

THE FOCUS OF INFECTION THEORY: A NEW LOOK AT THE POSSIBLE RELATION TO POSTSTREPTOCOCCAL SEQUELAE

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The role of focalization of infectious agents within certain tissues in the pathogenesis of human disease has been the center of extensive research in the last decade. The term infection is sometimes defined as the biologic host-parasite interrelationship that results in a manifestation of disease. A disease may result directly from the effects of microbes on cells and tissues. This process may be mediated by the physiologic and structural interference by "toxins" or metabolites or by the destruction of host cells used as substrates by the invading micro-organisms. Alternately, disease may result indirectly from reactions of the host, the microbes living in endosymbiotic relationship with the host. Hypersensitivity of the host tissues to some of the microbial products may also contribute to tissue injury by activating complex humoral and cellular factors naturally located in blood cells.

Although much knowledge has been gained in the field of infectious diseases from animal model studies, little is known about the factors that predispose to the localization of micro-organisms in a particular cell or tissue. Focalization of an agent may represent the earliest phase of infection at the site of primary entry into the body. On the other hand, infectious agents may arrive accidentally at tissues where defenses are insufficient or where an adequate substrate may be provided for optimal proliferation. For many years it has also been claimed that different forms of "trauma" to tissues may predispose to the localization of micro-organisms. The classic example cited is subacute bacterial endocarditis in which *Streptococcus viridans* is said to localize on heart valves previously damaged by a rheumatic process. Another example is osteomyelitis in which mechanical trauma to bones may sometimes play a role in the localization and persistence of staphylococci. However, very little is known about the role microbial toxins may play in injuring tissues and thus in predisposing them to the localization of

micro-organisms. If indeed such a localization does occur, how is it related to the disease process?

It is accepted today that insult to human tissues by group A streptococci may sometimes lead to the development of nonsuppurative sequelae (rheumatic fever, nephritis, arthritis). Various theories have been proposed to explain the nature of these complications. Direct toxic effects mediated by streptococcal toxins, immunologic reactions of the host to localized streptococcal antigens, as well as cross reactivity between streptococcal components and human tissues have been proposed to explain the nature of these diseases. The lack of an adequate animal model, however, has greatly hampered a better understanding of the role played by streptococci in the pathogenesis of these complications.

If we accept that specific group A streptococcal products are involved either directly or indirectly in the pathogenesis of rheumatic fever and nephritis, it is tempting to postulate a common sequence of events in the pathogenesis of these sequelae. Recent studies in our laboratory have indicated that focalization of streptococci in tissues of laboratory animals may depend on the synergistic effects of tissue trauma and arrival of streptococci at the damaged sites. A single intramyocardial injection of streptococci in rabbits resulted in the development of chronic granulomas at the site of injection, which persisted for many weeks. Neither trauma to the heart with a needle nor the intravenous injection of streptococci alone resulted in any heart lesions. On the other hand granulomatous lesions developed in the heart at the site of needle trauma when the streptococci were injected intravenously shortly after the initiation of tissue damage. The results indicated that "trauma" predisposed to localization of the bacteria. Many streptococcal products (streptolysins O and S, proteinase, erythrogenic toxin, nephrotoxin) may cause massive tissue damage to vital organs (heart, kidneys, liver, joints).

The possibility was therefore raised that damage to tissues with these products may predispose to the localizing of streptococci in injured tissues. Indeed, it was found that rabbits injected intravenously or intra-articularly with isolated streptococcal toxins followed by the intratonsillar or intraperitoneal administration of fluorochrome-labeled streptococci or of titanium dioxide particles resulted in the localization of the labeled streptococci and titanium dioxide particles at the sites in the heart, liver (Fig. 1), and joints (Fig. 2) injured by the toxins.^{1,2} Since it has also been shown that the proliferation of group A streptococci in the tonsils of rabbits results in

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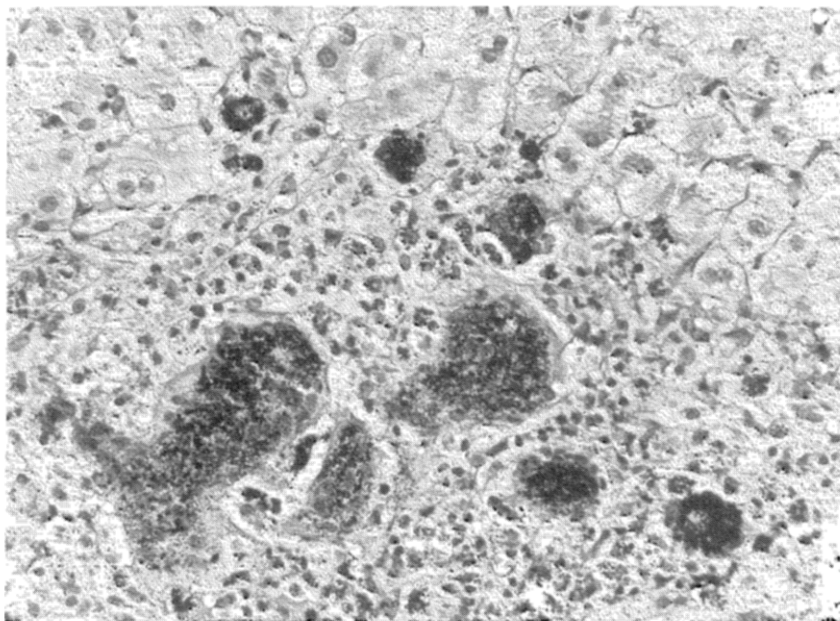


Figure 1. Giant cell granulomas induced in the liver of a rabbit by streptococcal toxins. Intraperitoneal challenge was effected by use of titanium dioxide particles. Note the accumulation of numerous particles in the giant cells. (Hematoxylin and eosin stain. $\times 340$.)

focal lesions in the heart presumably by the elaboration of toxins, it is conceivable that a focus of infection in the tonsils may seed bacteria to other tissues where they localize in sites specifically injured by a toxin.

Since most of the streptococci at the site of tissue injury were found within macrophages, the following sequence of events was postulated: Shortly after the initiation of tissue damage by toxins, chemotactic factors are released. Streptococci that were phagocytosed in the tonsils or in the blood are then translocated within phagocytes to the sites of damage induced by toxin. Also streptococci that may be found in the blood (bacteremia) may have been trapped mechanically within the lesions and may then have been phagocytosed in situ. The arrival of streptococci within tissue sites would be likely to be followed by degradation of their cell walls.

The long persistence and chronic inflammatory effects of streptococcal cell wall components on the tissues of rabbit have been studied extensively by Schwab and his collaborators.³ It was postulated that the perpetuation of the chronic inflammatory reaction in rabbit tissues was due to the slow and incomplete degradation of the streptococcal cell walls by the macrophages. As long as streptococcal antigens persisted in the tissues a chronic inflammatory process persisted. It is also conceivable that since the lysosomal enzymes of the leucocytes are responsible for the hydro-

lysis and degradation of intracellular bacterial cell walls, any qualitative or quantitative defects in the content of these enzymes will greatly impair the removal of the toxic components of the cell walls.

It is thus tempting to postulate that the chronic inflammatory lesions characteristic of the complications that arise following streptococcal infections may in part be the result of the persistence of some streptococcal product in the tissues. In this respect it is relevant to cite a number of studies on this matter. Studies by Laningen and Zaki, although still unconfirmed, have demonstrated the presence of membrane-like structures probably of bacterial origin in the Aschoff bodies of rheumatic carditis. Seegal et al. and Lindberg and Vosti have demonstrated the presence of streptococcal antigens in the glomeruli of humans and rats that developed glomerulonephritis following exposure to streptococci. Preliminary studies in our laboratory have shown that streptococci localize in the kidneys of mice pretreated with purified M-protein; this antigen has been shown by Kantor et al. to injure the glomeruli.

These studies raise the important question of whether a variety of other chronic diseases of humans characterized by massive infiltration of macrophages into tissues may not be caused by persistence of some microbial products in the phagocytes. A defect or lack of certain muralytic enzymes in these macro-



Figure 2. Arthritic lesion induced in the knee joint of a rabbit by the intra-articular injection of streptolysin S. The animals were challenged intratonsillarly with titanium dioxide particles. Note the accumulation of numerous particles in the hyperplastic synovia. (Darkfield microscopy, $\times 134$.)

phages may be responsible for such a long persistence. It would be important then to develop more sensitive analytic methods for the intracellular identification of microbial products and to assay specific hydrolytic (muralytic) enzymes within the macrophages that are responsible for the degradation and elimination of cell wall components of bacteria. The hypothesis of focal infection versus translocation of bacteria to other sites by no means implies that this is the only pathway for the pathogenesis of poststreptococcal complications. Further work along these lines is needed to shed more light on the possible role played by focal infection in the pathogenesis of chronic diseases with poorly understood etiologies.

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GENETIC CHANGES IN CANCER: CAUSE OR EFFECT?

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The initial alteration in the cancer cell continues to be a subject of controversy. Theories suggesting one particular mechanism as the initiator of neoplasia continue to proliferate. Older ideas of somatic mutation versus embryonic rest have given way to hypotheses of altered differentiation, template instability, and the "oncogene." Although most such concepts recognize altered genetic function in the cells of the fully developed cancer, there is no agreement as to whether the initial change is genetic or epigenetic, one change or many, reversible or irreversible.

It is the purpose of this brief commentary to support the view that irreversible genetic changes occur in almost all mammalian tumors before they reach macroscopic size, and also to suggest the improbability that one particular type of genetic alteration underlies all neoplasia.

At the cellular level there is considerable

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