THE PATHOLOGY OF THE HYPOPHYSIS

II. LYMPHOCYTIC INFILTRATION *

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In a study of more than 200 hypophyses in serial sections, 21 cases were encountered that showed areas of lymphocytic infiltration. The type of infiltration here reported is quite different from that which occurs about gummas and tubercles in the hypophysis, and there is little in the literature concerning it. The lesion was mentioned by one of us in a previous paper.¹ Pirone² observed lymphocytic infiltration in the hypophysis in hydrophobia; and M. Simmonds³ and Berblinger⁴ mentioned its occurrence in the vicinity of metastatic tumors in the posterior lobe. The 21 cases in our material have been studied with the hope of learning something of the nature and significance of the lesion. It has not been possible to investigate satisfactorily its relation to clinical symptoms because many of the patients from whom these hypophyses were obtained suffered sudden deaths and no anamnesis was obtainable.

It has been possible to divide these 21 cases into four groups as follows:

Group I. Those in which the area of lymphocytic infiltration was in immediate relation to one or more masses of colloid, either free in the tissues or inclosed in a space lined with epithelium.

Group II. Those in which the mass of lymphocytes was closely associated with one or more blood vessels and often resembled a potential lymph gland.

Group III. Those in which the lymphocytes diffusely infiltrated the tissues involved, without relation to blood vessels or colloid.

Group IV. Those in which the infiltration occurred as perivascular cylinders.

Border-line cases between Groups I and II occur. Without going into detail in individual cases, the following summary will suffice to present the essential features characteristic of each group.

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Each of the eleven cases in Group I showed one or more areas of lymphocytic infiltration in the middle lobe of the hypophysis. The location of these masses was rather constant. They lay very near the border line between the middle lobe and the neurohypophysis, frequently extending into the latter, and usually situated well laterally from the median plane. Furthermore, the infiltrating cells did not, in general, form a sharply circumscribed mass but gradually lost themselves in the surrounding tissues. In most of the cases the supporting tissue of the mass was the ordinary connective tissue which the cells had infiltrated. In two cases, however, the area suggested the follicle of a lymph node in appearance. The mass of infiltrating cells in almost all cases was quite near a small blood vessel. In all except one case it was intimately associated with colloid material, either lying free in tissue spaces, or inclosed in small "cysts." These cysts were more or less completely lined with low columnar or cuboidal epithelium and contained colloid that was vacuolated and strewn with desquamated epithelial cells. In one case, the desquamated cells had fused into a sort of syncytial mass containing a dozen or more nuclei. In two cases, plasma cells were present, either in the edge of the area of infiltration or nearby in the surrounding tissues. However, collections of colloid in the hypophysis are not always associated with lymphocytic infiltration.

The ages of the patients of Group I ranged from 20 to 50 years. All except two were 35 or more years old. There were only two women in this group. The pathologic changes found in other organs of the body varied greatly. One patient died from mitral stenosis, another from tumor of the brain, another from hemorrhagic encephalitis, the fourth from rheumatism and an ulcerative colitis of of undetermined origin, and the fifth from chronic meningitis three months after fracture of the skull. The remainder of the patients of this group died as a result of trauma. Microscopic examination of sections of different organs for areas of lymphoid infiltration was without result except in the case of the liver from the patient with ulcerative colitis.

Group II includes six cases. In these the supporting tissue in the areas of lymphocytic infiltration was typical reticulum. In all six cases, with possibly one exception, cells were present which resembled those that make up the germinal centers of a lymph node. These cells were not massed together as in a typical germinal center,

but were diffusely scattered among the lymphocytes in the central portion of the area. The infiltrations in this group were rather sharply circumscribed but did not possess a capsule. No plasma cells were found in or near the lesion in any case. The mass of lymphocytes in typical instances was not associated with colloid, either free or inclosed in epithelium-lined spaces. They did, however, have a rather constant and characteristic relation to blood vessels.

The posterior lobe of the hypophysis extends downward and forward into a cup-like depression in the anterior and middle lobes. In the median plane, its tip is separated from the middle lobe at the bottom of the depression by a mass of connective tissue in which is a plexus of blood vessels numbering from 5 to 20 in different sections. The infiltrating mass of lymphocytes in this group usually lies within this plexus between adjacent blood vessels. There is no tendency for the lymphocytes to surround one or more of the vessels, hence this lesion is distinctly different from perivascular infiltration.

This group contains four men and two women. The youngest patient was 12 years old, the ages of the others ranged from 35 to 55 years. One died of generalized miliary tuberculosis with tuberculous meningitis; another with chronic ulcerative tuberculosis of the lungs; one from chronic diffuse nephritis; a fourth from cerebral hemorrhage. All of these patients, except the 12-year-old girl, had varying degrees of arteriosclerosis.

In Group III (with two cases), the lymphocytic infiltration occurred in the anterior lobe. In one instance it involved the middle lobe and extended forward into the anterior lobe; in the other, it was limited to one lateral half of the glandular portion of this organ, which showed also a chronic hypophysitis. The infiltration in each case was diffuse, more so in one case than in the other. No plasma cells were found. One of these patients was a young woman, 20 years of age, who died of chronic alcoholism and exposure. The other, with the chronic hypophysitis, was a middle-aged man who died of lobar pneumonia.

In each of the cases of Group IV the infiltration was perivascular and located in the posterior lobe, usually near the capsule. The first of these patients suffered from an acute streptococcus meningitis, but the cylinders of perivascular infiltration were composed of lymphocytes. The second patient was an elderly man with marked chronic

myocarditis and arteriosclerosis of the coronary arteries, who had, two weeks before death, suffered an injury to the head which caused a slight hemorrhage in the pia and superficial part of the brain. The infiltrating cells in this case were different from those in any other case of this series, in that they resembled transitional or endothelial leucocytes.

DISCUSSION

The nature and significance of the lesion in these 21 cases is perhaps different for each of the four groups. While lymphocytic infiltration in the hypophysis of the type here described does not appear to have been previously reported; it has been described in the thyroid and adrenals. M. Simmonds⁶ found areas of lymphoid infiltration in 20 per cent of normal thyroids and in 80 per cent of thyroids in exophthalmic goiter. In this gland the lesion may appear in any degree from a small accumulation of lymphocytes to large areas with germinal centers and resembling in all essential respects, a follicle of a lymph gland. MacCallum⁷ thought that lymphoid infiltration of the thyroid in toxic goiters was due to the action of toxic or injurious substances. M. Simmonds⁸ believed that the accumulations of lymphocytes in the thyroid represent a reaction caused by the effects of an abnormal secretion. Kocher⁹ observed areas of lymphocytic infiltration in both exophthalmic and adenomatous goiters, both in the adenomas and in the adjacent tissues. They were not, however, characteristic of toxic goiters because they were occasionally found in normal thyroids and in simple strumas. In most cases the lymphocytic infiltration was not related to blood vessels; in a smaller number, it was perivascular. The accumulations of lymphocytes were most frequent in those sections in which the acini showed absence of colloid and multiple layers and desquamation of the epithelium, and in areas of atrophy of the thyroid tissue. Kocher considered lymphocytic infiltration as an expression of chemical changes in the thyroid. V. Gierke¹⁰ thought that lymphoid infiltration in exophthalmic goiters was associated with status thymico-lymphaticus. With this view both Simmonds⁸ and Kocher⁹ disagree.

Paunz¹¹ and others have described round-cell infiltration in the adrenals. Paunz thought that this condition was a reaction to a chronic infection or to a chronic intoxication which might be of

endogenous origin. This would partially explain the more frequent occurrence of this lesion in persons of middle age or older.

In as much as lymphocytic infiltration in the hypophysis occurs chiefly in or near that part of the gland which contains colloid, it would seem that this lesion in the hypophysis might be somewhat similar in nature to the similar condition in the thyroid. In Group I of our series of cases the similarity is all the more apparent because in this group the areas of lymphoid infiltration were definitely related to the presence of colloid. When the colloid was free in the tissue spaces, as in Case 1, it might stimulate the accumulation of lymphocytes just as any other foreign body might do. In those cases in which the colloid was inside an epithelium-lined cavity, it appears to be abnormal because: (1) it is vacuolated; and (2) contains many desquamated epithelial cells, as in the thyroid in many cases of toxic goiter; and (3) the epithelial lining of the "cyst" which contains the colloid is often abnormal in arrangement and in the number of layers of its lining cells. Whether, in these cases, the colloid is actually changed in quality it is not possible to determine from the data at hand. This possibility is suggested, however, by the fact that not all colloid-filled spaces are associated with round-cell infiltration.

None of the patients in our series showed any evidence of status thymico-lymphaticus. In only one was the thymus still present, and this was a young man 20 years of age. It is our opinion, therefore, that the lymphocytic infiltration in Group I is due to some local cause, possibly some change in the character of the secretion of the middle lobe. The presence of occasional plasma cells lends support to this view.

There is nothing about the accumulations of lymphocytes in the cases of Group II, on the other hand, that indicates a local cause. They occur, in their characteristic form, in a plexus of blood vessels, and are not directly related to the presence of colloid. The larger ones resemble an imperfect follicle of a lymph node: (1) in their rather sharply marked boundaries; (2) in the arrangement of the component lymphocytes; (3) in the reticular type of supporting tissue; and (4) in the presence of large cells with vesicular nuclei similar to those in the germinal centers of lymph glands. In other words, the areas of lymphoid infiltration in this Group are essentially like the lymphocytic accumulations in the lungs described by Arnold,¹² and in the

liver by Ribbert,⁵ Marcuse,¹³ and others. None of the patients in this group showed any indications of status thymico-lymphaticus. Three of them had tuberculosis, another, chronic nephritis; and two had marked arteriosclerosis. Hence it is possible that in this group of cases the occurrence of masses of lymphocytes in the vascular plexus of the hypophysis may be related to chronic infection or to chronic intoxication, as Paunz¹¹ thought was the case in the adrenals.

The presence of this type of lesion in the hypophysis is significant in another respect. Such accumulations of lymphocytes in other organs, as pointed out by Ribbert⁵ in the case of the liver, are intimately associated with lymphatics. The presence of these areas of lymphocytic infiltration is suggestive evidence, therefore, contrary to the opinion of Thaon,¹⁴ that this gland does possess lymph vessels.

Of the two cases in Group III, the lesion is easily explained as a part of a chronic inflammatory process in the anterior lobe of the hypophysis. The first case of this group, however, is the only one of its kind in this series, and we are unable to offer any plausible explanation of its presence.

In Group IV the infiltration is perivascular. In the first case the infiltrating cells were lymphocytes and the lesion was evidently an extension along blood vessels of an inflammatory process in the meninges. Simmonds¹⁵ mentions involvement of the hypophysis by perivascular extension in cases of tuberculous meningitis. The lesion in the second case was characterized by an accumulation of transitional or endothelial leucocytes about a blood vessel. It is not possible at present to suggest any explanation as to its cause or nature.

While these 21 cases fall rather easily into the four groups outlined above, no symptoms or physical findings were common to a sufficient number to indicate the existence of a clinical entity corresponding to the histologic lesion. The study of the patient and the post-mortem examination of the body were not made with this distinct object in view, however.

It is perhaps justifiable to consider this round-cell infiltration of the hypophysis as a definitely pathologic process, in the nature of a reaction to some sort of stimulus. It will be remembered that Simmonds⁸ found lymphocytic accumulations in 20 per cent of thyroids that were apparently normal. We have found this lesion in approximately 10 per cent of all of the hypophyses examined. Too little is

known of the pathology of this gland to state with certainty whether many of those examined were normal or abnormal. However, we are inclined to consider the lesion in Groups I, III, and IV as a reaction to some local stimulus or irritant, and in Group II to some extra-hypophyseal stimulus. To what extent this process or the condition which caused it interferes with the function of the hypophysis cannot now be stated.

SUMMARY

1. Twenty-one cases of lymphocytic infiltration of the hypophysis, a lesion that does not appear to have been previously described in detail, are reported.

2. The process occurs most frequently in the middle lobe, less commonly in the anterior and posterior lobes.

3. It has been found in about 10 per cent of all hypophyses examined, and has been compared with the similar condition sometimes found in the thyroid and adrenals.

4. In the hypophysis the lesion appears in four distinct forms, three of which are believed to be the result of reaction to a local stimulus, the other to be associated with chronic infection of some distant organ or with some chronic intoxication.

5. The data available are insufficient to justify an opinion as to the effect of this change on the function of the hypophysis.

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DESCRIPTION OF PLATE LIII

FIG. 1. Area of round-cell infiltration associated with colloid. Immediately below the area of infiltration is an acinus in which the epithelium is desquamated. X 70.

FIG. 2. Round-cell infiltration adjacent to blood vessels (at the left) and to abnormal acini (at the right). X 130.

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