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0014-4754/84/111178-04$1.50 + 0.20/0

Have we underestimated the importance of the thymus in man?

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Summary. Recent immunological research has concentrated on the complex and subtle interactions between T cells, B cells and accessory cells. In these studies, little attention has been given to the adult thymus gland. Modern textbooks of disease and anatomy all stress that the gland undergoes fatty involution with age in man but omit reference to the statements here and there in the literature that the gland is active and produces lymphocytes throughout life. To suggest that the bone marrow, which also builds up fat throughout life, is atrophic and not important to adult man would deny all modern hematological concepts. Yet few people today take a parallel view of the thymus except perhaps those investigating aging and thymic hormones. In both of these areas of research it is obvious that the thymus must be active throughout life for continued good health.
This brief review urges that a thorough understanding of the vital importance of the thymus in adult life is now needed. From it could emerge a new philosophy on the treatment of immune diseases in both the young (SCID and AIDS patients) and in the aged (autoimmune conditions and cancers) and it would aid our treatment of patients recovering from illnesses and from many drug treatments.
Key words. Thymus; thymic hormones; thymic atrophy.

The current awareness of the central role of the immune system to healthy life has been endorsed by the increased prevalence in the young of SCID (Severe Combined Immunodeficiency Disease), AIDS (Acquired Immune Deficiency Syndrome) and the great incidence of infectious diseases, autoimmune conditions and cancers in the aged[81] now that life expectancy has risen.

In all of the above conditions, the functional capacity of the T cells, and hence of the B cells, appears crucial to the course of the diseases. It is surprising, therefore, that so little attention is paid in adult man to the organ that produces the T cells of the body. Earlier research into thymic size and activity has resulted in most current textbooks dismissing the thymus as an atrophic or-

gan in adults since there is usually fatty involution with age. But the bone marrow also becomes fatty with age and although reduced in activity its continued cellular output is vital to life. The thymus, however, is currently only considered to be important before puberty, by which time it is assumed that all competent T cells have been generated (an apparently unvalidated assumption). More recent research too has tended to dismiss the adult thymus when it was shown[68] that cellular emigration from the thymus could be very low.

Have we grossly underestimated the power and value of this organ in adult life? I believe so, and evidence from many facets of thymic research is presented here to substantiate this view. Important in this respect is the lack of data on the size and activity of the thymus in normal adult man, in contrast to good information on the thymus of any animals, our increasingly sophisticated handling of lymphocyte subsets to elucidate details of cellular interactions, the purification of thymic hormone fractions and the increased knowledge of their functions.

Most authors agree, since the spate of anatomical work on the thymus around the turn of the century[7,8,25,26,86], that the thymus is maximal in size relative to body wt about the time of birth. The problem is that we do not know the size and activity of the thymus thereafter. Most work has been conducted on post mortem material, often taken from patients dying after chronic illness, or in poor nutritional states, and it is now known that both of these conditions cause the thymus to be smaller than normal[7,23]. Hammar in 1921[27], and several authors since[7,40,73] have pointed out that our estimates of thymus size are too low in adult life and that the idea of a completely involuted or atrophied gland should be abandoned. Yet still the view of the thymus as unimportant in adult life persists. Although the thymus has been studied in several disease conditions[6,22,24,38,48], few normal samples have been reported on[43,71,78,80]. However, all of the recent studies show good thymic architecture in adults and a wide degree of variation in size, with some reports of thymuses from old age resembling those at puberty.

Much more is known about the thymus in animals. Ontogenetically the thymus of most vertebrates is derived from similar sites[49]: the branchial pouches in the embryo which also give rise to part of the face and many important structures, including other glands such as the thyroid and parathyroid. In different animal classes, different pouches form the thymic rudiment from endo- and/or ectoderm, plus mesenchyme. Into this anlage, at a very early stage in embryogenesis, move waves of hemopoietic stem cells that seed the thymus[44] eventually to produce competent T cells. The thymus is the main site seeded, but it may not be the only one. It is quite possible that, following adult thymectomy, other sites in the body take over the function of T cell producers. An extra thymic cell producing site is indicated from work on nude mice (nu/nu) that lack a thymus. They have functional T cytotoxic and helper cells that do not always permit overt T cell responses, i.e. the thymus is necessary, not so much to make T cells, but more to allow them to become useful and diverse in the periphery[31]. In addition, nude mice, following thymus grafting, develop host cells with T cell features[46]. There is also evidence for T cell responses later in life in nude mice.

During development, the hemopoietic environment[65], as well as probably the prior commitment of invading cells, is important in establishing successful T cell multiplication and T cell maturation[35]. True T cell potentiality in immunological terms is only achieved after T cells leave the thymus (post-thymic T cells)[75]. Studies on the prothymocytes and T cell differentiation and maturation are currently very fertile areas of research which have added to our present theories of lymphocyte subpopulation interactions in the immune responses.

The work on thymic hormones[79] is potentially exciting for the future understanding of T cell production mechanisms, and provides evidence for sustained thymus activity in adult man. It is known that the output of at least one thymic hormone (FTS), that induces surface markers on T cells and T cell precursors, continues throughout life in man, reaching a stable plateau at 15–20 years and declining with age[15]. Thymectomized and athymic nude mice, and patients with the usually fatal Di George syndrome (no thymus), have no FTS. The level is often low in SCID patients, and their thymuses are small, but it tends to increase after bone marrow grafting parallel to the appearance of a thymic shadow. Thus the humoral function of the thymus can be stimulated in adult life by contact with colonizing stem cells (previously virtually absent in SCID patients). Analysis of other clinical conditions suggests that high levels of FTS and a higher than average peripheral T cell count (for age) can be associated with thymomas or conditions where the thymus is enlarged. The work of FTS is very strong supporting evidence for the continued activity of the thymus throughout life.

Perhaps the most controversial aspect of thymus activity is the assessment of cell migration. All researchers agree that the potential thymocyte production rate is enormous and that intrathymic cell death occurs, but opinions differ as to the numbers of cells leaving the thymus and their routes of egression[9,11,51,55,58,64,66]. In the last few years, nonspecific labelling of thymocytes by injected fluorescein isothiocyanate indicates that in the young mouse 1% of the thymus cells leave each day[69]. But even the authors of that paper admit that we are left with the problem that the thymus does not appear to have so many dead cells in it, and later[68], in discussing the only model that accounts for emigrant phenotype and medullary kinetics, it is pointed out that the cortex (and medulla) end up by theoretically having no function. In Scollay's words, "... if cellular events in the thymus can be likened to a jigsaw puzzle, then a few critical pieces are obviously missing". Since one critical piece is that the thymus contains numerous lymphatics, often full of cells[14,42,72], then it is not certain that the majority of cells die within the thymus. It is known from animal studies that there are numerous factors (so many that the list becomes exhaustive), that can cause rapid atrophy of the thymus. Although mechanisms are often little understood, some act by their cytolytic properties (corticosteroids)[13,33,47], by subtle prolongations of cell generation times that rapidly reduce cell output[87] or by decreasing proliferation during involution[19]. Al-

though cell cycle times vary within the thymus, mice have an approximate cell cycle time of 9 h in the cortex[57,87]; thus in 72 h seven generations of mitosis could give 128 cells. Multiply that by the number of prothymocytes in the subcapsular zone (where T cell proliferation begins) and thymic output may be regarded as astronomic. If the cell cycle time is reduced to 20 h[19,57], then the output per prothymocyte is only eight new cells in the same time. A large difference. Thus, on the assumption that many of the thymic cells do leave the thymus[14,42,45,85], peripheral T cell lymphopoenia could be rapid. Obviously factors that act on cell cycling can dramatically alter the thymic cellularity in three to four days. What are these factors with such an effect? Chemicals known to effect rapid thymus atrophy are numerous hormones[16,50,77] (including physiological levels of sex hormones and growth hormone[54,62,77], certain viruses[32,67], bacterial endotoxin[21], protozoa[30], tumors[17-19,57], antibiotics, e.g. streptozotocin[12] (nowadays used to model diabetes), X-irradiation[28,71], a wide range of miscellaneous chemicals, certain deficiencies, i.e. zinc[60] and, of great prevalence in many countries of the third world, starvation[3,34,52,61,63,83]. In addition, there is an enormous number of factors that are known to be immunosuppressive (for example, various drugs and heavy metals[41,84] and, since many of these act on mitosing cell populations (e.g. zinc deficiency conditions[60] and many anticancer agents such as folic acid antagonists, alkylating agents and analogues of pyrimidine bases[1]), these must surely affect thymocyte turnover rates. Also it is quite possible that the correct pattern of maturation of T cells could be impaired by exogenous factors so that the functional attributes of T cells could be compromised. This could easily occur in starvation if zinc deficiency conditions prevail as cell replication is more prone to error when zinc levels are abnormally low[10]. Many drug addicts, SCID and AIDS patients, diabetics and the elderly have very low body weights. Immune responses are poorer in malnutrition and protein deficiency[4,53,74] and infections and epidemics follow famines in man[20]. It is vitally important that a good balanced nutritional state prevails if normal cell turnover is to be maintained.

Thus it is easy to conceive of a vast variety of chemicals readily available to normal healthy adults that could slightly (temporarily) or chronically depress normal T cell output from the thymus or cause errors in T cell replication. Combinations of, for example, industrial or environmental pollutants, heavy smoking (relatively high Cd content and carcinogens), inadequate diet, elevated steroid or sex hormone levels and probably the prescription of certain medicaments could put individuals at a higher than average risk of immune impairment. Is this when opportunistic infections take their toll?

Does it matter if the thymus T cell output is reduced for a short period? Many research workers in the past would have said 'no'. Some T cells, probably a minor population including memory cells, are long lived and the number of T cells produced by the young thymus is vast. It has often been assumed that this output serves the body for the rest of life, but there is little evidence for this other than the fact that animals survive if thymectomized as adults (although subsequent immune responses are reduced[56,59,76] and that the numbers of circulating T cells decline with age in man[2]. While it is probable that a short-term reduced output could be tolerated by many healthy adults, to little or no effect, it must be remembered that most acute diseases (e.g. childhood illnesses in particular) leave patients vulnerable to further infection, and a cascade of illnesses can follow many drug treatments. The apparently impaired immune responses at these times could be due to a variety of causes but the hypothesis that reduced T cell production from the thymus is the root cause now needs to be investigated.

Another interesting and hitherto largely overlooked aspect of thymic function is that amongst many species of fish, amphibia, reptiles, birds and mammals (probably including man to a lesser extent), there are physiological variations in thymic weight, often attributable to the normal fluctuations in hormone levels. During these variations in activity, it is not uncommon to observe other forms of hemopoiesis (than lymphopoiesis), e.g. massive erythropoiesis in birds[39,82], granulopoiesis in several species[29,36,37] and an increase in thymic mast cell production[37]. It is also known that many of these activities in the bone marrow depend on T cell interactions for normal development. Is it then so surprising that many immunodeficient conditions in man also show disturbances in myelopoiesis? The entire lymphomyeloid system of the body is closely interrelated and almost certainly depends on the continued function of all parts for good health.

If normal thymus function can be compromised in these general ways, can a knowledge of its normal state of activity and function help the treatment of acquired (not congenital) immunodeficient syndromes? The old-fashioned remedies for ill health, of adequate food (to include to correct trace elements and perhaps zinc supplementation) and the removal of 'stress', should both allow the thymus to repopulate and to produce potentially immunocompetent T cells. The greater knowledge that we are now gaining of the precise actions of the several thymic hormones should in future enable the stimulation of different aspects of T cell production (clinical work on the use of FST is already showing very good results[15]). Ideally, too, perhaps only drugs that are known not to inhibit or affect mitosis in the body, or to cause thymic atrophy, should be prescribed to patients with impaired immune responses once the conditions is stabilized (although there will often be a conflict in the use of certain anticancer drugs as many patients develop cancers).

At the present moment I do not believe that we have accurately assessed the vital role of the adult thymus, and it is time that research was directed to understanding the thymus as a major organ in adults for the maintenance of a competent immune state and hence a long-lived healthy adult.

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0014-4754/84/111181-05$1.50 + 0.20/0

Structure and function of a calmodulin-dependent smooth muscle myosin light chain kinase

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Summary. In smooth muscle the M_r 20,000 light chain of myosin is phosphorylated by a calmodulin-dependent protein kinase. It consists of 2 subunits: calmodulin, an acidic protein of M_r 17,000 that binds 4 moles of Ca^{2+}; and a larger protein of M_r circa 130,000. Activation of the kinase is dependent upon their association in the presence of Ca^{2+}. Cyclic AMP-dependent protein kinase phosphorylation of the myosin light chain kinase occurs at 2 sites. It decreases the affinity of the kinase for calmodulin and a reduction in the rate of light chain phosphorylation occurs. The kinase has an overall asymmetric shape composed of a globular head and tail region for the skeletal muscle enzyme. Trypsin digestion of this kinase releases a fragment of M_r 36,000 from the globular region that contains the catalytic and calmodulin binding sites. Chymotrypsin digestion of the kinase from smooth muscle generates a fragment of M_r 80,000 that does not contain the calmodulin binding or cyclic AMP-dependent protein kinase phosphorylation sites. It is a Ca^{2+}-independent form of the kinase that phosphorylates the light chain of myosin. These structural features indicate a regulatory role for the kinase in smooth muscle phosphorylation and contraction.

Key words. Calmodulin; cyclic AMP; myosin; protein kinase; phosphorylation; smooth muscle (gizzards).