

fort has now been terminated in favor of open-cycle and electrolytic approaches.

Shinnar's comments illustrate the differences between the ideal and past or current practice, particularly in regard to recovering waste heat and minimizing the work required for separation. Considerable improvement would be needed in these areas in order to make closed-cycle thermochemical hydrogen economically feasible; one here must trade capital investment against operating costs to find the minimum total cost. We agree that a very important part of cycle selection, often ignored, is the minimizing of phase separation work by using "natural" phase separations as much as possible.

Processes A, B, and C do not violate the second law of thermodynamics, as implied by Shinnar. Specifically, if one supplies 18 kcal for losses and work at 600°C, and 30 kcal (for step B2) at 200°C, the ideal Carnot equivalent engine for process B would deliver 56.2 kcal, which is not far from the theoretical 56.7 kcal, considering possible inaccuracies in thermodynamic data and the simplified analysis. A proper analysis of processes A and C leads to the same conclusion.

The 1400°K thermochemical cycle proposed by Soliman *et al.* is quite similar to one that we evaluated earlier in our labora-

tory, and we agree that it looks relatively attractive on a heat efficiency basis. However, we hold to our earlier opinion that a limit of 1200°K seems realistic for safe process heat delivered across a heat exchanger in commercial reactors for the next two decades. For 1200°K maximum, the identified thermochemical cycles based on sulfates appear to involve unnecessary penalties in energy consumption. If the serious problems of heat exchanger integrity, corrosion, and containment of radioactive species at the 1400°K level can be solved, then the cycle of Soliman *et al.* or some other cycle could form the basis for a successful water-splitting process. Such a cycle might require integration in certain temperature ranges.

In summary, the basic concept of closed-cycle thermochemical hydrogen processes is sound but further detailed study will be required to determine whether they are practically and technically feasible and whether they will ever compete economically with electrolysis or other hydrogen production methods in the long term.

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## Iron and Susceptibility to Infectious Disease

One of man's most critical nutritional problems is iron-deficiency anemia (1). As Weinberg pointed out (2), however, administration of supplemental iron would be counterproductive if it did indeed neutralize an individual's defense against bacterial pathogens. Before we conclude, like the author of a recent letter to *Science* (3), that iron fortification of foods would be "irresponsible," we should take pains to determine whether the relevant experimental work in this area really supports Weinberg's arguments.

Serum transferrin is bacteriostatic because it binds available ionic iron and withholds it from bacteria, which require iron for growth. If transferrin iron-binding capacity is saturated, this potential bacteriostatic mechanism cannot operate. Many of the experiments designed to substantiate this function have been based on one of two assumptions: (i) that iron administered parenterally in the form of stabilized iron polymers, such as iron-dextran or ferric ammonium citrate, "saturate" circulating transferrin in vivo; or (ii) that iron-transferrin prepared in vitro, by adding inorganic ferric or ferrous salts, is identical

to iron-transferrin formed during the assimilation of iron in vivo. Neither assumption is valid.

Iron polymers react sluggishly, if at all, with transferrin (4, 5). Intravenous injections of polymers may easily deliver an amount of iron to the blood that greatly exceeds the iron-binding capacity of transferrin (6) before they are cleared from the circulation by the reticuloendothelial cells, which may then release a portion of this iron to transferrin for several days (7). After intramuscular or intraperitoneal injection of iron polymers, serum iron may equal or exceed the total iron-binding capacity for a few hours while the polymers are absorbed intact into the lymphatics (8). Such high concentrations of iron in the serum are only transient, but significant amounts of polymeric iron are meanwhile available for microbial growth. Under these circumstances, transferrin "saturation" have no physiological meaning. The data (6, 9) simply demonstrate that microorganisms can thrive on polymeric iron. The implications of these data should not be extrapolated to any but iatrogenic situations.

Stoichiometric Fe(III)-transferrin complexes are formed in vitro only when the ferric ion is presented to the protein in a suitably chelated form, for example, as iron nitrilotriacetate (10). Unfortunately, many widely used methods of saturating transferrin in vitro, including most current clinical procedures for measuring the total iron-binding capacity of human serum, continue to require inorganic ferrous or ferric salts as iron donors. Under such conditions, with O<sub>2</sub> present, ferrous ion is oxidized at a rapid rate at neutral pH, especially in the presence of serum transferrin or ceruloplasmin (11). The ferric ion formed by this oxidation immediately hydrolyzes to form polynuclear, high-molecular-weight complexes (12). When inorganic ferric salts are used to saturate transferrin, they rapidly hydrolyze to polymeric species and are in large part bound nonspecifically to the protein. All attempts to "saturate" transferrin with inorganic iron salts force the utilization of far more than stoichiometric amounts of iron to fill the two binding sites (5). The excess iron is present in a polynuclear form and is nutritionally available to microorganisms in vitro (13, 14).

As Weinberg noted (2), orally administered iron is generally not effective in promoting systemic infection. It is nearly impossible to saturate the transferrin of normal individuals by therapeutic oral doses of iron, partly because transferrin-bound iron is turned over rapidly in serum (15). Transferrin is not found fully saturated even after excessive intake of dietary iron in the rat (16) or man (17). There are no studies of bacteremia or systemic infections in animals whose serum iron levels were manipulated by strictly dietary means, that is, fed a low iron diet to produce iron deficiency or offered one of many suitable iron complexes which facilitate iron absorption and overloading (18). Experiments such as Kochan's (2, table 1; 14) are subject to the criticism that the variations in transferrin saturation were produced during the course of, or recovery from, an induced hypoferremic state, which may affect the levels of many other micronutrients or defense mechanisms. If there is real concern for the safety of dietary iron supplementation, it is important that experiments be developed with reasonable models to test the effect of transferrin saturation on bacterial infection in vivo.

The public health issues of dietary iron fortification are now being obfuscated by two arguments: The first is concerned with the potential danger of bacterial infection, as expressed in Weinberg's article; the second, with the danger that such iron will ex-

acerbate iron storage pathologies (19). The evidence for the first case appears to be a large body of data based on a poor understanding of the biochemistry and physiology of iron. Sussman (20) recently reviewed the same data and concluded, for reasons different from ours, that hyperferremia contributes little to the course of human infections. The threat of iron overload through fortification must be approached by developing accurate and reliable methods of assaying iron storage, not only to screen susceptible individuals, but also to provide criteria of effective iron assimilation. Recent successes with radioimmunoassays for circulating ferritin (21), which reflect iron stores but do not require uncomfortable bone marrow or liver biopsies, may encourage a large-scale trial of the health benefits of increased iron fortification of flour and bread (22).

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Let us distinguish between the possible hazard of receiving excess *parenteral* iron from the possible hazard of receiving excess *oral* iron. On the one hand, numerous experimental studies and retrospective clinical observations (1, 2) suggest that the incidence of systemic bacterial and fungal infection should be expected to increase in hypotransferrinemic persons (for example, newborns; kwashiorkor victims) who are injected with iron compounds. In contrast, few experimental studies have yet been performed to determine whether feeding excess iron to hosts prone to bacterial enteritis such as newborns would increase the incidence and severity of this condition. To what extent, then, have clinicians reported an increase in either systemic or enteric infection, respectively, in persons injected or fed prophylactic iron?

Between 1967 and 1973, nearly all Polynesian infants born in hospitals in the Napier-Hastings area of New Zealand were given iron dextran intramuscularly for 5 days starting on the second day of life. This practice has been stopped because the incidence of Gram-negative bacterial septicemias and meningitis that subsequently occurred in the iron-stressed infants was eightfold higher than in nontreated infants. The great majority of affected children were healthy at birth, of average weight, and did not suffer any recognized perinatal event likely to lead to infection. The clinicians concluded that "the safety of routine iron injections . . . must be seriously questioned" (3).

In kwashiorkor, patients are unusually susceptible to infection despite their continued ability to synthesize normal amounts of immune globulins. In contrast, their serum levels of transferrin are depressed; in patients with poor prognoses, the level is as low as 10 percent of normal. Intramuscular injection of iron compounds in some of these patients has resulted in overwhelming infection and death. The clinicians concluded that iron therapy should be delayed until transferrin synthesis could be restored by appropriate protein nutrition (4).

In feeding studies with rat (5) and guinea

pig (6) nurslings suckled animals developed normally, whereas all of the rats and some of the guinea pigs fed iron-supplemented milk formula developed diarrhea and died. Lactoferrin in colostrum and in maternal milk is an important antibacterial component provided that it is not saturated with iron (7). When guinea pig milk was supplemented with iron in the form of hematin, the number of coliform bacteria in the small intestine of the nurslings was increased by 10,000-fold (6). In tests in vitro (5), the powerful bacteriostatic action of human milk on coliform bacteria was neutralized by the same quantities (1 to 10  $\mu\text{g/ml}$ ) of supplemental iron that are incorporated in milk formulas fed to human infants (8).

Human infants with low birth weight and that have suffered an injury to the intestinal mucosa often develop a fatal necrotizing enterocolitis provided that they are fed milk formula rather than fresh human milk (5). Results of the studies with milk, cited above, suggest that the disease could be prevented or suppressed if the diet of the infants were to be supplemented with lactoferrin. Human lactoferrin has a greater affinity for iron as compared to bovine lactoferrin (9), but, of course, the latter would be more readily obtainable. Banked human milk is usually autoclaved or frozen so that its lactoferrin content might be somewhat reduced from that in fresh human milk.

In his well-reasoned review, Sussman (2) stated that a considerable body of evidence is accumulating to suggest that "iron plays an important part in determining virulence and possibly even pathogenicity in experimental infections." Fortunately, the serum ferritin method (10) for monitoring adequacy of body iron stores appears to be safe, reliable, and economical. Thus it should be possible soon to identify those individuals who are, in fact, iron deficient and to provide them with prophylactic quantities of the metal. Iron-sufficient individuals should be permitted the option of declining unnecessary and possibly hazardous exposure to excess iron.

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## Woodruffia metabolica: Exception to the Rule of Desmodexy Questioned

Golder (1) has concluded that *Woodruffia metabolica* is an exception to the rule of desmodexy. In this comment I show that Golder's conclusion (1) is predicated on the identity of nonhomologous structures. I emend the rule of desmodexy and several contingent definitions of cell structures in order that nonhomologs cannot be used to test the consistency of this rule. Furthermore, I show that *W. metabolica* does not except the emended rule of desmodexy.

Chatton and Lwoff (2) proposed the rule of desmodexy as "*Quelle que soit la course de la cinétie, le cinétodesme est à la droite des blepharoplastes*," that is, on the ciliate's right of the blepharoplasts or kinetosomes. The definition of kinety as a file or row of kinetosomes is generally accepted (3, 4). However, several definitions of a *cinéto-*

*desme* or kinetodesma exist. Chatton and Lwoff (2) defined a kinetodesma, which is composed of *fibres cinétodesmales*, as "*un fil ou une bandelette . . . qui unit les cinétosomes entre eux*." Nonhomologous ultrastructures are identified by this light-microscopic definition (1, 3, 5). Sleight (5) and Pitelka (3) recognized two categories of nonhomologous kinetodesmal structures: (i) classic kinetodesmal systems of holotrichous ciliates, in which Chatton and Lwoff originally observed *fibres cinétodesmales*, and (ii) Km fibers of heterotrichs. The Lkm fiber of *W. metabolica* (1) establishes a third category. The preceding structural categories satisfy Chatton and Lwoff's definition of a kinetodesma and thus may be used to test their rule of desmodexy. To avoid this confusion, Grain (4) emended the definition of

the components of kinetodesma thus: "*la fibre cinétodesmale est une fibre à structure périodique, qui prend naissance à l'extérieur du cinétosome, vers sa base, du côté antéro-latéral droit, au niveau des triplets 5, 6, 7, 8 et qui se coude pour devenir parallèle à la surface cellulaire en se maintenant dans l'ectoplasme*." But, kinetodesmal fibers not in the anterior right portion of a kinetosome [such as *Dileptus* proboscis kineties (6) and *Chilodochona* circumoral kineties (7)] do not qualify as such, although they satisfy the other qualifications of the definition. Furthermore, this definition, because of its spatial criterion (the right anterolateral side), makes the rule of desmodexy tautologous. To avoid these problems, the definition is emended as: The kinetodesmal fiber is a periodically striated fiber which arises near the base of the kinetosome, exterior to any or all of kinetosomal triplets 5, 6, 7, and 8, and extends toward or parallel to the cell surface. The triplets are numbered by convention (8). As Chatton and Lwoff (9) originally described kinetodesmal fibers in apostomatous ciliates, it seems reasonable to restrict this term to these structures or their homologs. Ultrastructural research on apostomes (10) has revealed that their kinetodesmal fibers are identified as such by the emended definition. These "classic" kinetodesmal fibers have been observed in many holotrichs (3, 4) and one heterotrich (11).

The rule of desmodexy emphasizes the constant relationship of kinetosomes and kinetodesmal fibers within somatic or nonoral kineties. As emended, the rule of desmodexy states that kinetodesma (an assemblage of overlapping kinetodesmal fibers) or nonoverlapping kinetodesmal fibers are to the right of the kinetosomes of a somatic kinety. In order to disprove the rule, nonhomologous structures may not be used; only kinetodesma or kinetodesmal fibers oriented other than to the right of a kinety or its kinetosomes will suffice. Neither the Km fiber of heterotrichs nor the Lkm fiber of *W. metabolica* may be used to except the rule.

The colpodid *Colpoda cucullus*, which apparently lacks a kinetodesmal fiber (12) and possesses an Lkm fiber homolog, is cited as a possible exception to the rule (1). A kinetodesmal fiber is observed in *C. maupasi*, a congener of *C. cucullus* (Fig. 1A), when fixation procedures different from those of Didier and Chessa (12) are used. *Woodruffia metabolica* is considered to be a colpodid (13). As kinetosomes and their fibrillar associates are very similar in taxonomically related forms (3, 4, 14), one would expect to find a kinetodesmal fiber

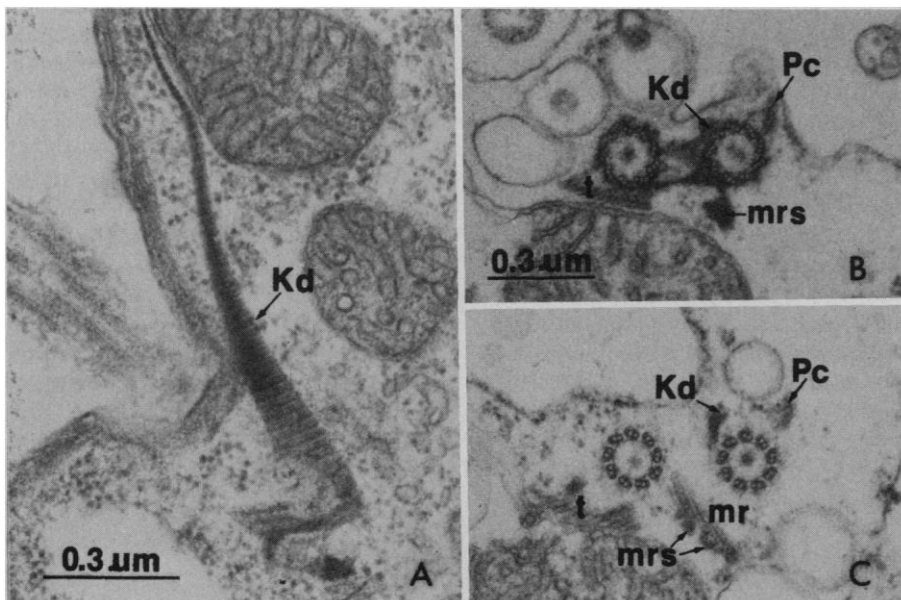


Fig. 1. (A) Longitudinal section of a kinetodesmal fiber (Kd) of *Colpoda maupasi*, to the right of the posterior kinetosome of a somatic pair. Specimens were fixed in glutaraldehyde in phosphate buffer and postfixed with osmium tetroxide ( $\times 57,000$ ). (B) Proximal transection of a kinetosome pair of *Woodruffia metabolica*, illustrating the origin of the kinetodesmal fiber homolog (Kd) near triplets 5, 6, and 7, the postciliary ribbon (Pc) at triplet 9, the transverse ribbon (t), and the microtubular ribbon support (mrs) ( $\times 45,000$ ). (C) Distal transection of kinetosome pair of *W. metabolica*, illustrating the separation of the kinetodesmal fiber homolog (Kd) from the kinetosome, the postciliary ribbon (Pc), the transverse ribbon (t), and the microtubular ribbon (mr) and its support (mrs) ( $\times 45,000$ ).