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THE THYMUS IN NUCLEOHISTONE METABOLISM

Margaret A. Kelsall

The thymus differs from other lymphoid tissues in being more sensitive to agents that deplete lymphoid tissues and in involuting at puberty. Absence of afferent lymphatics is the main anatomical difference between the thymus and lymph nodes. All lymphoid tissues except the thymus and that in the mucosa of the intestine contain afferent lymphatics and have large medullary lymph sinuses. The sparsity of lymph sinuses in the thymus may be the basis for the greater sensitivity of the thymus to stimuli which cause involution of lymphoid tissues. The presence of fewer lymph sinuses causes less dilution by tissue fluid and lymph of the hormone such as cortisone, and other lymphopenic agents which are carried in the blood to the thymus than occurs in other lymphoid tissues.

The thymus is composed primarily of lymphocytes which, as they develop, synthesize and store DNA and the amino acids present in thymus histones. This arrangement enables the thymus to play a highly specialized, although very significant, part in nucleoprotein metabolism. However, the thymus has this function primarily during childhood, because it begins to involute at puberty as nucleohistone synthesis increases in the gonads. The inverse relation of changes in the size of the thymus to gonadal function resulted in the idea that the thymus is an endocrine gland. However, Hammar (242), as early as 1910, realized that the thymus does not have a secretory function; and Hoskins, 1918, agreed in this opinion (242). In 1920 Dustin stated that “the thymus does not function by means of secretion”, and in this way it is unlike organs of internal secretion. Nevertheless, for many years experiments were designed to demonstrate that Hassall's corpuscles have an endocrine function. The idea that the thymus is an endocrine gland still persists (289, 643) with the result that some writers are unable to decide whether to classify the thymus as a lymphoid structure or as an endocrine gland and compromise by referring to it as the “thymus gland”.

As early as 1904, Bang reported 5 times as much nucleic acid in thymic tissue as in lymph nodes (364). Cooper in 1832 suggested that the “thymus gland” probably is designed to prepare a fluid well fitted for fetal growth and nourishment from the blood of the mother before the birth of the foetus (364). Later, Simon concluded that the thymus functions as a “sinking fund” of nourishment which is produced as a fluid secreted in early life (364). Simon also noted the sensitivity of the thymus to malnutrition and accordingly designated this structure as a “barometer of nutrition” (277). Dustin (149) considered thymocytes as regulators of nucleoproteins, and Klose in 1910, after learning that Bang in 1904 had
shown by chemical analysis that thymic tissue contains at least 5 times as much nucleic acid as lymph nodes, expressed the opinion “that furnishing nucleic acid to the organism” could be an important function of the thymus (364).

Reluctance to recognize the thymus as a lymphoid organ has been partly due to its differences in structure and embryonic origin from other lymphoid tissues. The thymic parenchyma develops from epithelium, chiefly from the entoderm of the third and fourth branchial clefts in most animals (289, 364), instead of the mesoderm, from which the lymph nodes arise (373). The thymus does not have afferent lymphatics (262, 364, 523), typical lymph sinuses (90, 262, 289), or true germinal centers (90, 289) as do lymph nodes, but the thymus is probably more vascular (289, 540). The possibility of a difference in embryonic origin (364) led to the belief that thymocytes are not the same as lymphocytes. Marine (364) points out the obvious fact that, although these cells resemble each other in having ameboid movement, similar morphologic characteristics, serological reactions, susceptibility to X ray injury, and general pathologic reactions, the available information is “insufficient to establish this identity”. Jordan, 1933, believed that thymocytes had a function similar to lymphocytes. Now the thymocytes are considered “genuine lymphocytes” (143) capable of becoming plasmacytes (583) instead of being, as Hammar, 1905, believed, analogous to lymphocytes (145). The thymus is now recognized as an important source of blood lymphocytes (364).

**Thymic Involution**

Accidental involution of the thymus occurs rapidly and at any age; normal involution of the thymus begins at the onset of puberty and increases with age (364). Most agents or conditions which induce accidental involution of the thymus, if continued, also cause involution of the other lymphoid structures. Hammar, 1905, states that the “massive migration and destruction of the small thymic cells” are brought about in some unknown way during accidental involution with the result that within a week the organ may shrink to one fifth of its previous weight. The relative destruction of the medulla and cortex varies somewhat with the different kinds of accidental involution (364).

The thymus is generally conceded to be more sensitive to lymphopenic factors than the other lymphoid structures (15, 130, 150); however, certain agents, such as certain arsenical preparations, are reported to deplete the systemic lymphoid tissue first (153). Kirschbaum, et al. (313) report that thymic tissue apparently is more sensitive than nodal tissue. This was especially noticeable in mice treated with both X rays and methylcholanthrene, which acted synergistically.

Thymic involution has been produced in a variety of ways. Dustin and his co-workers, 1913 to 1933, produced lymphoid involution in frogs and mammals by use of a wide range of agents, which they called “caryoclastic poisons” (153), such
as dyes, chemicals, X rays, toxic sera, and others. Dustin (150) and Dustin and Gregoire (153) show that certain agents which deplete the thymus have selective effects on the cells of different lymphoid structures and other tissues. Some agents appear to act directly upon the lymphocytes in the lymphoid tissue by causing pycnosis in a large percentage of the cells; others, such as vitamin deficiencies and hunger, appear to act indirectly by producing inanition.

One obvious cause of thymic involution is the release of adrenal cortical steroids. Thymic involution has been produced in normal animals by administration of ACTH (177, 398), by hypophysectomy in rats (177) and by administration of cortisone in rats and mice (86, 129, 273, 274, 519, 533, 554) and hamsters (116, 302).

The significance of sudden dissolution of relatively great numbers of thymocytes in accidental involution has not been determined. The assumption that the thymus synthesizes and provides a readily available source for many essential substances is one possible explanation of the response known as accidental involution. The sudden withdrawal of lymphocytes from the thymus is a reaction that provides other cells with histones, nucleic acids, and possibly certain other substances, including adenosine triphosphate. Dustin in 1931 (151) held that the diverse causes of rapid thymic atrophy, such as sickness, inanition, suppuration and formation of sex products (149) were a response to the need of the organism for a great amount of nucleoprotein.

Vascularity of the Thymus

It appears that the unusual vascular architecture of the thymus affords a logical basis for a morphophysiological interpretation of the extreme sensitivity of this lymphoid structure to lymphopenic agents (305).

The thymus of man is supplied by 4 to 6 blood vessels, which enter and leave in different areas. The arteries arise from the internal mammary, thyroid (268, 364, 373) and pericardial arteries (364). The larger thymic arteries pass along the interlobular connective tissue and send branches to penetrate and supply the lobules. These form a “plexus of sinusoidal capillaries with elongated meshes” in the medulla, while the cortex of the lobules is supplied by radiating capillaries (289). The thymic arteries in the rabbit, as in man, are multiple and do not enter at a hilus; the largest of them arises from the sternal artery (305). Smith, et al. (540) describe 5 vascular patterns of the mouse thymus. The thymic veins arise as sinusoidal capillaries (289) in the medullary regions and empty into the left innominate and thyroid veins in man (268, 373). The thymic veins are thin-walled, capable of enormous dilation, and, therefore, able to impound increased amounts of plasma proteins to facilitate lymphopoiesis and to prolong the action of retained substances which lyse the lymphocytes.
The thymus is the only lymphoid tissue, except that in the mucosa of the intestines, which does not contain afferent lymphatics and lymph sinuses; however, intestinal lymphoid tissue has an increased amount of tissue fluid from the absorption of liquids from the lumen of the intestine. Lymphatics of the thymus were first described in 1655 by Bartholinus (523); Warthonus, 1659, held that these lymph vessels should end directly in the subclavian vein without the intervention of lymph nodes, and Drelincourt also held this view for the lymphatics of the thymus in the dog (523). Afanassiew, 1877 (523), His, 1861 (262), Matsunaga, 1910 (364), and Marine, 1932 (364) hold that the lymphatics in the thymus arise from tissue fluid within the individual lobule and form plexuses of true capillaries in or on the periphery of the individual follicles, then form collecting interfollicular and interlobular lymphatics which pass from the interlobular connective tissue areas of the thymus in three directions toward its periphery to form the superior, ventral, and dorsal groups of lymphatics (523). These thymic lymphatics drain the thymus and constitute the afferent branches of 3 sets of lymph nodes in man: the superior nodes (2 in number), the anterior, or ventral anterior mediastinal nodes (4 to 7) and the dorsal nodes (2 on either side) (523). The efferent lymphatics of these three sets of thymic nodes empty into the subclavian vein, the cervical trunk, and/or the subclavian lymphatic trunk (523).

Functionally, the cortex of the thymus forms an extranodal cortex for the thymic lymph nodes since the afferent lymphatics arise in the cortex of the thymus. Correlated with this lymphatic arrangement is the presence of an inordinately large number of plasmacytes in the medullary region of these thymic lymph nodes (305).

Lymph sinuses are very rare in the thymus, and there is, therefore, less stasis of lymph and, consequently, less exchange with tissue fluid than occurs in lymph nodes; thus more favorable conditions are created for an unusually large uptake of intercellular substances by the developing thymocytes.

A résumé of the vascular differences and consequent changes in the intercellular fluid may suggest a basis for determining the chief functional differences between the thymus and the other lymphoid tissues of the body. The reasons advanced to account for the more rapid disintegration of lymphocytes in the thymus and the surprising extent of involution of this structure, when compared with that of the lymph nodes and spleen, following the interposition of various causes have not been established. It is suggested (305) that the absence of afferent lymphatics and consequent absence of afferent lymph and lymph sinuses which, by eliminating dilution by afferent lymph, is highly favorable for condensation of the substances which have passed from the very numerous sinusoidal blood capillaries into the intercellular fluid of the thymus may be the chief cause of the greater sensitivity of the thymus to lymphopenic agents.
Depletion of the thymus

Depletion of the thymus is due to the decreased formation of lymphocytes as well as to increased disintegration of these cells. The varied nutritional deficiencies that interfere with synthesis of nucleic acids and histones deplete the thymus as well as the other lymphoid structures. The effect of administered ACTH or cortisone in depleting the thymus, as well as other lymphoid tissues, is so striking and consistent that there has been a tendency in the last ten years to attribute depletion of lymphoid tissue to endogenous adrenal cortical steroids through stress reactions. Thymic involution in tumor-bearing rats has been considered a result of a hyperactive adrenal or of involution caused possibly by a pituitary factor not demonstrated in crude pituitary extract (38). However, this effect on the thymus in these animals could be a result of inanition, especially if the rats had reached the state of carcinemia. Varied conditions that decrease formation or utilization of DNA and amino acids, such as starvation, malnutrition, vitamin deficiency, or low protein diets, deplete the thymus as well as all other lymphoid tissues (305). Thus, inanition is a potent agent in producing thymic involution and interferes in evaluating the results of experimental work designed to demonstrate the effects of a single dietary deficiency on lymphoid tissue. The obvious result of such experiments should, at least in many cases, be attributed to secondary effects of the absence of the dietary substance being withheld.

The thymus, which Simons designated as the “barometer of nutrition” (277), is depleted by several types of dietary deficiencies (277). The extent of depletion of the thymus varies with the duration of inanition from a 75 per cent weight-loss from acute inanition to 90 to 100 per cent loss in chronic inanition (277). The depletion of the thymus by starvation was observed by Jonson in 1909 (223), Jackson, 1915, Stewart, 1916 (15), Jolly, 1914, Jolly and Saragea, 1924 (145), and the subject is reviewed by Drinker and Yoffey (145), Andreasen (15) and Marine (364). Hibernation also depletes the thymus in hedgehogs (441), frogs (152, 266), and probably other animals; marasmus and chronic illness deplete the thymus in man (90, 149, 400).

The extreme involution caused by starvation suggested that the thymus plays a significant part in normal nutrition (364, 573, 643) and that lymphocytes in the thymus contain “substances of importance to the growth of the individual” (15). Andreasen (15) and Jackson (277) evaluate the work of many investigators and show quite conclusively that hunger or inanition, in proportion to its severity and duration, may profoundly deplete all lymphoid tissue in animals. Many of these investigators report that the thymus is more severely depleted than any other lymphoid structure, especially in adult individuals. Jackson, 1915, and Stewart, 1916, found that chronic malnutrition resulted in marked weight loss by the thymus (15). Jolly in 1914, using prepuberal animals, found that after 6 to 7 days
without food the thymus of the dogs lost 68.1 per cent and that of the rabbits lost 87.9 per cent in weight (15). The thymus in a group of 22 3-month-old male and female rats without food for 7 days lost an average of 91.0 per cent of its normal weight, while the loss in fatty acids was 92.0 per cent of the normal weight (15). Andreasen (15) also found that when these starved young rats were realimentated, restitution of the thymus was much slower than that of the body. The thymus had regained only 50 per cent of its normal weight; the body weight was 95 per cent of normal on the eighth day of realimentation.

Chronic inanition depletes all lymphoid tissues (145, 277, 287, 288, 301, 305, 315); but Andreasen (15) found that in rats the thymus is initially more sensitive and that in progressive depletion it loses weight faster than the nodes, while the nodes lose weight faster than the spleen. Nucleic phosphorus loss was great in the thymus, but was not significant in the nodes and spleen. Accidental involution of the thymus occurs not only in children but also in adults. Wasting illness causes a more rapid atrophy of the thymus than of other lymphoid tissues (401). However, atrophy of the spleen and Peyer's patches occurs coincidently with atrophied thymi in children dying in a state of malnutrition and marasmus (121).

Involution of the thymus accompanying illness may be due to any one or a combination of several conditions (643). Decreased intake and assimilation of protein and B-vitamins and increased protein catabolism are common causes (401). The condition of status lymphaticus is now believed to be erroneously (643) held to explain the sudden deaths in which thymic hyperplasia was the only clue to the cause of the sudden death. The condition was consequently diagnosed as acute thymic hypertrophy (643) and was explained by Rokitansky as having caused death by mechanical means associated with enlargement of the thymus or with an unknown toxic factor (643). Paltauf associated the thymic hypertrophy with narrow aorta, cardiovascular hypoplasia, and lymphatism, and suggested that there was an interrelationship between the thymus and the adrenal glands (643). Recently, pathologists have attributed the cause of death in cases of status lymphaticus to other causes, such as anaphylaxis, and they hold that the size of the thymus is indicative of the normal condition in contrast to the smaller size of the thymus observed in autopsy following prolonged illness (643).

**Dietary Deficiencies**

Deficiency of amino acids or of single or multiple fractions of the B-complex depletes the thymus (121, 145, 377). Although it usually has a systemic effect in reducing lymphoid tissues throughout the body (120), infiltration of lymphocytes still may occur in some lesions, such as in the cornea in ariboflavinosis (400, 442), in the dermis underlying the thickened epidermis in pellagra (607), and in the medulla of enlarged adrenals (156).
A number of papers on the effect of amino acid deficiency on the thymus have appeared in recent years showing that deficiency of different essential amino acids depletes the thymus and other lymphoid tissues of lymphocytes. Young male rats fed a synthetic diet lacking only threonine, one of the essential amino acids in thymic histone, had the thymus excessively depleted compared with those of “starved control rats” and also had other deficiency effects which disappeared when the missing amino acid was added to the diet (515). Leucine deficiency also caused atrophy and other changes of the thymus (616). Deficiency of phenylalanine has been proved to cause atrophy of the thymus (513). This effect of phenylalanine is significant because it is an essential amino acid that is not usually identified as a component of thymus histone.

Deficiency of various fractions of the B-complex which have produced atrophy of the thymus in experimental animals include thiamine (537), riboflavin, pantothenic acid (559), folic acid (257), pyridoxine (469, 559), pteroylglutamic acid (PGA) (79), and choline (154). The cause of depletion of the thymus by absence of the B-vitamins is attributed to inanition (145) and loss of body weight (559). For example, Butler and Morgan (85) found a significant reduction in weight of the thymus accompanied by lymphopenia in pyridoxine-deficient rats, but they hesitated to attribute the loss in thymic weight and in number of circulating lymphocytes to pyridoxine deficiency, since the depletion of the thymus and fall in number of circulating lymphocytes in the deficient animals were considered to have been initiated entirely by inanition.

Dietary deficiency is a potent factor in thymic involution, as is shown by the fact that avitaminosis of thiamin, riboflavin, and pyridoxine causes progressive weight-loss, progressive atrophic changes in the wall of the gastrointestinal with mucosal hemorrhage, ulceration, and destruction of ganglionic cells in the plexi of Meissner and Auerbach in hamsters (413). Pyridoxine-deficiency causes development of lesions in regions of the lymphoid follicles and atrophy of columnar epithelial cells (69). Niacin-deficiency interferes with functioning of the Golgi apparatus (286) and causes mucosal lesions in the gastroenteron of man (442). Pellagra, which results from multiple vitamin B and other deficiencies (51), is accompanied by lesions in the gastrointestinal mucosa (442) and liver (209).

It is not surprising that a number of earlier investigators held the idea that “an abundant supply of the water-soluble B-vitamin stimulates the functional activity of the lymphoid tissue and increases the number of lymphocytes in the circulating blood” (121) and that withholding B-vitamins disrupts functional activity of the lymphoid tissue (120, 121).

The favorable effects of supplements of $B_{12}$ on the atrophic thymus of the chick apparently are related to its pteroylglutamic acid-content, because $B_{12}$ had no effect in the absence of PGA (79). Dietary deficiency of PGA is credited with
causing atrophy of the thymus, lymphopenia, and several other disorders in chickens (498). Aminopterin, an analog of folic acid, alone produced folic acid deficiency, with atrophy of the thymus, spleen, and bone marrow, and leukopenia when given to normal animals, but these deficiency symptoms did not appear when folic acid was administered with the analog (257). These results indicate that “for a certain period, a given amount of vitamin will completely nullify a given amount of antagonist” (257). This complexity is illustrated by the observation of Meites, 1951, that vitamin B₁₂ and aureomycin completely prevented thymic atrophy in young rats kept on cortisone and a diet deficient in B₁₂ for 30 days (275).

Although avitaminosis of certain B-vitamins depletes lymphoid tissue and causes lymphopenia, it is difficult to determine whether one or more fractions of the vitamin B complex were actually the causative agent, since inanition and absence of certain other vitamins or fatty acids (69), secondary infections (145) and a number of other agents or conditions cause lymphopenia and depletion of the thymus and other lymphoid tissue. Other sources of confusion lie in the variable results reported by earlier investigators who did not take into consideration the ability, or inability, of some of the laboratory animals to supply certain vitamins by intestinal biosynthesis or by coprophagy.

Apparently, deficiency of any of the B-vitamins causes anorexia and interferes with digestion, absorption, and internal synthesis of proteins, as indicated by presence of lesions of the gastrointestinal and liver (51). Absence of thiamin, riboflavin, or pyridoxine from an otherwise balanced diet reduced secretion by salivary and exorbital lachrymal (“pouch”) glands (80) and caused spasticity and “ballooning” accompanied by atrophic changes in the ganglionic cells, mucosa and muscular layer of the intestine (413) in Syrian hamsters. Thus, it is not surprising that absence of various vitamin B fractions may interfere with digestion and absorption, especially of other vitamins, amino acids, and components for synthesis of nucleic acids. Deficiency of B-vitamins also decreases the formation of certain co-enzymes and the synthesis of proteins and nucleic acids in lymphoid and other tissues. The effects on the lymphoid tissues are more obvious because the cells of these tissues, the lymphocytes, are storage cells for nucleoproteins.

In addition to increasing appetite and having functions in nucleic acid and protein metabolism, B₁₂, the cobalt vitamin, has a special function in hematopoiesis (90). It is a potent erythropoietic agent (227) and is an effective anti-pernicious anemia substance (227, 292, 596).

**Synthesis of Nucleic Acid**

Many of the B vitamins have functions in the synthesis of nucleoproteins and provide components for synthesis of the nucleotides, and indirectly, by acting as co-enzymes, in the synthesis of nucleic acids. For example, folic acid, together with
B12, thymidine, and the citrovorum factor (probably certain flavones) function in nucleic acid synthesis and in the synthesis of nucleosides from parent pyrimidines and purines (51, 102).

One pyrimidine precursor is orotic acid, which occurs in milk (195, 236) and appears to be the growth factor described by Novak, Hange, and Carrick in distiller's dried products (363), is similar to vitamin B13 in absorption spectra (363). The importance of orotic acid as a pyrimidine precursor in mammals cannot be accurately evaluated because there are other sources of pyrimidines and other means by which they are synthesized. For example, aspartic acid has been found to be a precursor of orotic acid and, therefore, of pyrimidine pentose nucleic acids (464). The functions of vitamin B12 in nucleic acid metabolism are difficult to determine because of various interrelations of B12 with the formation of other vitamins. Vitamin B12 is thought to play an important part in the preparation of carotene for conversion to vitamin A (258), and in stimulating synthesis of folic acid, which in turn stimulates synthesis of vitamin B12 (136). Numerous functions which have been ascribed to B12 in nitrogen metabolism include increasing the incorporation of circulating amino acids into tissues (98) and playing a part in synthesis of ribose, as is indicated by the finding that red cells from B12-deficient rats formed less ribose than did erythrocytes from controls (351). Vitamin B12 appears to function with folic acid in the formation of thymidine, the desoxyriboside of thymine, because thymidine can replace vitamin B12 in certain microbiological activities, while thymine can replace folic acid but not B12 (313). Another reason that B12 is believed to increase nitrogen retention is its capacity to increase the utilization of dietary protein and to aid in conversion of homocystine to methionine in rats (99). Opinions are divided, however, on the ability of B12 alone to promote growth in instances of methyl-deficiency. In some micro-organisms B12 is involved in synthesis of methionine, serine, and thymine, as well as purines (385).

Administration of B12 has been used to counterbalance several conditions that increase protein catabolism. Increased nitrogen retention following administration of B12 is important in evaluating changes in lymphoid tissues, for B12 increases nitrogen retention in pernicious anemia (310). Either oral or parenteral administration of B12 counterbalances the thyrotoxic condition produced in chicks by feeding 0.05 per cent iodinated casein in a corn-soybean ration (411). Emerson (164) also found that vitamin B12 counteracted the decreased growth rate following administration of desiccated thyroid gland to rats on a diet free of animal protein, and increased the growth of rats surviving thyroparathyroidectomy although the rate of growth was slower than in intact rats given B12 (386). Vitamin B12 also increased appetite and growth of male rats receiving large doses of thyroprotein or diethylstilbestrol, but did not increase the testis-weight (386). Wang, Scheid, and Schweigert (612) reported that decreased spermatogenesis and de-
generative changes in the thyroid were counteracted by feeding $B_{12}$. Vitamin $B_{12}$ and aureomycin protected the thymus in rats treated with cortisone, and an increase in $B_{12}$ also decreased the loss in spleen-weight in rats receiving 1 mg of cortisone daily (386).

The basic importance of $B_{12}$ in nucleic acid and protein metabolism is indicated by its ability to increase growth in mammals and bacteria and by its being essential to various processes, including embryonic development as well as hematopoiesis. Rege and Sreenivasan, 1950, found that adding $B_{12}$ to the media increased DNA production by Lactobacillus caeci (592). Deficiency of $B_{12}$ prevents growth of Lactobacillus leichmannii, Euglena gracilis and a B. coli mutant (217), and decreased the cytoplasmic basophilia of hepatic cells in rats (517). The cytological changes in the liver which occur in protein deficiencies are augmented by vitamin deficiencies that decrease the formation of vitamin-coenzyme transformations (323) and thus favor subsequent atrophy (90) and necrosis (233).

**Histones**

Lymphoid tissue, because of the lymphocytes it produces, is a synthesizing and storing tissue for the amino acids in histones. Small lymphocytes occur in blood, lymph, tissue fluid, columnar epithelial cells of the intestine (305, 416) and cerebrospinal fluid and transport not only the DNA but also amino acids as histones. Small lymphocytes also contain RNA, amino acids other than those in thymus histone, and other substances in the cytoplasm; however, the amount of cytoplasm is a very minor part of the cell. The small amount of RNA that the small lymphocyte contains may have a most important physiological function if, as is apparently the case, it serves as the source of ATP and/or of adenylic acid for synthesis of ATP.

Infiltrations of small lymphocytes localize and increase the concentration of essential amino acids, prevent a delay and imbalance and, in general, regulate the distribution of amino acids necessary for mitosis of cells in other tissues. In 1909 Huiskamp prepared nucleohistone from thymus (395), and Kossel in 1927 discovered that histones are combined with nucleic acids in cell nuclei (247) in a salt-like combination linkage (48). Lymphoid tissues, including nodes, thymus, and spleen, are good sources of histones (41, 140). However, the thymus is the richest source, a 25 per cent yield of histone having been obtained from the thymus of man and 27 per cent from the thymus of the ox (556). That lymphocytes have a high histone content has repeatedly been shown by extraction and precipitation of the chromatin of the nuclei (394, 397). Nucleohistone comprised 90 per cent of the “chromosomes” (chromatin threads of Mirsky and Pollister, 1943; residual chromosomes or chromosomes of Mirsky and Ris, 1947) of lymphocytes, while chromosomes from hepatic cells contained only half (45%) as much as lymphocytes (128).
Estimations of the percentage of histones in thymus nucleoprotein vary from 10 per cent, obtained by Pollister and Leuchtenberger (447), to 30 per cent obtained by Allfrey and co-workers, 1952 (567). Chromosomes of different tissues contain varying percentages of histones; for example, chromosomes of calf thymus contained 8.5 per cent histone, and Mirsky and Ris, 1949, show that chromosomes in calf liver contained 39 per cent histone (567); Swift (567) reports that the nuclei of lymphocytes and of hepatic cells have nucleic acid to histone ratios ranging from 1.2:1.0 to 1.6:1.0.

Several proteins in addition to nucleohistones have been found in nuclei of lymphocytes. Mayer and Gulick, 1942, found an alkaline soluble protein in nuclei in thymus of the calf (567). Kirkham, 1952, reported extraction of a globulin fraction from calf thymus which may account for the additional protein described by Pollister and Leuchtenberger, 1949, who stated that “total protein” in nuclei of the thymus gland of guinea pigs was several times greater than had been assumed from biochemical analysis (567). Mirsky and Pollister (396) describe a non-histone protein in chromosomin that contains about 1 per cent tryptophane; the chromosomin of Steadman and Steadman (556) has been reported to contain arginine, tyrosine, glutamic acid, asparatic acid, and tryptophane (128). From a qualitative standpoint the controversial status of chromosomin involves only glutamic and aspartic acid because the other amino acids are present in histones (249); glutamic and aspartic acids are very readily synthesized within the organism (249).

Most somatic nuclei contain histones in salt-like combinations with nucleic acid and protein (128, 616). However, sperm of certain species contain protamine, a simple form (249, 556). Nevertheless, histones in small lymphocytes are very important in metabolism of other cells. The small lymphocytes are the mature, non-dividing, and circulating form of this cell. They do not utilize the histones which they contain for their own metabolism because great numbers of histone-laden small lymphocytes disintegrate hourly, and mitosis in small lymphocytes is very rare and may be partly due to their high content of histones, because low histone content has been found in tumor cells and in normal cells in mitosis thus indicating that an excess of histones may inhibit cell division (556).

Thymus histone is an important protein because it contains most of the essential amino acids: arginine, histidine, lysine, leucine, isoleucine, threonine, methionine, and valine (41, 48, 75, 245, 314). The presence of most essential amino acids as components of histones in nuclei gives added significance to the disintegration of lymphocytes in the blood and in tissue fluid of connective tissue, because the histones in small lymphocytes hold, in an inactive form, most amino acids necessary for the formation of histones within or covering the chromosomes of proliferating cells.
Two amino acids which are essential in protein metabolism (162), phenylalanine and tryptophane, are not usually found in thymus histone. A trace of tryptophane in histones was reported by Kossel (247), but Steadman and Steadman (556) hold that thymus histone does not contain tryptophane. Two non-essential amino acids, tyrosine (249) and cysteine, are present in thymus histone (556). The absence of some amino acids in thymus histone may be just as significant in the metabolism of lymphocytes as is the presence of other amino acids. Cysteine, glutamic acid, and glycine do not occur in thymus histone (249). The absence of these three amino acids may be significant, because they are inhibitors of alkaline phosphatase (563). Alkaline phosphatase, which occurs in all animal cells, except hyaline cartilage (487), is very abundant in lymphoid tissue (144, 563, 593) where it occurs chiefly in the nuclei of the lymphocytes (435). Alkaline phosphatase catalyses the hydrolysis of orthophosphates from phosphomonoesters and has recently been found to function in transphosphorylation (563).

Protein Storage

The 'protein storage', or 'amino acid pool', is an elusive entity. Instead of being a definitely delimited structure, such as stored fat, it appears to be a reversible physicochemical process carried on at any site in the body when and where needed (197). That there is storage of protein in the various tissues and intercellular and circulating fluids of the body, which is available whenever needed, is indicated by investigations showing that when 20 to 30 g of plasma protein is lost it is replaced within 6 to 12 hours, presumably from fluid withdrawn from the tissues (400). This stored protein, in the form of amino acids in combinations, amounts to an estimated 2 to 3 kilograms in a normal person (197).

The idea that protein, as well as carbohydrates and fats, but in less quantity, is stored in the body is comparatively new. Until 1935 physiologists believed that there was very little replacement of protein in living tissue by dietary amino acids and that this was merely "to compensate for the 'wear and tear' of the body constituents" (25). Folin and Denis, 1912, explain the then current view that all absorbed protein not used in repair is catabolized and excreted by the kidneys. Borsook and Keighley, 1935, showed that, instead of being inert metabolically, dietary protein is highly important in the maintenance of the tissue- and plasma-level of free amino acids, in furnishing much of the material for synthesis of protein and peptides and, in general, in supplying the demands of "continuous synthesis and degradation of cellular protein" (25).

Whipple and co-workers, 1942, have shown that there is a definite relationship between diet protein and regeneration of plasma proteins and that the 'dynamic equilibrium' between the tissue and plasma proteins is to a great extent dependent upon proper maintenance of diet protein (209). Other works show that hypophyseal
growth hormone "facilitates nitrogen retention and protein synthesis", while adrenal cortical extract increases urinary excretion of nitrogen and potassium (197). By use of isotopes, it has been determined that the volume of pooled free amino acids in the human body represents 0.5 g nitrogen per kilogram of body weight (25). Boothly and co-workers hold that hypoactivity of the thyroid gland is conducive to storage of 'deposit protein' and, conversely, that thyroid hyperactivity antagonizes storage of protein and causes breakdown of the excess protein in hypothyroid myxedematous swelling in man (44). The adrenal cortex plays a part in maintaining the plasma albumin, but not the total plasma protein level (345). After adrenalectomy or hypophysectomy, the albumin plasma level falls, and the globulin ratio is definitely reduced (345). Thyroidectomy was followed by increased globulin, but it did not affect the albumin level (209).

**Other Lymphoid Structures**

The various lymphoid structures in man and most mammals play a part in nucleohistone metabolism which differs from that of the thymus chiefly in quantity and in the absence of a definite relationship with prepubertal development.

Lymphoid tissue in the spleen, lymph nodes, and intestinal lymphoid tissue also synthesizes and stores nucleoproteins. Lymph nodes are a protein synthesizing and storage tissue which are interposed between tissue fluid and the systemic blood vascular system. Large lymphocytes in germinal centers of lymph nodes retain essential amino acids by synthesizing nucleoproteins. The spleen is interposed between the lymph and blood streams, as well as between arterial and venous systems, and has multiple specialized functions. One function of the spleen is to serve as an organ in which plasmacytes develop in the splenic sinusoids, as was found in the hamster. Plasmacytes disintegrate and release their components, particularly RNA, which are passed through the hepatic portal venous system to the liver (300).

The nucleus of plasmacytes has the same function in histone metabolism as that of small lymphocytes. Drinker and Yoffey (145) review the various theories and conclude that one obvious fact in considering potencies of lymphocytes is that they can become plasmacytes, and Jordan and Morton (290) hold that the transformation of lymphocytes into plasmacytes occurs in areas of lymph stasis. Gonzales (219) states that the transformation of lymphocytes into plasmacytes is due to the influence of immunity reactions. Small lymphocytes and plasmacytes occur together in the connective tissues in areas of wound healing and subacute or chronic inflammation. The hydrolysis of histone derived from cytolized small lymphocytes would also localize and increase the availability of amino acids for protein synthesis in the transformation of plasmacytes from other small lymphocytes.

Intestinal lymphoid tissue includes Peyer’s patches, solitary follicles, the vermiform appendix, cecal lymphoid tissue, lymphocytes and plasmacytes in core of the
villi. Large lymphocytes in the germinal follicles in intestinal lymphoid tissue synthesize histones from amino acids during the formation of nucleoproteins. Most descriptions of the absorption of amino acids mention that the amino acids that enter the body are carried by the blood to all tissues where they become incorporated (249). However, the amino acids which pass through the lymphoepithelium covering the intestinal lymphoid patches are directly available for use in the synthesis of histones by lymphocytes as soon as they enter the intestinal lymphoid tissue. The formation of nucleoproteins in the nuclei of lymphocytes and in the cytoplasm of plasmacytes incorporates significant quantities of dietary amino acids directly from the lumen of the intestine without these amino acids having passed into the blood. Thus, the numerous lymphoid patches and aggregated cells in the mucosa of the small and large intestines have direct access to these dietary amino acids. The significance of this provision becomes apparent when one considers the total number of solitary follicles, Peyer's, and other intestinal lymphoid patches.

**RELATIONSHIPS OF THYMUS AND GONADS**

Involution of the thymus of man during puberty has been recognized for a long time. Calzolari, 1898, found that castration caused hypertrophy of the thymus and that injection of sex hormones or gonadotropic substances produced involution of the thymus in these rabbits (101). Gonadectomy or failure of development at puberty delays thymic involution (364). A review by Marine, Manley, and Baumann (366), indicates that gonadectomy produces or is followed by hypertrophy of the thymus and other lymphoid tissues, but that thymectomy has little, if any, effect on the development of gonads. Removal of gonads is followed by an increase in size of the thymus (443, 444), and in the weight of lymph nodes (101). Castration, however, of 50 to 60-day-old albino rats was reported to have retarded body growth of males by 25 per cent, but it accelerated body growth of the females by 31 per cent (445). Chiodi (101) observed that testosterone propionate produced thymus atrophy in castrated and normal male or female albino rats. However, more recent studies have indicated that testosterone increases the thymus and other lymphoid tissues. Administration of testosterone in normal animals increased nitrogen retention (439) and, according to Kochadran, 1944 and 1950, it reduced urinary nitrogen excretion, and increased deposition of protein in accessory sexual tissue of normal and castrated rats (539). Testosterone propionate (337) and various crystalline androgens (410) maintain spermatogenesis in hypophysectomized rats, but caused atrophy of the testis in non-hypophysectomized rats that received testosterone for 7 days (379). Other hormones also cause atrophy of the testis. Rats receiving thiouracil over 600 days did not have germ development in the testis (104).
The thymus of the hamsters that recovered from a total body X irradiation of 795 r was larger at 60 days after exposure than the thymus of controls of the same age. Since the gonads were atrophied when the animals were sacrificed, the increased size of the thymus in these hamsters was attributed to a permanent disruption of nucleic acid metabolism in the testis and ovary resulting in the thymus reassuming its prepubertal function in nucleohistone metabolism (303, 305). The results thus obtained parallel those obtained by gonadectomy.

**Effect of Thymectomy**

Effects of the destruction or removal of the thymus upon the gonads are not so striking as the effects of castration upon the thymus. Destruction of the thymus during the first few days of the rat's life retarded spermatogenesis (526); X irradiation of the thymus in newborn rats produced reversible aspermia (443). However, Putzu Donnedu (451) found in rabbits that if thymectomy were performed prior to puberty it produced little change in reproductive activity; if it was done during the adult state, this activity was reduced. Contrarily, Plagge (443) reported that total thymectomy of newborn rats did not alter growth of the testes, formation of hormones, or spermatogenesis, but that castration performed prepuberally or at puberty increased the weight of the thymus. Removal of the thymus was not found to hasten sexual maturity (365). The more rapid involution of normal and transplanted thymi in breeding rabbits does not necessarily suggest a "specific nerve influence" (365), but could be a direct result of increased protein catabolism or decreased nitrogen retention.

Other results of thymectomy include changes in various lymphoid organs. Perrier found hyperplasia of lymphoid tissue and the formation of large germinal centers in the spleen after thymectomy (362). Magnani also found hypertrophy of the spleen in young and adult rats after thymectomy; Matti found that primary hyperplasia was followed by atrophy of the spleen after thymectomy (362). Bayer held that there is mutual compensation between the spleen and the thymus as indicated by the fact that splenectomy increased thymic efficiency and that thymectomy increased splenic activity. The reproductive system would not be expected to be influenced by thymectomy in some species because other normal lymphoid tissues would probably compensate for its function in storage of nucleoproteins. The thymus of rabbits, for example, represents an average of about 12 per cent (11.33% in 5 rabbits) of the total lymphoid tissue (115), whereas the vermiform appendix represents about 33 per cent of the total weight of body lymphoid tissue. Since appendectomy has comparatively little effect on reducing lymphocytes (299), the thymus, which represents less than half this amount, would have very little, if any, demonstrable effect.

Some of the controversial effects of thymectomy have been attributed to pres-
ence of parathyroid tissue within the thymus (364). Haberfeld and Schilder, 1909, found accessory parathyroids in every rabbit thymus examined (364). Shapiro and Jaffe, 1923, demonstrated accessory glands in 12 per cent of a single histological section from the thymus of cats (364). Nicolas and Swingle, 1925, demonstrated accessory parathyroids in 35 per cent of their cats, and Farner and Klinger, 1920, in nearly every cat examined (364). Some of the early controversial work on the effect of thymectomy decreasing growth may be due to the presence or absence of functional accessory parathyroids, for Marine (364) points out that accessory parathyroids account for different results following extirpation of parathyroids. Among the many varied effects attributed to thymectomy is defective formation of the shell and albumen of bird eggs (471) while Gilmour (210) suggests that defective egg development may be due to the parathyroids being embedded or buried in the thymus. Gewers, 1930, claimed that thymectomized guinea pigs had defective calcification of the teeth (340).

The high incidence of accessory parathyroids may also account for the reports on development of rachitic lesions in thymectomized rats (428) and for altered osseous development in various animals following removal of the thymus (546).

Nutritional deficiencies cause atrophy of the testes and involution of the thymus. Most deficiencies of B-vitamins or of amino acids, which cause depletion of the thymus and other lymphoid tissues, also cause atrophy of the testes. Nucleic acid formation decreases in the testes as well as in the lymphoid tissue in conditions of deficiency of thiamin or certain other of the B-vitamins (81). Thus, it is not surprising to find that deficiency of any of the B-vitamins inhibits spermatogenesis (69). Jackson (277) reviews the literature on effects of deficiency of individual B fractions and makes the generalization that “the testes are especially susceptible to dietary deficiency of vitamin B”. Deficiency of $B_{12}$ for 4 weeks in rats decreased spermatogenesis and produced other degenerative changes of the seminiferous tubules and interstitial connective tissues (612). Atrophy of the testis has also been produced experimentally by diets deficient in various amino acids, including deficiency of phenylalanine (513), threonine (515) and arginine (294).
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