LYMPHOCYTES AND LYMPHOID TISSUE IN THE HUMAN PITUITARY ¹

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NINE FIGURES

INTRODUCTION

Erdheim ('04) described a circumscribed accumulation of unicellular lymph corpuscles between the Rathke’s cysts in pars intermedia. He said there was a central lightly staining area and that the whole gave the impression of being a lymphoid follicle.

Lymphocytes and lymphoid tissue have been described in the pars intermedia of the human pituitary by Simonds and Brandes ('25), Guizzetti ('26), Kiyono ('26), Schönig ('26) and Romeis ('40). Simonds and Brandes thought it was associated with a pathological condition; Schönig, however, found lymphoid tissue in the pars intermedia in 5 normal pituitaries, three of them from accident cases. Romeis found lymphoid tissue in the pituitaries of three executed young males.

It is the purpose of this paper to describe the incidence, location and histology of areas of lymphocytes and lymphoid tissue in a series of 100 human pituitaries varying from the newborn to 86 years of age.

The age, sex and cause of death are given in table 1, Shanklin ('48a). For other histological findings on this material

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the reader is referred to the paper by Shanklin (’51a) and earlier papers).

**Observations**

**Incidence.** Lymphocytes and lymphoid tissue were observed in 43 pituitaries out of the 100 investigated, hence 43.0% were positive. The youngest positive specimens were M 110 and M 248 both 3.5-year-old females, the oldest M 172 was an 83-year-old female.

The pituitaries were divided into the following 4 age groups: (1) newborn to 3.4, (2) 3.5 to 19.9, (3) 20.0 to 39.9, (4) 40.0 to 86.0 years. In group 1 there were 26 specimens, in group 2 there were 21, group 3 had 16 and group 4 had 37. None in group 1 had lymphocytes or lymphoid tissue, while 12 of the 21 (57.1%) aged 3.5 to 19.9 were positive, 9 of the 16 (56.2%) specimens aged 20.0 to 39.9 were positive, 22 out of 37 specimens (59.5%) in the oldest group were positive.

Of the females 3.5 years and older there were 28 specimens of which 10 (35.7%) contained lymphocytes and lymphoid tissue. There were 46 pituitaries from males 3.5 years and older, with 33 (71.7%) positive specimens. Therefore in comparable age groups only 35.7% female pituitaries contained lymphocytes and lymphoid tissue while 71.7% male pituitaries were positive.

There were 105 individual areas of lymphocytes and lymphoid tissue in the 43 positive specimens, an average of 2.4 areas per positive specimen. They varied from 1 to 6 areas per specimen. Of the 43 positive specimens 16 had a single area, 8 had 2 areas, 9 had 3, 5 had 4, 4 had 5 and 1 had 6 areas.

**Location.** Many areas of lymphocytes and lymphoid tissue were found in the pars intermedia. Among the total 105 areas observed 77 were in pars intermedia, 23 of them towards the capsule and 54 more centrally placed. Twenty-one areas were in pars nervosa; 10 in the antero-lateral part, 6 near the midline, immediately under pars intermedia and 5 deep in its substance. Two areas were found in the capsule around the pars anterior, two in the capsule adjacent to pars intermedia.
and two in the capsule of pars nervosa. A single area was found in the center of the stalk (fig. 3).

Sizes of areas. Two diameters were determined by measuring with the eyepiece micrometer, while the third was found by counting sections over which the area of lymphocytes extended and multiplying by 10, as each section was cut 10 μ. The shapes of the areas were extremely variable, in general the form was nearer to that of an ellipsoid rather than that of a cylinder or sphere. In order to get an approximation of the volume of each area their volumes were determined by using the formula for an ellipsoid \((\frac{1}{2}a \times \frac{1}{2}b \times \frac{1}{2}c \times 4/3 \times 3.1416)\), where a, b, and c are the lengths of the three major axes.

Twenty-three areas having volumes between .0004 and .0009 mm³ were classified as very small, 69 with volumes between .0010–.0094 as small, 12 with volumes .0012–.0528 as medium. A single area with a volume of .1331 mm³ was classified as large. The actual measurements of one area in each category is as follows: very small \(.05 \times .15 \times .18\) mm, volume .0007 mm³, small \(.13 \times .18 \times .48\), volume .0059, medium \(.20 \times .62 \times .81\), volume .0528 and large \(.36 \times .84 \times .84\), volume .1331.

Histology. Seventy-six areas of lymphocytes were classified as diffuse or group 1. The lymphocytes in group 2 or compact areas were located in a reticular meshwork, while those in the diffuse areas were found among ordinary collagenous fibers.

A typical group 1 area, found in pituitary M115 from a 40-year-old male, who died from progressive paralysis, is included in figure 4 and described. This area measured \(.11 \times .15 \times .23\) mm and was situated at the junction of the pars intermedia and the pars nervosa. It was bounded by several large colloid filled follicles, very darkly stained basophils and densely packed collagenous fibers. The supporting elements in the area were collagenous fibers with fibroblast nuclei among them. Most of the cells were evenly distributed small lymphocytes. An occasional medium-sized lymphocyte and several plasma cells were observed.
Another typical diffuse area in pituitary M 177, from a 35-year-old male, whose death was due to coronary atheroma, is included in figure 6 and described. This area measured $.16 \times .33 \times .44$ mm. It was also located in the pars intermedia near the pars nervosa. The area was bounded by several large thin walled blood vessels, colloid filled follicles and well-stained basophils. One side of the area was separated from the proximal border of pars nervosa by a broad band of densely packed collagenous fibers.

The small lymphocytes were fairly evenly distributed, except where they were separated from one another by strands of collagenous fibers and fibroblast nuclei that passed through the area parallel to its long axis.

Most of the 76 areas of lymphocytes classified as type 1 were located near colloid filled follicles, basophils or tubular glands; all elements associated with the pars intermedia. Twenty of these areas of lymphocytes were found near colloid filled follicles, but no basophils, 17 were near both colloid filled follicles and basophils, 16 were near basophils, but no colloid follicles, three were near tubular glands only and one was near both basophils and tubular glands. Four were situated near areas containing all three varieties of anterior lobe cells and 14 were found unaccompanied by any epithelium.

The lymphocytes in the areas located in pars nervosa were found free in the spaces between the pituicyte processes. In most cases where the areas were located in the proximal part of pars nervosa the lymphocytes were accompanied by basophils or colloid filled follicles that had extended in from the pars intermedia.

Areas of lymphoid tissue classified as group 2 are characterized by the presence of densely packed lymphocytes and a reticulum, hence are classified as lymphoid tissue. Twenty-nine such follicles were found in 20 pituitaries (figs. 1, 2, 5, 7 to 9). A typical area of group 2 is shown in figs. 1 and 2, specimen M 91 from a 40-year-old male, whose death was due to suicide by hanging. This area measured $.36 \times .84 \times .84$ mm. It was located near the center of the pars intermedia,
bounded anteriorly by an area of basophils in pars anterior, laterally by fairly large blood vessels and densely packed collagenous fibers and posteriorly by pars nervosa. No follicles, either with or without colloid, were associated with the area. The central part of the area had fewer cells and was more lightly stained than the surrounding parts. Stellate shaped reticular cells, with protoplasmic processes connected to one another, were clearly seen here. Their nuclei were oval to angular and had lightly stained sparse chromatin granules. The free cells in this area were mostly small lymphocytes and a few medium-sized lymphocytes. The part outside the central area consisted of densely packed small lymphocytes fairly uniformly distributed. They were not arranged in concentric layers. The area is a typical lymphoid follicle containing a young germinal center. Another area with a young germinal center is shown in figure 9.

None of these areas were surrounded by capsules. Of the 29 areas of lymphoid tissue classified as compact 12 of these areas were sharply circumscribed while in 17 of them the lymphocytes spread beyond the compact area into the surrounding tissues. In 5 of the areas the vascularity was classified as abundant, in 9 medium and in 15 scanty. Ten of these areas were located near colloid filled follicles, but with no basophils nearby, 6 were associated with both follicles and basophils, and 7 were near areas of basophils with no follicles. One area was near tubular glands and follicles, one near tubular glands and basophils and one near tubular glands only. Three were not associated with epithelium.

DISCUSSION

Erdheim ('04) found a lymphoid follicle in an adult pituitary. Simonds and Brandes ('25) found lymphoid tissue in the pituitary of a 12-year-old girl; three other positive specimens were from individuals 20 to 34 years old and 15 from patients 35 to 55 years of age. The 5 positive cases described by Schönig ('26) varied from 25 to 63 years. Three of his specimens were from accident cases; a 25-year-old male, whose
death was due to a stab wound, a 28-year-old male killed by
a fracture of the skull and a 30-year-old male killed in an air
accident. The three described by Romeis ('40) were from
healthy young males 20, 24 and 25 years old respectively.

Areas of lymphocytes and lymphoid tissue were not found
in 26 pituitaries in our series varying from the newborn to
3.4 years, however, two specimens 3.5 years were positive.
The percentages of positive cases 57.1, 56.2 and 59.5 in our
three age groups were strikingly similar. The incidence of
43.0% in our series appears to be very high compared to
10.0% found by Simonds and Brandes. We attribute the
higher incidence in our series to our more thorough examina-
tion of serial sections. Schönig and Romeis do not state the
number of specimens examined. Guizzetti ('26) referred to
lymphocytes as an occasional finding in the human pituitary.

We found a marked sex difference in our series for 71.7%
of the male pituitaries from individuals 3.5 years and older
were positive while only 35.7% of female pituitaries in that
age range were positive. Simonds and Brandes found lym-
phoid tissue in 5 females and 14 males but do not state the
number of pituitaries of each sex examined.

All authors are agreed that the pars intermedia is the most
frequent site for lymphoid tissue. Simonds and Brandes
found areas of lymphoid tissue in or near the pars inter-
media in 18 cases, once in pars anterior and once in the pars
nervosa. Schönig found it 4 times in pars intermedia and once
in the lateral corner of pars nervosa adjacent to pars inter-
media. In our series 93 of the areas were found in or near
the pars intermedia, or in pars nervosa near the pars inter-
media. Six areas were found in the capsule of the pituitary,
5 deep in pars nervosa and one in the stalk. Not a single area
was found in pars anterior.

The sizes of these areas is not given in the literature. Our
measurements show that they vary from very small (0004
mm²) to large (.1331).

Simonds and Brandes divided their 20 cases of lymphoid
tissue into 4 groups. Group 1 included areas of lymphocytic
infiltration in immediate relation to masses of colloid, in group 2 the lymphocytes were associated with one or more blood vessels and often resembled a potential lymph gland, in group 3 the lymphocytes were diffusely infiltrated, without relation to blood vessels or colloid, and in group 4 infiltration occurred as perivascular cylinders. In our opinion the relation of these areas to masses of colloid, either free or in follicles, is not significant, hence we have included in our series under group 1 areas corresponding to their groups 1 and 3. We believe that the presence of collagenous fibers, instead of reticular cells, the diffuse arrangement and the resemblance, or lack of resemblance, to a lymphoid follicle is the true basis for classification.

We classified 76 of our total of 105 (72.4%) areas as group 1 while Simonds and Brandes included 11 in this group. If we consider their groups 1 and 3 as corresponding to our group 1 there are 13 areas (65.0%) out of a total of 20.

The areas of lymphocytes described by Erdheim, Schöning and Romeis all appear to belong to our group 2 for they are lymphatic nodules with a reticulum. In our series 29 (27.6%) belong to this group while in those described by Simonds and Brandes 6 (30.0%) belong to group 2. The area included in our figure 3 may correspond to the perivascular cylinders of Simonds and Brandes for the lymphocytes are extended along the wall of an artery.

In a high percentage of cases lymphocytes and lymphoid tissue are found associated with follicles, usually containing colloid, basophils and occasionally tubular glands. Sixty-two of the 76 classified as group 1 and 27 of the 29 classified as group 2 in our series were associated with epithelium. Even lymphoid areas completely in the pars nervosa were often associated with basophils.

Simonds and Brandes interpret the presence of lymphoid tissue in the pituitary as a pathological process. They suggest that the colloid may stimulate the accumulation of lymphocytes just as any other foreign body might do. An examination of the excellent papers on the comparative anatomy and
histology of the mammalian pituitary by Hanstrom ('50, and earlier papers) does not include a single description of areas of lymphocytes, or of lymphoid tissue, hence one is led to believe they are not present. Most of the pituitaries described contain colloid, in some cases abundantly even in the posterior lobe (Hanstrom, '48, Hapale penicillata) yet lymphoid tissue is not present. Colloid filled follicles and cysts are frequently found in the human pars anterior (Shanklin, '48b, '49, '51b), but areas of lymphocytes are seldom found there. This absence of lymphoid tissue in the above does not support the viewpoint that colloid acts as a foreign body. Schönig says that in his 5 cases we are dealing not with lymphocytic infiltrations, but with normal lymphatic tissue. The three cases described by Romeis also support the viewpoint that occurrence of lymphoid tissue does not represent a pathological change.

Schönig suggests that the formation of lymphoid tissue is to be explained embryologically by the derivation of the pars intermedia from the buccal cavity. The epithelium of the pars intermedia has many potentialities; it may differentiate into chromophobes, acidiophils, basophils, ciliated or non-ciliated cells lining follicles and cysts, goblet cells, tubular glands, epithelium resembling that of the trachea (Shanklin, '51b) an integumentary type of epithelium (Shanklin, '51a). Lymphoid tissue is commonly associated with both oral and respiratory epithelium, therefore it is not surprising to find it in the pars intermedia.

We agree with Schönig that the presence of lymphoid tissue in the pituitary is a normal finding and is to be explained on a developmental basis.

**Summary**

1. Areas of lymphocytes and lymphoid tissue were found in 43 of 100 human pituitaries examined. None were found in 26 specimens less than 3.5 years. The positive cases were fairly evenly distributed over the remaining age groups. They occurred in 35.7% female and in 71.7% male pituitaries.
2. These areas were found most frequently in or near the pars intermedia associated with epithelium. None were observed in the pars anterior.

3. Group 1 includes lymphocytes scattered among collagenous fibers; group 2 includes typical lymphoid tissue with a reticulum, and resemble lymphoid follicles. The latter may have germinal centers. Seventy-six of the areas described were classified as group 1 and 29 as group 2.

4. Our studies suggest that these areas are a normal finding and that their presence in the pituitary is to be explained on an embryological basis.

LITERATURE CITED


PLATE 1

EXPLANATION OF FIGURES

All are photomicrographs of sections from the human pituitary and are stained with hematoxylin and cosin. All photographs are mounted with the anterior side up. All are areas in the pars intermedia except figure 3.

1 Compact area of lymphoid tissue with a germinal center; pituitary M 91 from a 46-year-old male. Death due to suicide by hanging. × 200.
B, basophils; C, collagenous fibers; F, follicle with colloid; N, pars nervosa; V, blood vessel.
2 Enlargement of the germinal center included in figure 1. × 700.
3 Area of lymphocytes surrounding a blood vessel in the stalk of pituitary M 100 from a 65-year-old male. Suicide. × 400.
PLATE 2
EXPLANATION OF FIGURES


6. Diffuse area of lymphocytes between pars intermedia and pars nervosa in pituitary M 177 from a 35-year-old male. Coronary atheroma. X 400.
PLATE 3
EXPLANATION OF FIGURES

7 Compact area of lymphoid tissue in pituitary M 210 from a 60-year-old male. Pellagra. × 400.

8 Another compact area of lymphoid tissue in pituitary M 210. × 400.

9 Compact area of lymphoid tissue, containing a young germinal center, in specimen M 220 from a 43-year-old male. Brain tumor. × 400.