The Myth of Thymic Atrophy

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"Age involution" in the sense in which it is commonly thought of today is a myth. The thymus does not atrophy at puberty; on the contrary, it exhibits its most remarkable changes during gestation.

In this study, 42 mature female guinea pigs reared on guinea pig pellets, lettuce and water all ad lib, were mated at the beginning of estrus, this day being designated for the purposes of the study as the day of conception and Day 1 of pregnancy. Animals were then sacrificed by a blow on the head as follows: 1 on the 16th day, 1 on the 20th day, 1 on the 24th day, 3 on the 30th, 2 on the 40th, 1 on the 45th, 2 on the 50th, 1 on the 52nd, 3 on the 55th, 4 on the 60th, 5 on the 63rd, 5 on the 64th, 4 on the 65th and 1 on the 70th day of pregnancy. Two animals were killed on the day of delivery, 2 were killed 1 day post-partum, 2 on the third day, 2 on the 8th day and 2 on the 13th day. The tissues were fixed in Zenker-Formol, embedded in cellloidin, cut at 6 microns and stained with hematoxylin-eosin-azure.

The guinea pig estrus cycle is approximately 16 days in duration; pregnancy is approximately 4 cycles in length. A previous preliminary study had shown that the guinea pig thymus changes its bulk and cellular constitution radically during the estrus cycle. It is as large as it ever was or will be just prior to ovulation; shortly thereafter it has largely depleted its cortical cells, undergone what may be described as extensive cortical changes consistent with myeloid metaplasia and become a shrunken and virtually invisible organ to the unskilled observer. No one has ever observed a solitary animal in successive cycles but it is reasonable to assume that cycling continues until cessation of sexual functioning. What happens when pregnancy intervenes?

I will not get into a great deal of minute detail regarding histologic changes but, in this communication, will present only the most prominent findings.

Although I know from earlier studies of the guinea pig estrus cycle that the thymus is largely depleted of cortical cells shortly after ovulation, the first animal in this series was sacrificed at 16 days into its pregnancy and showed marked regeneration. A heavy cortical layer was present and there was a moderately sharp demarcation between the cortex and medulla. Cells which are called Foë-Kurloff cells (called mast cells by others and by various names by other authors in other species) are present but not prominent. Some are seen in the draining lymphatic vessels. The picture at 20 days is similar; some of the intrathymic lymphatics are noted to be packed with emigrating cells. By 24 days, the picture is the classic one for the juvenile thymus -- there is very little space between lobules and the cortical/medullary areas are well-defined. The same picture holds for 30 days and 45 days.

By 50 days, there is noticeable diminution of the cortex and a moderate accumulation of distended plasma cells (F-K cells) in the cortex, medulla and lymphatic drainage. There is intense mitotic activity in the cortical lymphoid cells.

At 52-55 days, the diminished bulk is very apparent with marked increase in the septal width between lobules. The cortico-medullary margin remains sharp but the cortex has been greatly depleted by cell migration. In places, the F-K cells have accumulated and present the appearance of heavy layers; these accumulations usually represent a piling up in the large lymphatic channel at the cortico-medullary junction. Infiltration of cells into the septal lymphatics is a prominent feature. While present in considerable numbers, the F-K cells are definitely a minority group in every area, lymphoid cells predominating.

At 55 days, the cortex remains shrunken and has totally disappeared in some areas. There are heavy septal infiltrations of F-K cells; they are also scattered throughout the cortex and medulla and are found in
masses within the lymphatic vessels draining the tissues. Some of the intrathymic vessels are packed with them; in some places cords of plasma cells (F-K cells) are side by side with dense cords of lymphocytes.

The same picture continues for the duration of pregnancy with increasing depletion of the cortex and massive production and export of plasma cells loaded to capacity with secretion. Totally denuded medullary areas are common and such a thymus is nearly invisible grossly.

Following delivery, there is a rapid recovery of cortical bulk so that by 13 days post-partum, the thymus is again a large organ with a sharp cortico-medullary border and very little interlobular space. In short, it has gone from the appearance of a severely depleted and virtually invisible organ at term to become as large as it ever was or will be less than two weeks later. The recovery phase looks precisely like the picture seen during the estrus cycle in virgin females, with one exception. F-K cells continue to be found in moderately large numbers. I shall now have to go back and look again at the virgin material but I have no recollection of seeing F-K cells at that time.

It is of special interest to observe that the spectacular changes occurring in late pregnancy -- the massive outpouring of plasma cell forms and the dissemination of the thymic cortex throughout the body and the placenta via the circulatory system of the mother is not reflected in the thymus of the fetus. Here the picture remains what has been classically considered to be the normal fetal or juvenile appearance -- a large thymus with clear-cut cortex and medulla and without the plasma cell changes observed in the mother. Whatever combination of factors has caused the maternal changes has not crossed the placental barrier. This is worthy of intense study.

For those who may feel that I am describing a phenomenon peculiar to the guinea pig, let me say that I am not the first to observe this and that similar pregnancy changes in the thymus have been described in more or less detail for the mouse, rat, hamster, rabbit, and hedgehog and that similar but seasonal thymic changes have been reported in moles, cows, marmots, frogs, mallard ducks, mule deer and others. I have had only one opportunity to observe the thymus in a single section from a human pregnancy near term; Russell body plasma cells were present but not in the quantities demonstrated in the guinea pig. Fortunately -- but not helpfully -- it has been difficult to obtain human material in spite of promises of same from pathologists for more than 25 years. Interestingly, Ronconi in 1909 reported "atrophy" of the thymus in a human pregnancy.

While these findings might at first seem of only passing interest, as indeed they have been to numerous audiences since the early 1950's, I am hopeful that today they have been planted in more fertile soil. The September 1980 Editorial in The American Journal of Medicine is entitled "Pregnancy, A Temporary Fetal Graft of Suppressor Cells in Autoimmune Disease?" I think not. The September 13, 1980 issue of The Lancet contains a Letter to the Editor from Denham Harman concerning "Secondary Amyloidosis and Antioxidants". He notes that "Santoquin", a quinoline derivative, almost completely prevented spontaneous amyloidosis in male LAF mice. In a preliminary experiment by Dr. Clayton Feldman (then a medical student) in my laboratory over 20 years ago, it was shown for the guinea pig that chloroquin will, after preliminary treatment with an estrogenic substance, cause the same build-up of plasma cells in the intrathymic lymphatics that is seen in late pregnancy; hydralazine does the same thing. And I recall that at least one researcher has described the Russell body plasma cells of humans as a source of amyloid. The identical cells that I have called plasma cells have been described by others in the hamster as mast cells which is very interesting. The September 1980 issue of The American Journal of Medicine has another article entitled "Increased Immunoglobulin-Secreting Cells in the Blood of Patients with Active Lupus Erythematosus". In 1961 I presented a paper saying that LE cells as originally described by Hargraves were the same cells I have shown you today in the guinea pig thymus. I still think so. It is also intriguing to recall that in systemic lupus erythematosus there have been a number of reports of high fetal wastage.

Years ago in the United States and perhaps elsewhere even today, a mixture of thymus and pituitary was promoted for use in uterine inertia with the claim that the contractions produced were strong and rhythmic in nature and not tetanic as with pituitary alone; should this be re-investigated? In 1950 I presented a paper entitled "Thymic Function and Leukemia"; I am even more certain today that leukemia is a thymic disease and to the list I would add multiple myeloma, Hodgkin's disease, histiocytic medullary reticulocytosis and others as good candidates and I haven't even scraped the surface. A major problem has been the mental block keeping investigators from thinking of the thymus as a major producer and exporter of cells.

In passing, I feel obliged to comment on the fact that lists compiled of tissues involved in primary and secondary amyloidosis are notable for their absence of mention of the thymus while lymph nodes and spleen rank high. As in leukemia, where the apparent non-involvement of the thymus has been described as a paradox, the probability is high that the thymus is an exporter of amyloid producing cells rather than a repository for them.

It should also be noted in passing that many authors have described the thymic cells characterized today as plasma cells as PAS-positive cells in mice and other species.
It is my belief that any data on species-specific thymus weights is meaningless unless the sex, state of sexual activity, season of the year, stage of sexual cycle or presence of pregnancy is included. In addition, a statement of weight not correlated with the histologic appearance is equally meaningless if one is to use this determination as a reflection of thymic function.

If the thymus does decrease its activity with advanced age -- and there is a considerable body of evidence to suggest that it does -- and if this decrease does have a bearing on aging itself -- and there is some evidence to suggest this, then efforts to stimulate thymic function may be worthwhile in our attempts to extend both the quality and quantity of life. The nearly universal present conception of the adult thymus as an "atrophied" organ carries with it a qualitative feeling that it has become an organ which has passed the point of manipulation. It may well be the case that the thymus is capable of responding but the organs calling the tune have themselves grown weary; if this be true, then the "wasted" thymus may yet prove to be a "waiting" thymus.

Lest we are too inclined to ascribe all of these changes to pregnancy only, similar variations, including the plasma cell proliferation, have been described in non-pregnant hibernators.

May I say here that very little of what is reported today is entirely new; most of it has been seen before, some of it 70 years or more ago. And so I lay claim to no discoveries.

In conclusion, if Walford is correct in his statement that, "It is an old scientific dictum that even one piece of highly pertinent evidence which contravenes a theory may destroy it", it follows reasonably that the old ideas regarding "thymic atrophy" are a myth and deserve to die. Indeed, their existence has posed a dreadful impediment to research and the search for truth. As a physician who has carefully reviewed the old concepts for signs of life, I now pronounce them dead.

(References on Request)