Infection and the Compromised Host

Clinical Correlations and Therapeutic Approaches

Second Edition

Edited by
James C. Allen, M.D.

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Preface to the Second Edition

The prior edition of this book attempted specifically to categorize mechanisms present in the human body which have proven or presumptive roles in defense against infection and to delineate those diseases in man in which specific compromises in those mechanisms occur. It was our hope to correlate the defective defense and the type or types of infections incurred, as a step toward understanding this complex relationship. While to some degree this effort was successful, it was perhaps more effective in indicating the complexity which exists in the relationship between invading microbe and its intended victim. That edition served, however, as a usable summary of clinically applicable immunology as it relates to infections in the compromised host. Significant advances in our knowledge of the various defense systems operative in the intact human being have occurred, but our understanding of the basic structure of those systems has remained essentially intact during the few years since that edition appeared. From this point of view, that edition may now be considered incomplete, but not truly obsolete. It was, therefore, our decision to complement the contents of that edition, rather than approach a simple revision.

Extensive information is now available concerning two therapeutic approaches to the problem of recurrent infections in compromised hosts: granulocyte transfusion and immunization. Chapters assessing the state of our knowledge about these important areas are included. *Pneumocystis carinii* infections are perhaps unique in being clinically expressed primarily if not only in compromised hosts; extensive information on the occurrence, diagnosis, and treatment of this infectious process is now available and is summarized herein. Finally, we have extended our look at human diseases which by proof or by inference are associated with compromised defense mechanisms. Infections as a complication of bone marrow transplantation, sickle cell anemia, alcoholism, the collagen disorders, and diabetes mellitus are critically reviewed. Analysis of the state of defense mechanisms in each is provided, as well as an interpretive view of the infections incurred by patients so involved.

It is our belief that the contents of this volume will provide a significant and usable extension of the reader's information about infections and the compromised host.

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Preface to the First Edition

In spite of progression of our skills in the chemotherapeutic and medical management of infections, these diseases continue to represent a frequent cause for patient hospitalization and of patient death. In addition, infections comprise an extremely large proportion of the iatrogenic diseases of current medical practice, resulting as they do from multiple aspects of medial care. Within this category infections complicating our chemotherapeutic manipulations in the treatment of malignant processes or in the prevention of rejection of a transplanted organ are an all too frequent problem. It is of some interest that in spite of the fact that infections are often a significant clinical byproduct of treatments which alter host defenses, our concern with them lags significantly behind our concern with the development of agents to damage these defenses effectively.

During recent medical history, a number of patients have made themselves known to research physicians because of recurrent episodes of life-threatening infection, and have been demonstrated to have a very selective defect in the battery of normal host defenses. These patients have been used fruitfully in the exploration of the normal mechanisms of host defense, the results of which are documented in this monograph. On the other hand, a careful analysis of the infections involved has largely been ignored, although these are the problems of greatest concern to the patient.

It is our purpose in this monograph to examine those situations in which host defenses against infection are impaired, with special emphasis on an analysis of the infections which result. In the process, there will be an extensive review of host defense mechanisms and our current understandings of their functional significance, as well as of those situations in which heritable defects or chemotherapy are associated with increased susceptibility to infectious disease. Wherever possible, we will try to draw a correlation between that defensive parameter which is deficit and the specific microbial agents which invade the host, helping the reader see what is known about the correlation of the various aspects of these defenses and susceptibility to specific microbial agents.

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Contents

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Granulocyte Transfusion: A Current Appraisal

JEFFREY McCULLOUGH, M.D. and PAUL G. QUIE, M.D.

The relationship between leukopenia and infection has been apparent for many years. As the granulocyte count falls below 1000/me there is an increased risk of infection which is further increased by the duration of granulocytopenia (Bodey et al., 1966). An inadequate number of functional granulocytes may be due either to granulocytopenia or to functional defects with a normal level of circulating granulocytes. The increasingly common and aggressive treatment of patients with hemologic malignancies and aplastic anemia has made granulocytopenia common. During the late 1960s almost 80% of deaths in these patients were due to infection. Because of the success of platelet transfusion in the treatment of hemorrhage due to thrombocytopenia, there has been much interest in transfusion of granulocytes for the management of infection in leukopenic patients.

Treatment of infection by elevating the level of circulating granulocytes is not new. During the 1930s there were unsuccessful attempts to stimulate proliferation of new granulocytes or maturation and release of cells from the bone marrow by injection of leukocyte extracts. In the 1950s granulocyte replacement was attempted by transfusing blood from patients with polycythemia vera and by cross circulation of granulocytopenic patients with normal individuals or leukemic patients with elevated granulocyte counts. Because of the small number of granulocytes in the peripheral blood of normal humans, collection of cells for transfusion has been a difficult problem. Chronic myelogenous leukemia patients were used as donors during the 1950s

and 1960s. The development of the blood cell separator was a major technical advance which allowed collection of large numbers of cells from patients with chronic myelogenous leukemia (CML) and from normal donors.

The first granulocyte transfusions, done with cells collected from CML patients, provided much of the data and fundamental concepts of granulocyte transfusion in use today. These pioneering studies were carried out by Dr. Freireich's group at the National Cancer Institute (1965) and Mathé and colleagues in France (Schwarzenberg et al., 1967). Usually patients received one or two transfusions of a large number of cells ($1\text{–}5 \times 10^{11}$) and results could be temporally related to the transfusion. These studies showed that:

1. There was a direct relationship between the number of cells transfused and the increment in leukocyte count;
2. There was a direct relationship between the pretransfusion granulocyte count and the intravascular recovery of transfused cells;
3. Transfused CML cells appeared in inflammatory lesions when studied with the Rebuck skin window;
4. Transfused CML cells persisted in the bone marrow;
5. Increases in the number of circulating granulocytes occurred over a longer period of time than expected, probably due to maturation in the bone marrow of transfused CML cells; and
6. There was a dose-response curve showing that the likelihood of clinical improvement and reduction in the patient's temperature following transfusion was directly related to the number of cells transfused.

It should be emphasized that some of the results of these early studies using CML cells cannot be expected with today's techniques. The dose of cells transfused was as much as 10 times greater than presently available and there was probably engraftment of transfused CML cells in the bone marrow. Before further consideration of granulocyte collection and transfusion, a brief discussion of granulocyte production and kinetics is pertinent.

Granulocyte Production and Kinetics

The average daily production of granulocytes is approximately 160×10^7 cells/kg (Cline, 1975). This is equivalent to approximately $1.1 \times$

10^{11} granulocytes/day in the average sized adult. The granulocyte has a life span of 10–14 days. The first 8–11 days are spent in the bone marrow, where proliferation and maturation occurs. The granulocyte is then released from the bone marrow into the peripheral blood where it circulates for approximately 10 hr. The size of the total blood granulocyte pool is estimated at 70×10^7 cells/kg or 4.9×10^{10} granulocytes in the average sized adult. While in the peripheral blood, approximately half the granulocytes are in a circulating pool and half in the marginal pool. The marginal granulocyte pool is composed of cells not in the axial stream but loosely adherent to the walls of small vessels and in equilibrium with the circulating pool. Thus, the circulating granulocyte pool contains approximately 2.5×10^{10} granulocytes and it is these cells which are observed in the routine leukocyte count. After a brief intravascular life span, the granulocyte moves into the tissues, where its major biological activities occur. In contrast to other blood cells such as red cells or platelets, the granulocyte merely passes through the intravascular space in transit from its site of production (bone marrow) to its site of function (tissues). The number of granulocytes in the intravascular space is only a small proportion of the total body granulocyte pool. Leukapheresis techniques presently in use remove $.8–2.5 \times 10^{10}$ granulocytes. By comparison, 2.5×10^{10} granulocytes are available in the circulating granulocyte pool, and an additional 2.5×10^{10} are immediately available in equilibrium in the marginal granulocyte pool. The combination of the circulating and marginal granulocyte pools represents only approximately 1/20 of the average daily production of granulocytes or 1/200 of the total body stores of granulocytes. Thus, present collection techniques do not remove sufficient granulocytes to be a risk to the donor and actually do not even lower the donor's granulocyte count (McCullough, 1979). This also means that the number of granulocytes available for transfusion is quite small in relation to the body's normal production.

Collection of Granulocytes for Transfusion

Granulocytes can be collected by: 1) continuous flow centrifuge leukapheresis (CFCL) using the IBM Blood Cell Separator, Aminco Celltrifuge, or the IBM 2997 Blood Cell Separator; 2) intermittent flow centrifuge leukapheresis (IFCL) using the Haemonetics Model 30; 3) filtration leukapheresis (FL) using the Fenwal Leukapheresis pump or

the Leukopherator; 4) gravity leukapheresis; or 5) harvesting of buffy coats from ordinary units of whole blood. A detailed discussion of granulocyte collection techniques has been published elsewhere (McCullough, 1979) and is not germane to this book. However, some consideration of collection techniques will be included here to emphasize the effects of different collection techniques on cell function, the dose of cells obtained by different techniques, and risks of leukapheresis to the granulocyte donor.

Continuous Flow Centrifuge Leukapheresis (CFCL)

The first instrument designed for granulocyte collection was the IBM Blood Cell Separator, which operates with a continuous flow of blood, thus coining the term continuous flow centrifuge leukapheresis (CFCL). The general operation of CFCL instruments is as follows. The donor undergoes two venipunctures, one in each arm, blood is pumped from the donor, and citrate anticoagulant is added immediately. Anticoagulated whole blood enters the centrifuge bowl where it is separated into red blood cells, buffy coat, and plasma, each of which leaves the centrifuge separately. The buffy coat is diverted into a collection bag and the red cells, plasma, and most of the platelets are recombined and returned to the donor's opposite arm. Since it is desirable to process a large volume of blood through the centrifuge, large (14- or 16-gauge) needles or catheters are used. The rate of blood flow out of the donor and through the centrifuge bowl is controlled by the speed of the pumps and the centrifuge speed is variable so that the degree of packing of the buffy coat into the red cell layer can be controlled. Usually, 8–10 liters of donor blood (twice the donor's blood volume) are processed during a 3½-hr procedure. The volume of blood outside the donor at any time is approximately 250 ml.

CFCL using these techniques produces only $2–5 \times 10^9$ granulocytes (Table 1.1), which is equivalent to the granulocytes in 2–4 units of fresh whole blood. Therefore, it has been necessary to modify CFCL to produce more granulocytes. These modifications introduce additional risks to the donor which will be discussed later.

Recently a new blood cell separator (IBM 2997) has been introduced which uses a belt-like chamber instead of a centrifuge bowl for separation of whole blood into red cells, plasma and granulocytes or

platelets. The instrument is a CFCL process generally similar to other CFCL procedures except for the separation chamber. Present experience with the instrument is limited, but it appears it will produce a much larger number of granulocytes than previous CFCL techniques (Table 1.1).

Intermittent Flow Centrifuge Leukapheresis (IFCL)

In IFCL the donor may undergo one or two venipunctures. The blood is pumped out of the donor's vein, citrate anticoagulant is added, and the blood enters a plastic disposable centrifuge bowl where red cells, plasma, platelets and granulocytes are separated. These blood components are pumped out of the bowl separately, in sequence instead of simultaneously as in CFCL. When granulocytes have been obtained, the blood flow is reversed and the plasma, red cells, and most of the platelets are returned to the donor. The cycle of filling the centrifuge hole, harvesting the granulocytes, and returning the remainder of blood to the donor is repeated six or eight times. This requires 2½–3½ hr, during which approximately two-thirds of the donor's blood volume is processed through the instrument. Granulocyte concentrates collected by IFCL also contain very small numbers of granulocytes ($3–4 \times 10^9$), unless the technique is modified (Table 1.1).

Modifications of CFCL and IFCL

In the unmodified form neither CFCL nor IFCL produce sufficient numbers of granulocytes from normal donors to allow successful transfusion. Two general types of modification of these centrifuge leukapheresis techniques have been used: 1) increasing the efficiency of

Table 1.1. Approximate Number of Granulocytes $\times 10^{10}$ Obtained From Normal Donors by Different Leukapheresis Techniques

	Modification of Technique			
	None	HES	Steroids	HES + Steroids
CFCL	4	10	10	22
IFCL	3	10		20
FL	15		25	
IBM 2997		11		35
Gravity leukapheresis				17

granulocyte removal from whole blood passing through the centrifuge by adding rouleaux inducing agents to improve the separation of granulocytes from red cells, and 2) elevation of the donor's granulocyte count by administration of corticosteroids before leukapheresis.

Hydroxyethyl starch (HES) is the rouleaux inducing agent presently in most widespread use. When a 6% suspension of HES is added to the donor blood while it circulates through the centrifuge, granulocyte yields are increased to approximately 10×10^9 (Table 1.1). HES is a branched chain polymer of glucose originally developed for use as a blood volume expander. It has been considered safe for use in normal donors, reportedly is not immunogenic, and does not interfere with blood coagulation in usual doses. Very little data have been reported which allow establishment of the incidence of adverse reactions due to HES during leukapheresis. Recently there have been unpublished reports of anaphylaxis due to HES and lichen planus-like lesions occurring in a donor who received HES. Small but measurable blood levels of HES have been found 250 days after a single infusion. Thus, information presently available is not of the extent and detail that would be ideal to allow its routine use. Although HES is presently approved by the Food and Drug Administration for use in normal donors undergoing leukapheresis, further studies defining its metabolism and long term effects are desirable.

It is well known that corticosteroids induce a peripheral blood granulocytosis, probably by 1) slowing the egress of granulocytes from the vascular pool and 2) increasing the rate of release of granulocytes from the bone marrow. Since the granulocyte yield from leukapheresis is directly related to the donor's granulocyte count, steroid treatment of donors is effective. The number of granulocytes contained in the concentrate can be increased to approximately 10×10^9 by steroid treatment of donors (Table 1.1). Prednisone, dexamethasone, hydrocortisone, and etiocholanolone have been used. Prednisone (60 mg) or dexamethasone (4–8 mg) can be given orally the night before leukapheresis. Intravenous injection of dexamethasone or hydrocortisone immediately before leukapheresis does not significantly improve the granulocyte yield because of the lag time in elevation of the donor's granulocyte count. Only one leukapheresis center has experience with etiocholanolone and the present unavailability of this drug has ended its use in leukapheresis.

Although the effects of steroids are well known, administration of these drugs to normal individuals volunteering as blood donors raises new considerations. The minimum useful dose and its frequency of safe administration have not been established. The ethics of subjecting normal individuals to corticosteroids deserves further discussion by the blood banking and blood donor community.

Filtration Leukapheresis (FL)

In FL the donor undergoes two venipunctures—blood is pumped out one vein, anticoagulated with heparin, and passed through several cylinders containing nylon fibers. Most of the granulocytes adhere to the nylon fibers while the remainder of the blood is returned to the donor's opposite arm. As with centrifuge leukapheresis systems, a large volume (8–10 liters) of the donor's blood is processed through the filters. After a predetermined time or volume of blood has been processed, the system is flushed to elute the granulocytes from the nylon for concentration and transfusion. In contrast to centrifuge leukapheresis systems, however, the high efficiency of granulocyte trapping by the fibers results in much higher yields of granulocytes (Table 1.1). Fifteen to 40×10^9 granulocytes are obtained with the usual FL procedure. This represents 3–10 times the number of granulocytes obtained by centrifuge leukapheresis procedures. Because granulocytes are not separated by differential centrifugation, rouleaux induction is of no advantage and therefore not used in FL. Steroids have been used to elevate the donor's granulocyte count with the hope of improving granulocyte yields; however, results are mixed and it is not clear whether this is advantageous. The efficiency of granulocyte trapping by the nylon is already quite high and filters may become saturated. In addition, steroids may reduce granulocyte adherence to the nylon filters and therefore actually decrease yields. However, steroid treatment of FL donors is common, but mainly because such treatment reduces some adverse donor reactions which appear to be unique to FL.

Gravity Leukapheresis

In this procedure plastic bags are used to remove standard units of whole blood from an identified donor. Erythrocytes are sedimented by gravity after addition of HES and returned to the donor following