A new concept of the cellular basis of immunity

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This paper will present experimental evidence indicating that the lymphoid system is composed of two distinct cell populations each with a separate embryologic origin and different morphologic and functional characteristics. Recently (Cooper and associates, *Nature*, 1965), experimental delineation of these two components was accomplished in the chicken, an observation that led to the recognition of a similar division in mammals. The chicken has two gut-associated lymphoid organs, the thymus and the bursa of Fabricius. Bursectomy plus total body irradiation of the newly hatched chicken completely ablates the bursa system. These birds lack plasma cells in the large, pyroninophilic lymphocytes that constitute distinct lymphoid follicles in spleen, they are agammaglobulinemic, but fully capable of manifesting cellular immunity as characterized by homograft rejection, delayed hypersensitivity, and graft-host reactivity. The thymus-dependent follicles, and plasma cells constitute the immunoglobulin-producing system. Thymectomy plus irradiation reduces the number of small lymphocytes of the blood and impairs the chicken’s capacity to effect cellular immunity. Although their immunoglobulin production system is intact, these chickens are less able to produce specific serum antibody. These two systems are also recognizable and dissociable in mammals. In mammals, the thymus-dependent system is represented by small lymphocytes in blood and in tissue accumulations; the immunoglobulin-producing system by the germinal centers and plasma cells. The tonsils appear to be the primordium of this latter system. The normal immune response is the result of the interrelationship of these two systems and an understanding of this interrelationship would seem to be the next objective.

**DISCUSSION**

Dr. Philip Fireman, University of Pittsburgh, Children’s Hospital, 125 DeSoto St., Pittsburgh, Pa. I would like to point out that one has to be very cautious in relating these studies of the immune mechanisms in the chicken to the immune mechanisms in man. Dr. Cooper has mentioned several studies of patients with lymphopenia and dysplasia of the thymus, which we have referred to as thymic dysplasia, in which there was dysplasia of the Y-globulins. One of these reports specifically mentioned that on visual examination the tonsils were small; it is unfortunate that the tonsils were not examined histologically.

We have recently had the opportunity to study another child with lymphopenia and thymic dysplasia. This patient had plasma cells present in the spleen and lymph nodes; the serum contained increased concentrations of γM-γglobulins but was deficient in the 7S γ2- and γ1-globulins. All the lymphoid tissues, including the tonsils and appendix, were carefully examined histologically and these tissues, except for the presence of plasma cells in the spleen and lymph nodes, resembled the tissues of patients with thymic dysplasia and agammaglobulinemia. Therefore, it is difficult to relate the development of the plasma cell and immunoglobulin synthesis to the development of tonsils in this patient. Much more information is needed before the tonsils can be considered the primordium of the plasma cell in man.

Dr. Angelo M. DiGeorge, St. Christopher’s Hospital for Children, 2600 N. Lawrence St., Philadelphia, Pa. 19133. A group of patients that has not, to my knowledge, come to the attention of investigators interested in the immunologic function of the thymus in man are the infants born with congenital absence of the thymus. Such infants are not to be confused with patients who have the Swiss type of agammaglobulinemia or the ataxia-telangiectasia syndrome. I became interested in congenital absence of the thymus in the past year when at autopsy we found no trace of thymus in 3 infants who also had congenital absence of the parathyroid glands as the “primary” abnormality. The concurrent absence of both structures is not surprising if one recognizes that both are derived from common primordia. Furthermore, this association has been previously recorded although its physiologic significance has not been recognized.

About 4 months ago, when yet another infant with congenital hypoparathyroidism came our way, we anticipated that the thymus might likewise be absent (especially since none could be seen on roentgenograms of the chest) and we have been studying the immunologic competence of this infant ever since. Thus far, we have found that this infant (9 months of age) has normal circulating lymphocytes, normal plasma cells in lymph node biopsies, and normal circulating immunoglobulins. On the other hand, he has severe “rashing” in spite of adequate control of his serum calcium level. Furthermore, he has had frequent infections including oral moniliasis, but he has a negative skin test to Monilia antigen and a negative delayed hypersensitivity response to 1-chloro-2,4-dinitrobenezene. And finally, he has failed to reject a homologous skin graft after 3 months.

Now it is true that we do not have positive proof that this infant was born without a thymus, but our demonstration of normal immunoglobulin production in the presence of defective cellular immunity (defective delayed hypersensitivity responses) is completely analogous to the thymectomized chicks of the Minnesota group. These immunologic findings in an infant with congenital hypoparathyroidism strengthens the evidence to support our argument that this infant has no
thymus. Should we ultimately prove absence of the thymus in this infant, it would be the first clear-cut demonstration of the function of this structure during fetal life in the development of cellular immunity in man. I bring these observations to the attention of the audience to urge others who may have infants with congenital hypoparathyroidism to study their immune competence since a significant percentage of such infants will also have congenital absence of this thymus. I have found in recent months that immunologists with whom I have consulted in regards to our patient have been reluctant to accept the notion that an infant with no thymus would have normal immunoglobulins and normal total blood lymphocyte counts. This is because their concepts of congenital absence of the thymus are closely interwoven with the facts known about the Swiss type of agammaglobulinemia. However, if we apply the findings of Dr. Cooper and his colleagues in the chicken to man, it would seem that infants who did not have a thymus during fetal life should have a defect only in cellular immunity (our patient) and infants who have no thymus and no immunoglobulin-producing system (tonsil?) should have the Swiss-type agammaglobulinemia.

These would then complete the analogy Dr. Cooper made between the bursectomized chick and the Bruton type of agammaglobulinemia in which primarily the immunoglobulin system is defective.

Dr. Cooper. Dr. Fireman, we feel that we have provided clear experimental evidence of a division of the lymphoid system into two distinct and highly specialized cell populations. Experimentally, this division has been accomplished in both birds and mammals. I would also like to point out that this dichotomy was first suggested by clinical observations.

To reiterate, the following clinical situations appear to represent congenital defects in the normal differentiation of one or both lymphoid systems. In the Swiss type of agammaglobulinemia both the thymus system and the immunoglobulin production system are congenitally absent. These patients lack both cellular immunity and immunoglobulin synthesizing capacity. The sex-linked agammaglobulinemic patients (Bruton's type) have an intact thymus system and cellular immunity but are deficient in tonsillar development, germinal centers, plasma cells, and immunoglobulin-synthesizing capability. The converse defect is exemplified by those cases recently reported by Allibone, Goldie, and Marmion (Arch. Dis. Childhood 39:26, 1964) and by Nezelof and co-workers (Arch. Franc. Pediat. 21: 897, 1964). In these patients, the thymus system was congenitally deficient in the presence of an essentially normal immunoglobulin production system and immunoglobulin synthesis. The findings in Dr. DiGeorge's patient fit closely with the findings in this patient group.

Obviously, all the body cells originally came from one cell. However, it is of basic biologic importance and clinically useful to understand the point at which specialized differentiation begins. This provides a starting point for the study of the induction and controlling factors of differentiation. In this context, the recognition of a division of the lymphoid system into two major cell systems represents a significant conceptual advance. Our experimental evidence also indicates separate embryologic sites of origin for each of these cell systems. We have presented strong circumstantial evidence that the tonsils may represent the embryologic source organ for the immunoglobulin-producing system. This hypothesis is a useful one in that it can be tested experimentally and it serves to focus clinical study of patients with developmental defects of the immune system.

Whatever the embryologic source of the immunoglobulin production system, we believe this perspective provides new insight into the development and function of the lymphoid system.

5. Bacterial variants in urinary tract infections

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One mechanism for chronicity of urinary tract infections may be persistence of bacteria as protoplast or L-form variants which are resistant to antimicrobial agents. A PPL0 medium was modified to support growth of L forms and was used to investigate this problem. Ninety-five urine samples from 40 patients with chronic bacteriuria and 30 urine samples from 10 patients with renal disease other than chronic pyelonephritis were studied. All specimens were cultured in the usual way for classic forms of bacteria. A portion of each specimen was mixed with sucrose to provide osmotic stability, then passed through a 0.45 μ filter to exclude classic bacteria, and the filtrate was inoculated on to L-form and standard media.

Samples from 15 per cent of the patients with chronic bacteriuria grew L forms. In those instances in which the L form reverted on subculture, the organism was found to be identical with the original infecting organism. L forms were found both with and without the presence of classic bacterial forms, and in the presence and absence of antibiotic therapy. No L forms were found in the urines of the control group of patients with renal disease other than chronic pyelonephritis.

The study was extended to the experimental induction of L-form renal infection in rats. A stable L-form culture was injected intraruminally with angiotensin. Persistence of the L form in renal tissue was found for prolonged periods of time.