EDITORIAL

The Thymus and Lymphoid Proliferation

By William Dameshek

In this issue, a review is presented by Arnason, Jankovic and Waksman on some of the functions of the thymus gland, bearing particularly upon its relation to lymphocytes and immune reactions. This gland, long known as an obscure collection of lymphoid or paralymphoid cells, has recently jumped into prominence as possibly the “master gland” controlling the immune response. Jacques Miller, working at Chester Beatty Institute in London, and Robert Good and his group of Minneapolis have demonstrated that thymectomized newborn mice are unable to respond effectively to antigenic stimulation, either in the form of skin transplants or of soluble antigens. Miller demonstrated that the lymphocyte:granulocyte ratio in thymectomized mice was reduced and that a conspicuous deficiency of the germinal centers of lymph nodes developed. Previously (1956) Metcalf’s experiments had indicated the presence of a lymphocyte stimulating factor (LSF) in the thymus. From these various observations, it could be postulated that the thymus had a controlling action upon the production of lymphocytes.

In a recent publication, Burnet discussed the possibility that the thymus gland produced “first level” lymphocytes which were immunologically uncommitted, but that when these cells lodged in suitable tissues such as lymph nodes and spleen, they had the possibility of becoming committed to specific antibody production, when stimulated by antigen. This was quite a reversal for Burnet, whose clonal selection hypothesis had indicated that at birth or shortly thereafter all immunologically competent cells were already committed to the production of single antibodies in response to single, specific antigens. Thus, the antigen, when it entered the body, would wander about until it found its predestined specific clone of immunocompetent cells or immunocytes.

This Jerne-Burnet concept of multitudes, or in less drastic terms of perhaps hundreds, of genetically determined clones of antibody producing cells which could react specifically only to specific antigens was, it must be confessed, a bit difficult to swallow. Fortunately, Burnet’s recent work with the Bielschowsky strain (NZB/BL) of New Zealand mice, having a genetically determined autoimmune hemolytic anemia, led him to modify his theory considerably. These unusual mice presented the investigator with the first opportunity to study a spontaneously developing autoimmune disease in the experimental animal. Highly inbred mice of this strain, first discovered by the Bielschowskys and studied by Helyer and Howie at the University of Otago in New Zealand, developed the characteristic features of auto-

*The term “immunologically competent cells” has come into wide use in recent years. Although an excellent term, it is quite unwieldy. The proposed word “immunocompetent” represents a first attempt at abbreviation, that of “immunocyte,” a somewhat more radical approach.
immune hemolytic anemia, including the positive Coombs antiglobulin test, at the age of 3–12 months. In studying these mice, Burnet found that 1) transmission of the disease to young mice of the same strain could be achieved by the injection of spleen cells, 2) that the thymus of the affected animals showed germinal centers and plasma cells (i.e., presumed antibody production), and 3) that thymectomy could prevent the development of the hemolytic state. Interpretations of these experimental data led Burnet to his postulations of two "levels" of lymphocytes—one in the thymus, the other elsewhere in lymphoid and splenic tissue. Although Burnet considered that under normal conditions, the thymic lymphocytes were uncommitted, under abnormal conditions, as in the genetically determined autoimmune hemolytic anemia (and perhaps in other autoimmune disorders), "forbidden" (committed) clones of abnormal immunocytes might be present. When these clones reacted with normal body-own antigens—in the thymus or elsewhere—abnormal autoantibody could result. Whether or not these speculations had any merit, it was nevertheless clear that the thymus must now be reckoned with in any cellular theory of immunity. Burnet's original hypothesis of clonal selection, resting as it did on the foundation of predestined, fully committed clones, thus appeared to be in need of some modification.

That the thymus gland was concerned not alone in immunity but in leukemia as well has been known for some time. Thus, it was evident that the leukemia of mice often began in the thymus. Law and J. H. Miller in 1950, and previously McEndy, Boon, and Furth, had demonstrated that thymectomy in young mice reduced greatly the incidence of spontaneous leukemia in high leukemic strains of mice. When the thymus was retransplanted in the mice, the incidence of leukemic development was no longer reduced. L. Gross showed that by removing the thymus of mice given "Passage A" leukemic filtrates, there was a complete lack of development of leukemia, whereas 63 per cent of positive controls developed leukemia. When the conditions of the experiment were modified by giving the leukemic filtrate first and removing the thymus one month later, leukemia developed in 43 per cent of the cases, but in approximately one-third of these, this was of the myelogenous (chloroleukemic) type, rather than of the otherwise invariably lymphocytic variety. In this connection the interesting relationships between certain leukemic proliferations, particularly those of the lymphocytic and plasmocytic varieties, and certain autoimmune disorders are brought to mind. Some leukemias are simultaneously autoimmune, and it may be difficult in a given instance to say where autoimmunization ends and leukemia begins. Perhaps, as Burnet suggests, both autoimmune disease and lymphocytic leukemia begin in the thymus.

The thymus thus appears to be essential for lymphoid proliferation, whether immunologic or leukemic. Without the thymus, at least shortly after birth, immunity does not develop, nor can lymphocytic leukemia be readily induced in the experimental animal. This points up again, if emphasis is still needed, that the immune reaction is fundamentally a cellular one and one in which the lymphoid system is the primary participant. To be sure, the plasmocyte is concerned with humoral antibody, but it would seem that this cell is
derived from a primitive lymphoid-appearing cell for which the rather unfortunate term "hemocytoblast" has been recommended by a special committee. Perhaps "immunoblast" might be a better term for this cell.

From the clinical standpoint, the interesting and by now well-known disorder of agammaglobulinemia and the less well-known one of "lymphocytophthisis" (Glanzmann and Riniker) or "lymphocytosis" (Hitzig and Willi) may well be based on congenital atrophy or dysfunction of the thymus. Infants with the latter disease are emaciated, develop numerous infections, show extreme lymphocytopenia in the blood and marked lymphoid and splenic atrophy at postmortem examination. Complete absence of all immunoglobulins ($\gamma 1$, $\beta_2A$, $\beta_2M$) has been noted by Barandun et al. and by Hitzig and Willi. The former authors pointed out that this condition was far more severe than the "agammaglobulinemia" first described by Bruton, then studied extensively by Good. Although the Swiss authors did not mention the status of the thymus gland in their cases, it is of interest that in four autopsied cases of agammaglobulinemia reported by Gitlin et al., the thymus was atrophic in all four cases, and markedly so in two cases. In a recent case of "lymphocytosis and agammaglobulinemia" described by Rosen, Gitlin and Janeway, the thymus "was a small remnant of tissue weighing less than 1 Gm." It contained no Hassall's corpuscles and no small thymocytes. These clinical data, in which lymphoid atrophy, agammaglobulinemia, and thymic atrophy were simultaneously present, appear to have their experimental counterparts in a remarkable wasting disease induced by Sherman et al. in hamsters. When male hamsters were thymectomized shortly after birth, wasting, diarrhea, striking lymphoid and splenic atrophy, agammaglobulinemia, and death occurred within 2 weeks. Thus, from both clinical and experimental data, it is apparent that absence of the thymus gland in the perinatal period results in a complete loss of lymphoproliferative activity, leading to a failure of the immune response, agammaglobulinemia, and to a wasting disease. It is of considerable interest that the "wasted," thymectomized hamster has almost identical features with the "runted" graft vs. host mouse.

Thus, all of a sudden, it would seem, the limelight has been focused on a hitherto rather neglected and scantily regarded gland. This comes about at a time when there is so much of a revolutionary nature going on in the fields of immunity and transplantation, and in their relationships to the lymphocytes and plasmocytes. From both the clinical and the academic standpoints, hematologists cannot fail but to be excited by these recent developments, with their promise of even more striking advances to come.

REFERENCES


William Dameshek, M.D., Director, Blood Research Laboratory, New England Center Hospital, and Professor of Medicine, Tufts University School of Medicine, Boston, Mass.
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WILLIAM DAMESHEK