Investigating The Child with Frequent Infections

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Children frequently present with a history of repeated infections. When these infections are serious and respond poorly to normally successful treatment programs, suspicion of a basic defect in one or more host defense mechanisms may be raised. In such cases defects in humoral or cell-mediated immunity, phagocytic cell functions or the complement system must be sought. Much of our knowledge about the development and functions of these cooperating but independent systems allows clinical observations to provide a generally accurate prediction of the nature of the defect involved. The degree of sophistication with which the systems can be evaluated and the possibilities for therapeutic manipulation are rapidly increasing. In this article are outlined the basic pathophysiological mechanisms needed to approach these increasingly recognized problems.

Repeated, severe and frequently fatal infections provide the major problem for the 4000 (estimated) children in the United States with severely compromised host-defense mechanisms. Partial, less severe, defects are being increasingly recognized, making it all the more important for the pediatrician whose suspicion is aroused to understand the nature and pathophysiology of such defects and the way to investigate them.

Children in the first 5 yr of life are certainly less well equipped to handle infections than older children. According to the Bills of Mortality for the city of London for the year 1750, 50% of children were dying before their fifth birthday. Most of these children died from infection. Apart from the lack of useful therapeutic procedures and the total lack of an appreciation for hygiene a further two factors compromised infection fighting. Malnutrition certainly compromises the efficiency of the immune system (1) and was no doubt a major problem in that period. However, a second problem, still with us today, is the slow and, therefore, inadequate nature of the primary immune response itself. If one were to be allowed to redesign the human immune system, the major improvement one could suggest would be in this area.

Today, as then, children are born with three weapon systems almost ready to do battle with the microorganisms to which they are rapidly introduced. These defenses consist of a specific immune system mediated by lymphocytes, a reticuloendothelial system mediated by the body's phagocytic cells, and a complement system composed of 11 serum proteins. Interaction between the three systems is essential for health.

With good good nutrition and hygienic conditions, infections, though common in young children, are infrequently serious problems. Nevertheless, the defense mechanisms are not perfect in the normal child, and it is easy to understand how a further reduction in host defense efficiency secondary to abnormalities within such systems can result in life-threatening infection.
The fundamental problem when talking about children who have too frequent infections is in deciding who they are. When are frequent infections too frequent to be explained away by environmental considerations thus arousing a suspicion of inadequate defense mechanisms? In general, when an experienced pediatrician says a child is having too many infections to fit into the normal spectrum of such occurrences an inefficient host response to infection should be suspected. Many, indeed most, of these recurrent infections will be due to local factors (e.g., inadequate drainage from sinuses, cystic fibrosis, etc.) These must be considered before the rarer, more basic defects covered in this discussion. In the absence of such local factors, especially in patients with the "clues" listed below, basic defects should be considered.

Many children have six to eight respiratory infections per year (2), and this may be increased if there is exposure to older siblings and other children. In the immunologically normal child such infections are mild, with little fever, last a few days, and characteristically the child recovers completely between infections. One's suspicion should be raised if a child suffers an even greater number of infections of unusual severity. Frequently infections in immune-deficient children are of prolonged duration, are associated with unexpected complications and are associated with organisms one usually considers to have a low degree of pathogenicity. Commonly bacteriostatic antibiotics usually effective in the management of a particular bacterial infection prove ineffective as host mechanisms cannot complete the destruction of the organism. In such circumstances the following defects should be considered, and appropriate evaluations initiated.

The primary immune deficiencies can be divided into five categories listed here in order of frequency (3). (1) isolated humoral immune deficiency (50–75%); (2) combined cellular and humoral immune deficiency (25%); (3) isolated deficiency of cell-mediated immunity (5%); (4) phagocytic cell anomalies (1%); (5) complement deficiencies (1%).

Any of the above can result in a patient presenting with frequent infections. The clinical history, however, may suggest a specific defect. A child with an intact defense mechanism may suffer one attack of bacterial pneumonia, meningitis, sepsis, or osteomyelitis; two such episodes would strongly suggest a possible humoral defect as bacteria are dealt with by this system and abnormality here is the most common immune deficiency. However, complement and phagocytic cell defects can present similarly.

A child who has had a smallpox vaccination with a normal response almost certainly has no major defect in cell-mediated immunity. A child who has experienced the exanthem of a viral illness, e.g., measles, likewise has demonstrated a normal cell-mediated reaction as these rashes are manifestations of T-cell responses to the virus (4). Conversely, a stormy time with measles or chickenpox, recurrent moniliasis, or a severe vaccinal reaction suggests problems within the CMI system.

There follows a brief description of the major relevant facts required for an appreciation of the primary immune deficiencies.

The immune system is composed of two independent but frequently cooperating mechanisms. One results in the production of antibody by plasma cells and is controlled by lymphocytes derived from the bone marrow and thus referred to as "B" lymphocytes (5). The other provides cell-mediated immunity (CMI) and utilizes physical contact between lymphocyte and antigen for destruction of the latter. The lymphocytes for this system are educated in the thymus and are called "T" lymphocytes (5). It is only within these lymphocyte-mediated systems that
specificity and memory are found. They are the generals of the host defense mechanism, while the soldiers consist of phagocytic cells and complement components.

During fetal life lymphocytes are programmed with surface-bound antigen-recognition units that allow each lymphocyte to recognize one antigen, or more correctly one section or determinant of an antigen (6). As we are programmed to recognize many thousands of different antigens, it follows that there can be very few lymphocytes capable of recognizing one antigen. Hence, the first encounter with an antigen (microorganism in our context) results in a slow and relatively inefficient response. This response does include division of those lymphocytes involved in the reaction with a subsequent expansion in the number of cells (memory cells) that can recognize that organism (7). The immune response of such lymphocytes is more sophisticated and efficient than the response of their parental cells.

In the normally germ-free intra-uterine environment B and T cells do not encounter antigens and thus we are born without a population of memory lymphocytes and cannot make an optimal response to first postnatal encounters with pathogens. To partially protect the newborn infant, a considerable amount of maternal IgG crosses the placenta and provides the infant with antibodies against those antigens the mother's immune system has dealt with (8). As this antibody has a half-life of 26 days, it can protect the child for only 4 to 6 mo during which time he will make his own primary response to many organisms (9).

Functionally, antibodies provide our primary defense against bacteria while the cell-mediated immune system protects us from viral, fungal, intracellular bacterial and protozoal infections (10).

**Humoral Immune Deficiencies**

In man, B lymphocytes from the bone marrow begin to populate lymph nodes by 12 wk of gestation. They have on their surface an immunoglobulin receptor for antigen that, on encountering said antigen, will trigger a humoral immune response (11). The B lymphocyte will undergo a number of divisions forming memory B lymphocytes and plasma cells which are factories manufacturing the antibody that was on the surface of the B lymphocyte from which it was derived (11). Plasma cells secrete 2000 molecules per second of this antibody. The early B lymphocytes have receptors for antigens composed of IgM on their surface but later, B lymphocytes develop with IgG and then IgA on their surface (12). As the plasma cell product is related to these surface receptors, the primary immune response is mainly IgM in character while later responses produce mainly IgG antibodies. Cells with IgG on their surface are the progeny of cells with IgM on their surface, while cells with IgA on their surface are the progeny of IgG-bearing cells (13). Thus, the M → G → A progression is reflected clinically as defects at each step have been described, the most common being the arrest of the production line at IgG resulting in isolated IgA deficiency (14).

The IgA system has a special role to play in protecting our mucosal and intestinal surfaces, and at birth the concentration of IgA in saliva is higher than in the serum suggesting a development of the secretory IgA system independent of the serum IgA system (15). In addition, the lymphoid-associated epithelial cells of much of the intestinal mucosa manufacture a special molecule called secretory component which can attach to the secretory IgA and greatly aid in its delivery to the mucosal surface (16).

Antibodies are efficient at eliminating bacteria, as once combined with the
organism they can (depending on class) activate the complement system and phagocytic cells producing a powerful inflammatory response in which the bacteria are killed and eliminated (17).

Defects of humoral immunity range from a congenital sex-linked agammaglobulinemia through an isolated IgA deficiency to a temporary state of prolonged hypogammaglobulinemia of infancy. Quantitative immunoglobulin determinations (not immunoelectrophoresis) and the examination of saliva or tears for IgA provide an excellent screening test for such deficiencies. The discovery of a severe defect calls for the enlistment of a clinical immunologist to further classify the defect and advise on treatment. A negative Schick test provides evidence of the development of antibodies against diphtheria while iso-hemagglutinins indicate at least a capacity for IgM production. An immunological laboratory can assay peripheral blood for B lymphocytes. Normally they make up 35% of the lymphocytes in human peripheral blood (18). They are absent in congenital agammaglobulinemia. The laboratory can also stimulate B lymphocytes in tissue culture and look for antibodies against human antibodies found in the serum of some patients with a selective immunoglobulin abnormality (19).

Treatment of these conditions involves a number of nonspecific measures common to all immune deficiency problems as well as the administration of gamma globulin. Such children require extraordinary amounts of pediatric care but the results are well worth the effort. These children should have their own bedroom when possible and within reason should be kept away from sources of infections. Their teeth should be kept in good repair. If they have any antibody-forming capacity, killed vaccines should be administered. As chest infections are their most common problem, they require the same attention to drainage, etc. that is required for the child with cystic fibrosis. Commercial gamma globulin should be given to such children except those with isolated IgA deficiency. For them it cannot help as commercial preparations contain only tiny amounts of IgA; however, it can be harmful as the small amount of IgA that is present will be antigenic for these children and anaphylactic responses may develop (20). The correct amount of gammaglobulin to give is the amount that keeps the child free of systemic infections. This usually requires the serum IgG level to be maintained above 200 mg/100 ml and to do this a dose of 0.7 ml/kg of the 16 g/100 ml concentrated gammaglobulin is usually required. The concentrate spontaneously aggregates forming macromolecular complexes that activate the complement system and cause shock if given intravenously, hence the need for deep im injections of the globulin.

Cell-Mediated Immunity

From 10 wk of fetal life the thymus, which has descended through the neck with the parathyroid glands to overlay the great vessels of the heart, turns pluripotential stem cells into T lymphocytes that will mediate the cellular immune system (21). These cells live in the paracortical area of lymph nodes and around the general centers of the spleen, and in the white pulp of the spleen. They compromise 60–65% of the lymphocytes found in peripheral blood. They recognize antigens via a surface recognition unit (11) and on so doing divide to form memory cells and effector or "killer cells" that make physical contact with antigens and release a host of pharmacologically active agents called "lymphokines." These are responsible for recruiting, nonspecifically, other cells into the battle and produce the inflammatory response that eliminates the target of their attack (22).

When stem-cell defects cause immunodeficiency, neither the microenvironment of
the bone marrow nor the thymus can educate lymphocytes resulting in combined immune-deficiency syndromes. Isolated defects due to thymus abnormalities are less common. The best-known isolated defect is the DiGeorge syndrome (23) in which failure of thymus differentiation is associated with parathyroid abnormalities and disturbances of the great vessels, an obviously “pinpointable” embryonic disaster, or these structures all arise from the third and fourth pharyngeal pouches and descend together through the neck (24). Such children commonly have distinctive facial features and clinically frequently present because of hypocalcemic fitting. Their chest x-rays show a lack of the normal thymic shadow, and their immune problems lead to serious viral and fungal infections. Partial defects in the CMI system are being increasingly recognized.

T cells can be visualized at work by stimulating them to produce a dermal delayed hypersensitivity response. In the neonatal period this can be achieved by intradermal challenging with phytohemagglutinin (PHA), a T-cell mitogen that produces a small (5–10 mm) reaction at 24 hr. In older children positive skin reactions to Candida albicans, mumps, or streptokinase–streptodornase are good indicators of intact cell-mediated immunity. Negative reactions to all three, while not proof of a defect, are enough to rouse suspicions. The further evaluation of T-cell function involves enumeration of peripheral blood T cells and in vitro stimulation of T cells with phytohemagglutinin, Candida albicans, and seeing if the T cells in question can take part in a mixed lymphocyte reaction. Such tests are readily available at all major centers. For combined immune deficiency bone marrow from a perfectly histocompatible donor (usually a sibling) must be transplanted to the patient. Although such marrow is hard to come by, at least two dozen successful transplants have been reported (25). Thymic deficiencies require the transplantation of fetal thymic tissue which has been very successful in a number of cases (26). Defects in postthymic T-cell function occasionally improve with the administration of transfer factor, a dialyzable product of healthy human leukocytes. The latter has been particularly successful in treating chronic mucocutaneous candidiasis (27). T- and/or B-cell defects may be associated with abnormalities in other systems producing many syndromes but the immune defects can all be reduced to the above terms.

Complement

Circulating in serum are 11 inactive complement proteins that can interact in chain-reaction fashion once the first component (called Clq) is activated by changes in the heavy chains of IgG or IgM antibodies bound to antigen (28). The cascade that follows, wherein one activated component activates the next step in the reaction, results in a general amplification of humoral immune responses and some specific pharmacological effects. Many of the activated components, apart from pushing the reactions forward, are pharmacologically active in one or more of four areas. Some cause vascular smooth-muscle relaxation, others cause an increase in capillary permeability, while others either attract macrophages or lyse cell membranes (28). All of these effects greatly aid in the production of an inflammatory response. These powerful molecules are kept in check by a series of serum inactivators of complement. This pathway, activated by antigen-antibody complexes is called “the classical pathway.” Nonimmunological happenings, e.g., endotoxin, can activate an alternate pathway that bypasses the first three steps of the classical sequence (28). Such activation may involve complement in many nonspecific inflammatory responses. A deficiency of a complement component that is vital to the sequence reaction as a whole, effectively inactivates the system. So far inborn errors of
complement in man have produced deficiencies in C1, C2, C3, C5, C6, and C7. All cases have been associated with either repeated infections or the systemic lupus erythematosus cluster of diseases (28).

When infections cannot be attributed to lymphocyte or phagocytic abnormalities, the complement activity of serum or a major individual component such as C3 should be measured. Complement may be low secondary to utilization by antigen–antibody complexes in diseases associated with this phenomenon. In these, complement levels usually rise with treatment and complement activity is seldom reduced to 10% of normal as is common in the inborn errors of the complement system. Treatment of primary complement failure is limited to fresh plasma infusions and the general care described above.

**Phagocytic Cells**

Once several of the complement components have bound to an antigen–antibody complex they promote phagocytosis by macrophages, etc. This so-called opsonic activity of complement will help in the ingestion of a microorganism, but it is up to the phagocytic cell to kill the infecting agent. The ability to swallow is not necessarily related to the ability to kill and it is in this latter area that problems arise leading to grossly inadequate protection from bacterial infection. Inside phagocytic cells biochemical reactions involving a hexose–monophosphate shunt and numerous intracellular enzymes dispatch the organisms (29). Failure of the hexose–monophosphate shunt mechanism results in an early death from infection. The full-blown form of this defect produces a syndrome known as Chronic Granulomatous Disease of Childhood (30). In addition to a spleen scan to detect a congenital absence of the spleen, the easiest way to approach a diagnosis of defective phagocytic killing is via the nitro-blue tetrazolium (NBT) test (31). NBT is a colorless dye but when added to macrophages that are utilizing the hexose–monophosphate shunt the dye is reduced to the purple formozan. This test is available in many centers and is a good screening test for chronic granulomatous disease. More sophisticated tests include the creation of a “skin window” (Rebuck) by abrasion of the skin with subsequent observation of the cells that pour into the injured area and quantitative bacterial phagocytic assays (32). There is currently no satisfactory treatment for such children, but the intensive research into phagocytic metabolism, current in many institutions, may provide rapid improvements in this area. These children require continuous antibiotic coverage.

The neonate in London in 1750 had a 70% chance of surviving his first year, much better odds than those available to the undiagnosed child with a host-defense impairment in America in 1974. However, with a wider appreciation and understanding of the possible defects that can occur and the manner in which they can be defined, such afflicted children will have an increasingly greater chance of being restored to health, allowing them to defect from the ranks of children who present with frequent and severe infections.

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