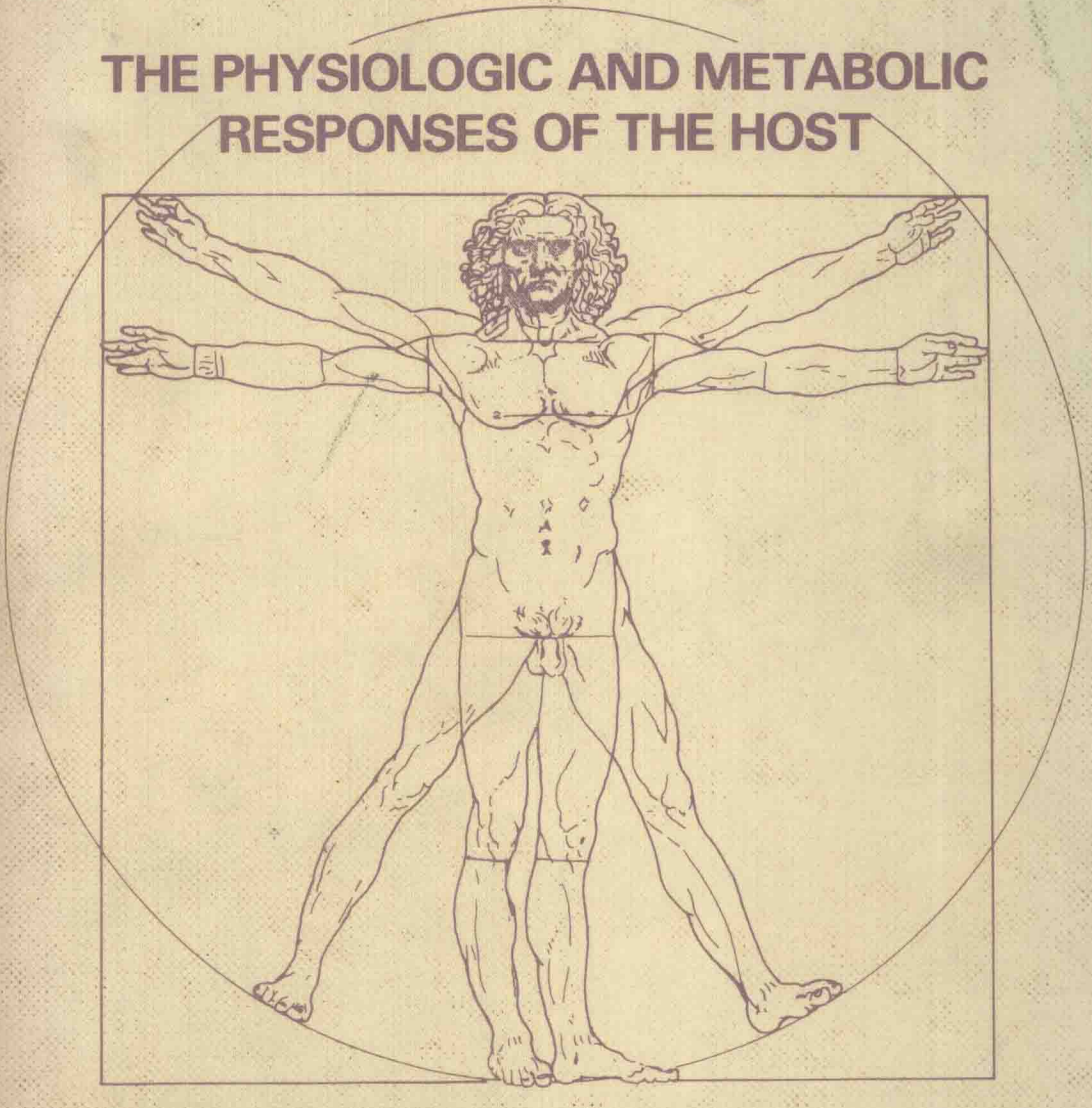
INFECTION

THE PHYSIOLOGIC AND METABOLIC RESPONSES OF THE HOST



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ELSEVIER / NORTH-HOLLAND

Infection: The physiologic and metabolic responses of the host

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ELSEVIER/NORTH-HOLLAND BIOMEDICAL PRESS
1981
AMSTERDAM — NEW YORK — OXFORD

ISBN 0 444 80336 X

PUBLISHED BY:

Elsevier/North-Holland Biomedical Press,
1 Molenwerf, P.O. Box 211,
1014AG Amsterdam,
The Netherlands

SOLE DISTRIBUTORS FOR THE U.S.A. AND CANADA:

Elsevier/North-Holland Inc.,
52 Vanderbilt Avenue,
New York, NY 10017

Library of Congress Cataloging in Publication Data

Main entry under title:

Infection, the physiologic and metabolic responses of the host

Bibliography: p.
Includes indexes.
1. Infection—Complications and sequelae. 2. Host-parasite relationships. I. Powanda, M. C. (Michael C.) II. Canonico, P. G. (Peter G.) [DNLM: 1. Infection—Physiopathology. 2. Infection—Metabolism. QW 700 I426]
RB153.I53 616'.047 81–15283
ISBN 0–444–80336–X AACR2

Printed in The United Kingdom

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Prologue

Though the use of analogy to describe biologic phenomena often lacks precision, there is sufficient correspondence in nature that in presenting the complex system by which man and microorganism come to terms, a simile may be appropriate as introduction. A host, continually confronted by a plethora of microbes seeking a niche in which to flourish, may be compared to a nation. The existence of this nation depends upon regulating, within broad limits, the assortment of internal and external social, economic and political forces by which it is beset. Nations need not be continually at war with potential enemies, but must always be alert and must have a well developed system to respond to a wide variety of insults, transgressions and dangers, while concomitantly carrying out the day-to-day activities required for maintenance, growth and development. Whenever possible a nation makes use of its natural, passive barriers, the absence or loss of such barriers need not betoken invasion but does facilitate colonization. So too, man has natural barriers (skin, cilia, mucous secretions) which, if absent or compromised, e.g., as in large burns, allow nominally harmless parasites to overwhelm and by default become pathogenic. Nations place sentinels at borders to discourage transgressors. These sentinels may be armed so as to deal with minor incidents and possess a communication system so as to provide warning should a major confrontation be perceived as imminent. The body has a very effective armed sentinel system, the resident phagocytes seemingly found in every tissue, and supported by circulating granulocytes and monocytes. Even in minor armed conflicts bystanders get hurt, so too if the body's sentinels are not held in check or the site of conflict not cordoned off, considerable unnecessary damage can be done.

Though continually besieged, it is only occasionally that the threat is of sufficient magnitude to provoke armed combat. Such conflicts require redefinition of priorities. In the case of the body, the hepatic industrial center increases its production of defense items, such as the acute-phase proteins, drawing heavily for raw materials on skeletal muscle. Whenever possible, raw materials are stockpiled for use in raising defenses and for repair and rebuilding after the conflict. Recycling thus becomes important as does the more efficient accumu-

lation of raw materials. For example, the liver sequesters and the intestinal tract increases its uptake of zinc, a necessary cofactor for amino acid, protein and nucleic acid metabolism and a requisite for wound healing. This occurs in response to signals from phagocytes heralding the presence of inflammation. As in any industrial country with limited natural resources, a protracted conflict in the absence of sufficient input of supplies eventually compromises the ability to continue the struggle or to rebuild even if the battle is won. Intake of raw materials during the conflict, especially if it is protracted, or during the recovery phase, must be adequate in amount not only to fuel the fight, but also to aid the repair. The composition of the raw materials provided may have to be altered so as to most effectively nourish all sectors of the economy without inducing perturbations that might compromise attaining complete recovery.

The metabolic and physiologic sequelae of infection depicted in Fig. 1 are clearly not inclusive, but are representative of the changes which do occur during nearly every acute infectious illness, irrespective of the nature of the etiologic agent. Selected aspects of these host responses to infection will be discussed in detail by the contributors to this volume. The format of Fig. 1 is an attempt to convey the dynamics of the process, the progression of events, by which the host responds to the detected presence of a microbe. This scheme also emphasizes that longitudinal rather than single time-point studies are necessary if one is to understand these host-parasite interactions. The time scale is arbitrary since it appears that, particularly in the case of fatal illnesses, the same pattern of metabolic and physiologic alterations occurs regardless of the duration of the illness. For these sequelae to occur, the microorganism must not only be present in sufficient numbers to pose a potential threat, but also the threat must, in fact, be perceived as such by the phagocytic system. Though these sequelae can be elicited as a result of phagocytosis of microorganisms, it seems that the only requirement is phagocyte activation. Activation may occur via membrane perturbation, since endotoxin and drugs such as poly (I) · poly (C) and colchicine can stimulate mediator release and produce metabolic responses akin to infection. There is considerable evidence that the mediator of fever and the metabolic adaptations is a substance variously termed leukocyte endogenous mediator, endogenous pyrogen or crude leukocytic extract.

Though the format of Fig. 1 might suggest that the pattern of responses to infection is without variance, this is not entirely true. There appears to be a degree of variation in the timing and extent of response as a function of species, host as well as parasite. Generally, alterations in trace metal and nitrogen metabolism await the onset of fever. However, there are instances such as Rocky Mountain spotted fever in guinea-pigs, wherein the hypoferremia and increase in plasma copper are detectable before the onset of fever, but are amplified during the febrile phase. Moreover, hypoferremia, hypoalbuminemia and increased concentrations of acute-phase proteins persist even after fever has subsided and recovery is occurring. During typhoid fever in man, hypozincemia and transient hypoaminoacidemia precede the febrile phase by 2—3 days

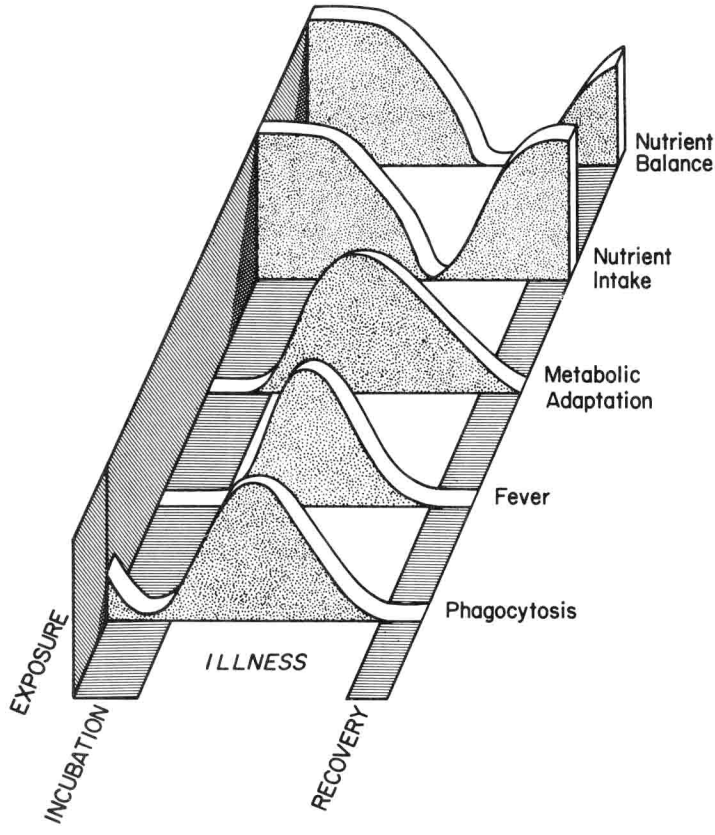

Fig. 1. Stylized representation of host metabolic and physiologic responses to acute infection. The values for each variable have been normalized to fit within a 0% (minimum) to 100% (maximum) range. The period of illness has been defined to coincide with the duration of fever. Phagocytosis or at least phagocytic cell activation precedes the onset of illness. There may be an initial burst of phagocyte stimulation at the time of exposure which may subside if there is considerable latency between the period of exposure and the onset of illness. In some instances certain of the metabolic responses to infection, such as alterations in plasma trace metal and amino acid concentration, occur prior to overt illness and many metabolic perturbations persist for hours, days and even weeks thereafter. Anorexia usually is apparent soon after the onset of fever and unless a determined effort is made to supply nourishment, nutrient intake falls toward zero. Negative nutrient balance begins shortly after the onset of fever, and since it is a cumulative phenomenon, persists for days or even weeks after nutrient intake returns to normal.

and increased acute-phase protein concentration persists even after lysis of fever.

Wasting and negative nitrogen, salt and trace element balances occur even in mild illnesses of short duration and persist for days and even weeks after the patient is free from symptoms. Anorexia of itself does not account for the deficits, since the losses are often far in excess of what would occur during fasting.

If these deficits persist for an appreciable time as the result of inadequate nutrition during the convalescent period, the host risks reinfection. In children, this cycle of malnutrition and infection leads to increased morbidity and mortality and diminished growth. To compensate for the infection-induced deficits in children, additional protein relative to energy intake is recommended and may be appropriate in adults as well. Nutritional intervention may be required at any time during infection and even in uninfected patients with a high risk of becoming infected, e.g., severely ill cancer patients receiving radiation or chemotherapy. It is conceivable that to obtain optimal results, the composition of such nutritional supplementation may have to be altered during different phases of the infection or in the case of renal and hepatic dysfunction.

Though wasting and negative nutrient balances are classic manifestations of severe infections, one should not lose sight of the considerable alterations in metabolism which take place within the body wherein massive amounts of trace metals, nitrogen, carbohydrate and lipid may be purposefully redistributed, far in excess of that which is excreted. It has been proposed that a number of these metabolic and physiologic responses, notably fever, trace metal redistribution and increased acute-phase protein production, act in concert to protect the host against infection, to facilitate the development of immunity, and if tissue damage occurs, to promote wound healing. If this hypothesis can be substantiated it could provide the basis for a multifaceted therapeutic system combining antimicrobial agents, nutritional support and drugs designed to amplify beneficial host responses whilst muting inappropriate or harmful reactions, in effect tailoring a general anti-inflammatory system to efficiently protect against a specific pathogen.

Many of the metabolic and physiologic alterations discussed in this volume occur not only during infection, but also following severe injury and major surgery as well as during any disease in which there is a prominent inflammatory response. It is quite likely that these alterations are a part of a rather general host response to inflammation, whatever the etiology, and are elicited by a common mediator. Thus, much of what has been said of these alterations in terms of affecting the outcome of an infection may also apply to other diseases and injury as well. In fact, considering the seemingly general nonspecific nature of these responses, some of the metabolic and physiologic alterations may be directed more toward injury than infection and this may operate at cross-purposes in a patient who is both injured and infected.

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Infection: The physiologic and metabolic responses of the host *edited by M. C. Powanda and P. G. Canonico*

Activation and deactivation of neutrophils

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I. INTRODUCTION

Neutrophils constitute a very mobile organ of host defense. These cells can accumulate rapidly and in great numbers within any vascularized tissue in response to signals generated at sites of infection. The mobility of neutrophils and the readiness with which they may be redistributed in the body are critical to the role of these cells in host defense. The purpose of this chapter is to review current information and concepts about the mechanisms by which neutrophils sense the invasion of tissues by microorganisms, alter their normal patterns of circulation, arrive at sites of infection, and initiate antimicrobial functions.

These cellular mechanisms are reviewed with respect to the activation of responses that affect the mobility and distribution of neutrophils and also with respect to the regulation and inactivation of these responses.

In considering the activation and deactivation of neutrophils, it is important to remember that these cells do not represent a normally latent system of phagocytes which become active only with acute infection or with some other insult to the body. Neutrophils are short-lived blood cells; they are produced, released into the circulation, and then eliminated by the body in great numbers every day ($\simeq 10$—$15 \cdot 10^{10}$ cells/24 h in a healthy human adult). It has been recognized for many years that uninterrupted production, circulation and turnover of these cells are critical for the maintenance of an uninfected state. It is known, for example, that large numbers of neutrophils are continuously delivered to mucosal surfaces of the body, particularly in the gastrointestinal tract (Teir et al., 1963; Klinkhamer, 1963), where a variety of microorganisms reside and proliferate as normal flora. The constant supply of neutrophils to such sites clearly constitutes an important part of the barrier against microbial invasion, for when production and turnover of neutrophils cease, overwhelming sepsis with organisms from this normal flora quickly ensues. It is likely that a constant turnover of neutrophils also subserves clearance functions by which noninfectious materials such as the debris of dead cells, and macromolecules that have been recognized as antigens, are removed and degraded to reusable or excretable constituents (Boggs et al., 1967; Murphy, 1976). Hence, when microorganisms gain access to normally sterile tissues and acute infection occurs, neutrophil-dependent host defenses are not simply activated from a latent state. Rather, the production, distribution and turnover of these cells are expanded and reoriented. The basic mechanisms by which neutrophils respond to acute infection are undoubtedly closely related to those that subserve their normal tasks of clearance and the maintenance of tissue sterility.

It is appropriate to consider the mechanisms of neutrophil activation and deactivation from the perspective of the cell surface. Cell surface events initiate the processes by which microorganisms are ingested and killed by neutrophils, as they do with fixed phagocytic cells of the reticuloendothelium. However, for neutrophils, events at the plasma membrane also control the location in the body at which these specialized functions are carried out, by promoting adherence of neutrophils to selected capillary beds and by directing the migration of cells into infected tissues. Surface events which control the mobility and distribution of neutrophils in the body are particularly critical for the activation and deactivation of neutrophil host defense functions and therefore are the focus of this review. The mobility and distribution of neutrophils reflect certain specialized functional attributes of these cells: their capacity for stimulated adhesion to other cells and surfaces, their ability to change their shape and squeeze through narrow gaps between endothelial cells, and their ability to wander into extravascular spaces and to respond to chemotactic stimuli with directed migration. Diverse in vitro techniques have been developed and used

in recent years to study these functional attributes of adhesion, motility, shape change and chemotaxis, and these techniques [reviewed extensively elsewhere (Klebanoff and Clark, 1978; Gallin and Quie, 1978)] have permitted very detailed analysis of the cell biology of neutrophil activation and deactivation. It should be kept in mind, however, that almost all of the current understanding about basic mechanisms by which neutrophils are directed to sites of need in the body comes from observations made in in vitro experimental systems, although the basic in vivo phenomena of neutrophil accumulation at inflammatory foci have been recognized for more than a century.

II. FUNCTIONAL ARCHITECTURE OF THE NEUTROPHIL PLASMA MEMBRANE

The neutrophil plasma membrane is constructed in such a way that it can interact with a wide variety of molecules that are soluble in extracellular fluid or attached to the surfaces of other cells or microorganisms. Through these interactions, neutrophils sense and respond to molecules of different biochemical classes (proteins, oligopeptides, lipids, carbohydrates) and different functional classes (chemotactic factors, opsonins, hormones, neuromediators, and cell surface proteins such as fibronectin), and it is evident that each of these classes of stimuli can mediate or influence phenomena of neutrophil adherence and motility. It is apparent that mediator molecules may be sensed both by distinct stereospecific receptors on the plasma membrane and by direct interactions with membrane lipid. It is also evident that mediator-membrane interactions are closely linked with active ion-transport channels and with membrane-associated enzyme systems and that activated ion transport and enzymes in restricted portions of the plasma membrane direct the subsequent function of the whole cell. Finally, it is evident that stimulation of the neutrophil membrane response apparatus has direct consequences upon the ability of the cell to respond to subsequent stimuli.

Functional components of the neutrophil plasma membrane are presented schematically in Fig. 1. This schema is derived more from inference than proven fact and is based upon current concepts of cell membrane structure (Singer and Nicolson, 1972; Singer, 1975) in which globular protein complexes are visualized as floating in the membrane lipid bilayer. It is presented as a diagrammatic outline for discussion. Until recently, studies of neutrophil plasma membrane composition have been complicated by difficulties in obtaining surface membrane preparations of convincing purity (DePierre and Karnovsky, 1973; Dewald et al., 1979; Klempner et al., 1980). Nonetheless, it has been apparent that the plasma membrane of neutrophils, like other cells, contains a significant amount of protein (protein/lipid ratio $\simeq$ 1.0—1.3) (Woodin and Wieneke, 1966), and freeze-fracture, scanning electron micrographs (Moore et al., 1978; Amherdt et al., 1978) have indicated that much of this

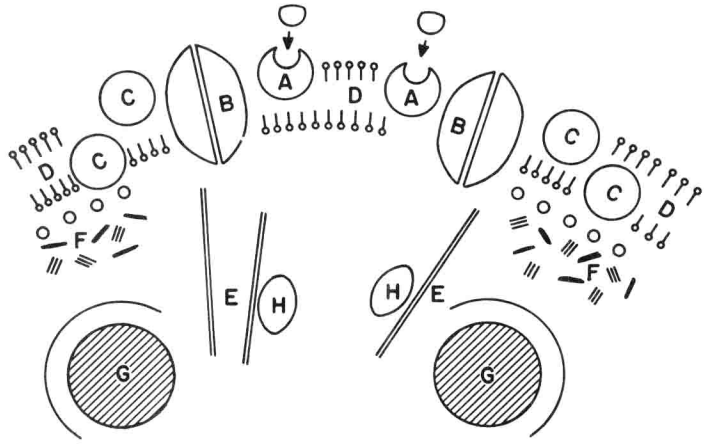

Fig. 1. Functional components of the neutrophil plasma membrane. A, membrane receptor complexes; B, transport channels; C, membrane-associated enzyme systems; D, membrane lipid bilayer; E, microtubules; F, contractile proteins; G, cytoplasmic granules; H, cytoplasmic enzyme systems.

protein is contained in movable, globular complexes that float in the lipid bilayer of the membrane as depicted by the model of Singer and Nicholson (1972).

A. *Membrane receptors*

Of particular importance to the neutrophil's ability to sense stimuli are various, distinct receptors on the plasma membrane. Specific, saturable receptors have been identified for several different purified chemotactic factors, for the opsonic fragment of C3, for the Fc portion of immunoglobulin, and for cholinergic and adrenergic agonists, and it is likely that distinct receptors for other mediator molecules will be found with time. The existence of specific chemotactic factor receptors was first recognized with studies of pure, radiolabeled, *N*-formylated oligopeptides which had been shown previously to be potent chemotactic factors (Day et al., 1977; Williams et al, 1977; Aswanikumar et al., 1978). A stereospecific receptor on the neutrophil surface for these oligopeptide chemoattractants had been suggested by their high potency and structure-activity specificity (Schessinger, 1976). This receptor, which is demonstrable on both rabbit (Aswanikumar et al., 1978) and human (Williams et al., 1977) neutrophils, is saturable and has been shown to have relative binding affinities for different oligopeptides which match the relative potencies of these molecules as chemotactic factors (Schiffmann and Gallin, 1979). Furthermore, this receptor has been found to be specific for phagocytic cells. The so-called bacterial chemotactic factor secreted by certain gram-negative organisms in culture (Schiff-

mann et al., 1975) has been shown to compete with the synthetic *N*-formylated oligopeptide chemoattractants and thereby appears to stimulate neutrophil function via the same receptor (Schiffmann and Gallin, 1979). Another chemoattractant of bacterial origin, pepstatin A, a pentapeptide protease inhibitor, also appears to interact with neutrophils via this same receptor (Nelson et al., 1979a). The complement-derived chemotactic factor, C5a, on the other hand, does not compete with these chemotactic factors for receptor binding, but instead interacts with a distinct, saturable receptor which has been studied recently by Chenoweth and Hugli (1978) using purified ^{125}I-labeled C5a. Evidence for yet another distinct, chemotactic factor receptor on the neutrophil surface has been provided by Spilberg and Mehta (1979) who investigated the binding characteristics of a purified, radiolabeled chemotactic factor produced by the neutrophils themselves. These studies have indicated that neutrophils can sense chemotactic stimuli through a family of distinct receptor sites; however, the structural characteristics of these receptors have not been clarified. Analogies with receptors on other cells (Hauser and Troxler, 1974; Raferty et al., 1976) suggest that chemotactic factor receptors are protein complexes within the membrane, although binding of the oligopeptide chemoattractants to neutrophils was not found to be diminished appreciably by prior exposure of the cells to proteases (Schiffmann and Gallin, 1979). Nonetheless, studies by Goetzl and Hoe (1979) have indicated that free amino and sulfhydryl groups are functionally critical determinants for chemotactic factor receptors in general. While some chemoattractants may interact with protein receptor complexes in the neutrophil membrane, a fatty acid derivative of arachidonate metabolism, 12-(6-hydroxy)-5,8,10,14-eicosatetraenoic acid (HETE), which has been shown to have chemotactic activity for neutrophils, appears to stimulate the cells while becoming incorporated directly into membrane lipid (Stenson and Parker, 1979). It can be argued that the development of diverse chemotactic factor receptor systems on the neutrophil plasma membrane has been favored by evolution, for this diversity permits the cell to sense a wide variety of signals that may be generated at sites of infection.

Not only are chemotactic factor receptors diverse, but their availability for ligand interaction is also variable depending upon the maturity and functional state of the cell. Studies with the human promyelocytic leukemia cell line, HL-60, have shown that the development of chemoattractant receptors on these cells coincides with their degree of functional maturity, as the cells are induced artificially to mature in vitro (Fontana et al., 1980), and it is likely that the maturation of normal neutrophil precursors in the bone marrow is also characterized by an increasing expression of membrane receptors. It is also evident from comparative studies of receptor numbers on peripheral blood neutrophils and on exudate neutrophils that the number of receptor binding sites may increase once a neutrophil becomes engaged in an inflammatory response (Schiffmann and Gallin, 1979). The appearance of new receptor binding may reflect the expression of 'cryptic' receptors as suggested by studies of Liao and

Freer (1980), or it may represent the delivery of new receptor sites to the cell surface as a result of degranulation and fusion of granule membranes with the plasma membrane (Gallin et al., 1978b; Fletcher and Gallin, 1980). Receptor numbers also appear to be affected by the consequences of receptor-ligand interactions, for there is evidence that both the receptors for C5a and for the oligopeptide chemoattractants may be internalized and degraded once chemotactic stimuli have elicited a functional response from the cell (Chenoweth and Hugli, 1980; Niedel et al., 1979; Sullivan and Zigmond, 1980).

Chemotactic factor receptors also have considerable mobility within the plasma membrane, and this receptor mobility appears to be critical for the neutrophil's ability to translate the stimulation of chemotactic factor-receptor interactions into oriented cell movement (Zigmond, 1978). Binding sites for the lectin, concanavalin A (analogues of which have been found to be chemoattractants for neutrophils (Van Epps and Tung, 1977)), can be redistributed on the neutrophil surface and tend to flow to the rear of cells that have assumed an oriented shape (Ryan et al., 1974; Oliver, 1976). In addition, adhesion sites for albumin-coated latex beads, which are induced by exposure of neutrophils to chemotactic peptides, have also been found to move to the rear of cells that have become oriented and are migrating toward a source of chemoattractant (Smith and Hollers, 1980).

In addition to chemotactic factor receptors, other receptors have been identified on the neutrophil surface which are directly involved with the initiation of cell function. Receptors for the Fc portion of immunoglobulin (Henson, 1969; Messner and Jelinek, 1970) and for opsonic complement fragments, in particular C3b (Henson, 1969; Verhoef et al., 1977), have been recognized for more than a decade as components of the neutrophil plasma membrane. It has been suggested by the work of Van Oss and Gillman (1972a, b) that neutrophils may interact with particles or surfaces in a nonspecific manner dependent on the relative hydrophobicity of the foreign surface, and that opsonins facilitate the attachment and ingestion of particles merely by increasing their hydrophobicity (Van Oss and Gillman, 1972a, b). Recent studies, however, have achieved a direct quantification of distinct, saturable receptor sites for Fc (Alexander et al., 1979) and have demonstrated that Fc and complement receptors elicit distinct functional responses by neutrophils (Mantovani, 1975; Ehlenberger and Nussenzweig, 1977; Newman and Johnston, 1979). Nonetheless, as with chemotactic factor receptors, the structure of opsonic receptors remains unclear. The opsonic receptors, like receptors for chemoattractants, appear on the plasma membrane of neutrophil precursor cells as they mature (Ross et al., 1978; Herborn et al., 1979); their distribution within the membrane is mobile (Gallin et al., 1979); their presence on circulating neutrophils is variable (Gilbert et al., 1979), and they are more readily demonstrated on exudate neutrophils than on blood neutrophils (Klempner and Gallin, 1978). These receptors are known to be critical for the attachment and ingestion of opsonized microorganisms by neutrophils, but they also appear to be closely linked topo-