatitis that salmonella bacteria were formerly thought to be the etiologic agents of each of these conditions. In children with sickle cell disease, bacterial infection is still the single most common cause of death, and the incidence of bacterial meningitis is 300-fold greater than in normal siblings (*26*).

The incidence of bacterial infection is far higher in children with kwashiorkor than in normal children, and there is evidence that administration of iron to patients with abnormally low transferrin levels may result in overwhelming infection and death (*25*). Patients with acute leukemia have a high frequency of candidiasis, those with hemochromatosis have a high rate of salmonellosis, and listerellosis is a complication of various malignancies associated with hemolysis (*23, 24*). The high prevalence of infection in newborns is well known; for example, the incidence of neonatal bacterial meningitis in the United States is 1 per 2000 births and, even with prompt chemotherapy, mortality exceeds 65 percent (*27*). Two-thirds of these infections are caused by gram-negative enteric bacteria that rarely cause meningitis in older infants.

At least one iatrogenic example of stress being caused by excess iron has been reported. Following a single injection of iron sorbitol citrate, patients with chronic pyelonephritis had an

exacerbation of their infection as demonstrated by increased urinary output of white blood cells. No increase in white blood cells occurred in noninfected controls or in patients with noninfectious renal diseases (*28*).

Hypoferremia

A corollary to the foregoing discussion is that conditions resulting in hypoferremia should be of advantage to the host and of disadvantage to the microbial invader. A second possible corollary is that, upon invasion, hosts should attempt to become transiently hypoferremic. Evidence is available to support each of these corollaries.

In experiments in vitro, samples of serums extracted from guinea pigs that had been injected with such hypoferremic materials as *E. coli* endotoxin, cell wall extracts of tubercle bacilli, or living tubercle bacilli (BCG strain) gained bacteriostatic activity in proportion to their loss of iron. The activity could be neutralized simply by adding exogenous iron (Table 2). The decrease and subsequent increase in iron saturation of transferrin (Table 2) resulted from a decrease and an increase in the concentration of iron in the plasma rather than from any variation in concentration of the protein (*9*).

In experiments in vivo, endotoxin was injected into mice 24 hours prior to infection with *S. typhimurium*. (The hypoferremic action of endotoxin is maximal between 16 and 24 hours after injection.) The bacterial inoculum permitted 50 percent of the test animals to survive for 6 days whereas 50 percent of the controls died within 4 days (*7*). In a different study, desferrioxamine B, the siderophore useful in therapy of hemochromatosis because it can be excreted by the kidneys as an iron chelate, was injected 1 day prior to, on the same day, and 1 day after the inoculation of mice with *L. monocytogenes*. The amount of bacteria required to kill 50 percent of the test animals was increased 30-fold over the controls by this treatment (*7*).

Upon invasion by microorganisms, hosts could conceivably become hypoferremic by a variety of mechanisms, but evidence exists for only two (*13*). First, intestinal assimilation of iron is decreased (*2*). In children injected with vaccines or suffering from infections, the depression of assimilation was found to be consistent and profound, and to be independent of the hosts' state of nutrition, growth rate, reserves of iron in the bone marrow, iron saturation of transferrin, concentration of iron in the plasma, and hemoglobin level. The depression of assimilation bore no relation to the rate of assimilation when the hosts had recovered. In a different study with adults, an average of 7.2 percent of an oral dose of ^{59}Fe-labeled iron was absorbed into the blood of normal persons, whereas only 1.0 percent of the dose was absorbed by febrile patients (*2*). Similarly, intestinal absorption of iron in rats was decreased when the animals were injected with *E. coli* endotoxin (*2*).

Table 2. Correlation of hypoferremia with bacteriostatic action of guinea pig serum. The bacteriostatic action is expressed as the number of generations of tubercle bacilli in 14 days. Data modified from Kochan (*9*).

Time after treatment (days)	Fe saturation of transferrin (%)	Bacteriostatic action	
		No Fe	18 μM Fe
	Control		
1	85.6	11.5	11.8
	Treatment with E. coli *endotoxin*		
1	17.5	0.0	0.0
2	42.1	0.0	10.6
3	60.2	0.0	11.8
5	74.7	8.7	12.0
10	93.8	12.5	11.6
	Treatment with living BCG strain of M. tuberculosis		
3	86.2	10.5	11.5
7	79.4	9.1	10.6
14	75.0	4.3	9.5
21	75.3	0.4	9.1
28	68.6	0.0	9.7

Second, hosts invaded by microorganisms or microbial cell materials store an increased amount of iron in their livers. This process is induced also by injection of leukocytic endogenous mediator (LEM) (*3*). This low molecular weight protein is released from leukocytes of test animals into their plasma within 2 hours of inoculation of either microorganisms or endotoxin. When extracted from the plasma and injected intraperitoneally into infection-free rats, LEM induced a 31 percent increase of iron in liver within 6 hours (*3*).

These alterations of iron distribution are generally accompanied or followed by fever; possibly the rise in host temperature serves further to restrict accessibility of iron to the invading microorganisms. It will be recalled that microbial synthesis of both siderophores and secondary metabolites is suppressed by elevated temperatures (*13*).

Nutritional Immunity

The role of iron-specific nutritional immunity in protecting hosts from bacterial and fungal diseases apparently is most important during the period between the time of invasion and the onset of microbial cell multiplication. Very promptly after invasion, the host becomes hypoferremic, thus enhancing the ability of transferrin to withhold iron from siderophore molecules that the entering microbes might synthesize. Moreover, when exogenous iron was injected intravenously into guinea pigs at any time from zero to 6 hours after intramuscular injection of *Cl. perfringens*, death from infection ensued within 18 hours; in contrast, if iron was injected at 8 hours, the animals had already begun to kill the bacteria, and all of the hosts recovered (*22*).

Perhaps different host species vary in the extent to which they rely on iron-specific nutritional immunity. Inasmuch as the normal iron saturation level of transferrin is dangerously high in guinea pigs and moderately high in rabbits and mice, these three kinds of hosts might need to have alternative compensatory defense mechanisms. Yet the three species react in a manner identical to that of hosts such as human beings and cattle that have low iron saturation levels; namely, injection of iron lowers their resistance, and inoculation of microbes or microbial products induces prompt hypoferremia.

Might cryptic disturbances in iron metabolism during the lifetime of individual hosts permit resurgence of latent infections such as tubercular lesions? And could therapy with desferrioxamine B lower the level of iron saturation so as to provide a more favorable milieu for use of anti-infective chemotherapeutic agents? Of course, the siderophore drug could not be used were it merely to transfer iron to invading pathogens rather than to withdraw the metal by way of kidney excretion. Nonetheless, experience with the experimental listerial infection described previously indicates that, at least for listerellosis, the drug might have therapeutic efficacy.

Siderophores such as enterochelin are synthesized by bacterial contaminants in food as well as by intestinal bacteria. To what extent are we dependent on these microbial ligands to protect us against potentially dangerous enteric pathogens? Should our foods be fortified with siderophores? And to what extent does lactoferrin in milk af-

ford protection against intestinal pathogens? Would consumption of iron-fortified milk increase the incidence and severity of bacterial intestinal diseases?

Is nutritional immunity specific only for iron or might such other nutrilites as inorganic phosphate (P_i) or zinc be involved? Human beings infected with gram-negative (but not gram-positive) bacterial pathogens reduce the quantity of their P_i in their plasma to a level that is suboptimal for microbial growth (*29*). Moreover, human beings as well as other animals quickly become hypozincemic upon being invaded by either microbes or microbial products. Fungi require more zinc than do bacteria for growth, and patients with high amounts of zinc either in their plasma (because of intravenous feeding), or in their urine (as in diabetes), have a high incidence of candidal infections in their tissues or urogenital tracts, respectively. Growth of tumor cells requires zinc, and the hypozincemic response in some patients with neoplasms may be a defense mechanism. Moreover, dietary deficiency of zinc in rats causes inhibition of growth of a variety of tumors (*30*).

Since rapid growth of tumor cells requires iron as well as zinc, might it be possible to obtain tumor growth remissions by repeated injection of agents that are both hypoferremic as well as hypozincemic? Microbes and microbial products have long been known to cause a decrease in rate of growth of some tumors, and in the past several years, BCG has been administered to human beings as an experimental adjunct to cancer chemotherapy (*31*). Generally, repeated injections are employed; in some cases weekly, and in others, as few as four injections per year are given. To determine whether or not the hypoferremic and hypozincemic action of BCG is temporally associated with its antitumor effect, the concentrations of iron and zinc in the plasma of such patients should be monitored weekly. It may be observed in Table 2 that, in guinea pigs, the maximal hypoferremic effect was achieved 4 weeks after a single inoculation of BCG. In some patients, inoculation with BCG causes hyperthermia that might further interfere with iron availability to the tumor cells. Moreover, the hypoferremia and low grade fever that often occur in patients with tumors might be natural aspects of their defense mechanisms.

Summary

All living cells have a quantitatively similar need for iron, and all must form or be supplied with compounds that they can use to solubilize and transport the metal. Proteins such as transferrin and lactoferrin that are employed for these functions by mammalian and avian hosts can, to some extent, withhold the metal from the siderophores of invading bacteria and fungi. To reinforce this withholding process, invaded hosts promptly become hypoferremic by halting intestinal assimilation of iron, and by increasing liver storage of the metal. The concomitant development of fever by hosts may serve to exacerbate the iron famine of the invaders inasmuch as synthesis of microbial siderophores is restricted by elevated temperatures. However, if hosts are hyperferremic (because of liver destruction, hemolytic diseases, neonatal status, or excess iron introduced by way of diet or injection) or hypotransferrinemic (as in kwashiorkor), they are exceedingly susceptible to even a small number of invading bacterial or fungal pathogens.

The attempt by hosts to withhold iron from invaders is termed "nutritional immunity"; the concept may embrace such other nutrilites as P_i and zinc. Nutritional immunity might also be a component of defense against growth of tumor cells. As adjuncts to both antimicrobial and antitumor chemotherapy, it might be possible to use clinical procedures to strengthen nutritional immunity.

References and Notes

1. A. L. Schade and L. Caroline, *Science* **100**, 14 (194→ *ibid.* **104**, 340 (1946).
2. C. H. Beresford, R. J. Neale, O. G. Brooks, *Lancet* **1971-I**, 568 (1971); R. Dubach, S. T. E. Callendar, C. V. Moore, *Blood* **3**, 526 (1948); S. Cortell and M. E. Conrad, *Am. J. Physiol.* **213**, 43 (1967).
3. R. S. Pekarek, R. W. Wannemacher, Jr., W. R. Beisel, *Proc. Soc. Exp. Biol. Med.* **140**, 685 (1972).
4. J. B. Neilands, in *Inorganic Biochemistry*, G. Eichhorn, Ed. (Elsevier, Amsterdam, 1973), p. 167.
5. G. A. Snow, *Bacteriol. Rev.* **34**, 99 (1970).
6. T. W. Burrows, *Curr. Top. Microbiol. Immunol.* **37**, 59 (1963).
→ C. M. Forsberg and J. J. Bullen, *J. Clin. Pathol.* **25**, 65 (1972); G. C. Chandlee and G. M. Fukui, *Bacteriol. Proc.* (1965), p. 45; C. P. Sword, *J. Bacteriol.* **92**, 536 (1966); J. J. Bullen, L. C. Leigh, H. J. Rogers, *Immunology* **15**, 581 (1968).
8. C. M. Martin, J. H. Jandel, M. Finland, *J. Infect. Dis.* **112**, 158 (1963); R. R. Brubaker, E. D. Beesly, M. J. Surgalla, *Science* **149**, 422 (1965); J. Fletcher and E. Goldstein, *Br. J. Exp. Pathol.* **51**, 280 (1970).
9. I. Kochan, *Curr. Top. Microbiol. Immunol.* **60**, 1 (1973).
10. C. A. Price and E. F. Carell, *Plant Physiol.* **39**, 862 (19€→ K. Higuchi, *J. Cell Physiol.* **75**, 65 (1970); E. D. Weinberg, *J. Infect. Dis.* **124**, 401 (1971); A. Bovallius and B. Zacharias, *Appl. Microbiol.* **22**, 260 (1971).
11. C. E. Lankford, *Crit. Rev. Microbiol.* **2**, 273 (1973).
12. J. A. Garibaldi, *J. Bacteriol.* **110**, 262 (1972).
13. E. D. Weinberg, in *Trace Element Metabolism in Animals*, W. G. Hoekstra, J. W. Suttie, H. Ganther, W. Mertz, Eds. (University Park Press, Baltimore, in press), vol. 2, chap. 17.
14. T. D. Wilkins and C. E. Lankford, *J. Infect. Dis.* **121**, 129 (1970).
15. W. C. Wheeler and J. H. Hanks, *J. Bacteriol.* **89**, 889 (1965).
16. E. J. Wawszkiewicz, H. A. Schneider, B. Starcher, J. Pollack, J. B. Neilands, *Proc. Natl. Acad. Sci. U.S.A.* **68**, 2870 (1971).
17. M. Luckey, J. R. Pollack, R. Wayne, B. N. Ames, J. B. Neilands, *J. Bacteriol.* **111**, 731 (1972).
18. E. D. Weinberg, *Adv. Microb. Physiol.* **4**, 1 (1970); *Perspect. Biol. Med.* **14**, 565 (1971).
19. I. Kochan, C. A. Golden, D. R. Spriggs, *Infect. Immun.* **9**, 34 (1974).
20. H. J. Rogers, *ibid.* **7**, 445 (1973).
21. L. Caroline, C. L. Taschdjian, P. J. Kozinn, A. L. Schade, *J. Invest. Dermatol.* **42**, 415 (1964); H. J. Rogers, *Immunology* **12**, 285 (19→ J. J. Bullen and H. J. Rogers, *Nature (Lond.)* **224**, 380 (1969); R. R. Brubaker, *ibid.* **57**, 111 (1972); A. L. Schade and L. Caroline, *Science* **104**, 340 (1946); A. L. Schade, *Biochem. Z.* **338**, 140 (1963).
22. J. J. Bullen, G. H. Cushnie, H. J. Rogers, *Immunology* **12**, 303 (1967); J. Fletcher and E. Goldstein, *Br. J. Exp. Pathol.* **51**, 280 (1970); A. Wake, H. Morita, M. Yamamoto, *Jap. J. Med. Sci. Biol.* **25**, 75 (1972).
23. E. D. Weinberg, *Tex. Rep. Biol. Med.* **30**, 277 (1972).
24. L. Caroline, F. Rosner, P. J. Kozinn, *Blood* **34**, 441 (1969); L. Caroline, P. J. Kozinn, F. Feldman, F. H. Stiefel, H. Lichtman, *Ann. N.Y. Acad. Sci.* **165**, 148 (1969).
25. H. McFarlane, S. Reddy, K. J. Adcock, H. Adeshina, A. R. Cooke, J. Akene, *Br. Med. J.* **4**, 268 (1970).
26. E. Barrett-Connor, *Medicine (Baltimore)* **50**, 97 (1971).
27. H. D. Riley, Jr., *J. Infect. Dis.* **125**, 420 (1972).
28. J. D. Briggs, A. C. Kennedy, A. Goldberg, *Br. Med. J.* **2**, 352 (1963).
29. E. D. Weinberg, *Dev. Ind. Microbiol.*, in press.
30. W. DeWys and W. Pories, *J. Natl. Cancer Inst.* **48**, 375 (1972).
31. F. C. Sparks, M. J. Silverstein, J. S. Hunt, C. M. Haskell, Y. H. Pilch, D. L. Morton, *N. Engl. J. Med.* **289**, 827 (1973).
32. Supported in part by a research grant from the Department of Animal Health and Nutrition, Commercial Solvents Corporation, and by PHS grant HD-03038-03.