tions of pathologic urines now in progress in this laboratory, check determinations are being made of urea by the Folin-Pettibone phosphoric acid method, and the Doremus-Hinds hypobromite method, using the modified technic described above.

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## AN ETIOLOGIC STUDY OF HODGKIN'S DISEASE

SECOND NOTE *

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In a preliminary note recently published,[1] we reported that by repeated injection of the diphtheroid organism cultivated by us from cases of Hodgkin's disease, there had been produced in monkeys lesions of the lymph-nodes showing all the essential features of early Hodgkin's disease in man. Up to that time we had been unable to demonstrate that the organism could survive in the monkey for any great length of time, and therefore we felt that we could not assert that we had produced Hodgkin's disease in the monkey, or that we had even demonstrated any great pathogenicity of the diphtheroid organism for that species.

Since making that report, however, the course of our experimental work has demonstrated fully the pathogenicity of the culture we were using, and has further shown that the virulence of the organism to the monkey may easily be increased even to the point of producing death of the animal after a relatively acute illness. While the histologic picture of the enlarged lymph-nodes of the monkey taken three months after the successful inoculation, leaves no question as to the relation of the lesion to that of human Hodgkin's disease of the same duration, the great difficulty seems to be to secure infection and at the same time to avoid so great virulence as to produce extensive necrosis and softening and even suppuration. The working space between these two limits seems very narrow.

Extensive necrosis and leukocytic infiltration of the glands may seem foreign to the usual chronic picture of the lymph-nodes in Hodgkin's disease, yet a recent clinical case has demonstrated that even in man the virulence of the organism may be such as to lead to these features. With an apparent duration of six months, there is in this case marked involvement of cervical, axillary and mediastinal glands, febrile reaction and leukocytosis (44,000). While the excised glands show all the elements of well-developed Hodgkin's disease, there are, in addition, extensive areas of necrosis, softening and leukocytic infiltration. Yet culturally, the diphtheroid organism, which was obtained from both cervical and axillary glands, was the only organism to grow.

At present, our results indicate that the survival of an animal for the requisite length of time is all that is needed for a demonstration of the chronic lymph-node picture seen in the well-developed case of Hodgkin's disease.

Thus, since our experiments demonstrate that the diphtheroid organism is pathogenic for the monkey, that it produces a progressive enlargement of the lymph-nodes, with lesions similar to those of Hodgkin's disease in man, and further that the blood-changes in the monkey are similar to those in man, we feel fully assured of the etiologic relationship of the diphtheroid organism (*Bacterium hodgkini*) to Hodgkin's disease.

The experiments which have led to this conclusion are in outline as follows:

MONKEY 1 (covered by previous note).—Repeated injections with diphtheroid organism between April 19 and June 30, 1913, with production of a chronic lymphadenitis, characteristic of early Hodgkin's disease. July 6, excision of glands for histologic study. Implantation of portion of gland into right axilla of Monkey A3.

Death of Monkey 1 from intussusception occurred before infection was secured.

MONKEY A3.—Female rhesus.

July 6, 1913, lymph-nodes all small, shot-like. Under ether, tissue from Monkey 1, made up of parts of three lymph-nodes, introduced into axillary space. Fascia and skin closed by separate sutures.

July 9, skin wound slightly pulled apart, but clean. Fascial sutures holding well.

July 19, wound cleanly healed. A group of enlarged glands palpable in right axilla.

August 4, three enlarged glands still palpable in right axilla.

September 24, animal found dead, having died during night after gradual decline.

Post-mortem examination showed in right axilla a group of enlarged lymph-nodes, from 10 to 15 mm. in diameter, with softened areas from which, on incision, a thick puriform necrotic material was expressed. Extending upward from these nodes was a suppurative process reaching to the highest point in the axilla and involving the chest wall. The organs showed multiple metastatic abscesses in lung, heart, liver and pancreas. A hyperemic splenic tumor and cloudy swelling of the viscera were present.

Histologically, while the areas of necrosis and leukocytic infiltration were the most prominent feature of the picture in the adjacent parts of the nodes, there were all the elements of the Hodgkin's picture: distortion and disappearance of architecture; great proliferation of endothelioid cells, with marked development of endothelioid giant-cells, in some places with lobed nuclei, and proliferation of fibroblasts with both fine and patchy sclerosis. Eosinophil cells were found only occasionally (apparently due to exhaustion of the marrow as indicated by marrow sections).

The spleen showed a hyperemic tumor, pulp and sinuses being filled with red blood-cells. In addition the malpighian corpuscles showed a lesion distinct from the usual hyperplasia which results in a sharp outlining of the germinal center and a thick collar of lymphocytes. In this spleen, however, there was irregular and extensive proliferation of the endothelioid cells, with numerous mitotic figures present. Many of the cells were of the size and character of the endothelioid giant-cells in the lymph-nodes. There was also some fibroblastic proliferation in and adjacent to the corpuscles. A scattering of eosinophils was seen.

At the post-mortem examination, a culture was taken from the axillary lymph-nodes, and a pure culture of the diphtheroid organism was obtained. This grew very feebly for several generations but finally acquired greater power of growth. This culture was used in inoculating Monkey 3.

MONKEY 3.—Female rhesus. Received April 11. Negative to von Pirquet test. April 26, first injection of two slants of a twenty-four-hour growth of culture X. F. A. subcutaneously into right thigh. Subsequent to this and up to August 17, ten injections of the same organism were made in the same location, and with the uniform result of the development of

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1. Bunting, C. H., and Yates, J. L.: An Etiologic Study of Hodgkin's Disease, THE JOURNAL A. M. A., Nov. 15, 1913, p. 1803.

induration and glandular enlargement which subsided gradually. On one occasion, June 21, inoculation resulted in the formation of a subcutaneous abscess from which the diphtheroid organism was recovered in pure culture. This was subsequently used for inoculation in the hope that it might have acquired some increased virulence.

October 25, there were but shot-like glands in the right groin and it was felt that the animal was refractory to the culture.

October 31, inoculation was made into the right axilla of the scrapings in salt-solution of 3 slants of an almost invisible growth on egg-medium of the diphtheroid organism recovered from Monkey 3. The salt solution suspension appeared almost clear. There was no immediate sharp glandular reaction and one week later no sign of reaction along needle track.

December 6, there was a large, lobulated, indurated mass along pectoral edge and extending high in axilla, and consisting of enlarged glands distinct in outline but with connecting sclerosis. The lower glands were over 1 cm. in diameter, while high up in the axilla the glands appeared about 5 mm. in diameter. At the most prominent low point was a softened area with discharging sinus. The material discharged on pressure was a thick white material resembling broken-down glands.

December 19, the wound was still discharging, and in the left axilla was an infected skin wound (apparently self-inoculation) with several enlarged lymph-nodes palpable above it.

December 31, a second softened area appeared in the right axilla about 3 cm. above the first.

LEUKOCYTE COUNTS IN MONKEY 3

| | Total | N. | E. | B. | S.L. | L.L. | L.M. | Tr. |
|---|---|---|---|---|---|---|---|---|
| April 17 ..... | 15,600 | 34.2 | 1.4 | 0.2 | 54 | 3.8 | 1.0 | 5.4 |
| July 2 ..... | ..... | 22.4 | 7.8 | 0.2 | 57.4 | 5.8 | 0.2 | 6.2 |
| July 12 ..... | 19,000 | 25.2 | 4.2 | 0.2 | 60 | 4.2 | 0.4 | 5.8 |
| October 31 ..... | ..... | 49.4 | 4.8 | 0.0 | 37.2 | 4.0 | 0.0 | 4.6 |
| December 6 ..... | 13,000 | 42 | 0.8 | 0.0 | 46 | 4.2 | 0.4 | 6.6 |
| December 19 .... | 15,000 | 48 | 0.2 | 0.0 | 38.8 | 4.0 | 0.0 | 9.0 |
| December 31* ... | ..... | 70.2 | 0.0 | 0.0 | 19.4 | 2.2 | 0.0 | 8.2 |

* December 31, 4 nucleated red cells to 500 leukocytes were found.

N=neutrophils; E, eosinophils; B, basophils; S. L., small lymphocytes; L. L., large lymphocytes; L. M., large mononuclears, and Tr, transitionals.

MONKEY 2.—Male rhesus, received from New York April 11. April 19 the first injection of a twenty-four-hour slant-growth of the culture X. F. A. was made into the right tonsillar region. When it was found that the enlargement of the cervical glands that resulted did not persist, the place of injection was changed to the cervical subcutaneous tissue, on account of the difficulty of reaching the tonsil without etherization. Three injections were made in the neck region. Then on June 30 the place of inoculation was changed to the right axilla. Here six injections were given, the dose being increased, until on August 17 four slants of a twenty-four-hour growth were injected. The intervening injections had resulted in the development of axillary induration, associated with glandular swelling which had persisted for about a week after the injection. After August 17 no injections were given. On September 15 a moderate enlargement of the right axillary glands was noted. This continued, and on November 1 there was in the right axilla a large, lobulated mass roughly 2.5 by 3 cm. in diameter; apparently made of five or six discrete glands with a certain amount of interglandular sclerosis.

November 23, under cocain, a gland was removed, cultures made, tissue fixed for study, and a portion of the gland implanted in Monkey A4.

Macroscopically the gland showed large, opaque, softened, necrotic areas, surrounded by more translucent hyperplastic tissue. The softened material had the consistency neither of true pus nor of tuberculous caseation.

Histologically, the gland showed areas of necrosis infiltrated by leukocytes. There was some scarring of the gland. Outside of the necrotic areas the architecture of the gland was lost. The tissue was cellular, showing relatively few lymphocytes, but large numbers of endothelioid cells, many of which had very large nuclei, of the giant-cell type. Eosinophilic infiltration was present and marked in some areas. There was a periglandular sclerosis.

LEUKOCYTE COUNTS IN MONKEY 2

| | Total | N. | E. | B. | S.L. | L.L. | L.M. | Tr. |
|---|---|---|---|---|---|---|---|---|
| April 17 ..... | 32,000 | 50.6 | 8.0 | 0.0 | 34.6 | 2.0 | 0.8 | 4.0 |
| April 21 ..... | 15,600 | 71.6 | 4.0 | 0.8 | 15.6 | 2.6 | 0.2 | 5.2 |
| April 24 ..... | 24,400 | 65.4 | 3.8 | 1.2 | 20.0 | 2.4 | 0.6 | 6.6 |
| October 28 ..... | 19,000 | 44.6 | 7.2 | 0.4 | 37.6 | 2.6 | 0.0 | 7.6 |
| November 14 ... | 20,000 | 35.8 | 7.0 | 0.0 | 42.8 | 4.3 | 0.4 | 9.7 |
| December 31 .... | ..... | 46.3 | 2.9 | 0.4 | 33.7 | 5.6 | 0.4 | 10.7 |

One nucleated red blood-cell to 500 white blood-cells noted October 28; 1 November 14, and 2 to 500 December 31.

A pure culture of the diphtheroid organism was found in one serum-tube on which a piece of gland was planted.

December 6, the wound was perfectly healed, but an area of softening had developed at some distance from the wound and at the lowermost prominent point of the enlarged mass.

December 26, the skin was found necrotic at one point over this area, and a thick necrotic material exuded on pressure. A diphtheroid organism was found in smears from this material.

December 31, skin sinus appeared healed and dry. No further softening.

MONKEY A4.—Large male rhesus.

November 23, right axilla shows only small shot-like glands high up. Under cocain anesthesia, a piece of gland from Monkey A2 was implanted in the right axilla. Fascia and skin were stitched separately.

December 6, wound was found perfectly healed. Several moderately enlarged glands were felt above site of implantation.

December 19, several enlarged glands in axilla formed a mass roughly 2 cm. in diameter.

# THE CORRECTION OF THE FIXED STRUCTURAL TYPE OF SPINAL LATERAL CURVATURE*

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## INTRODUCTION

Notwithstanding the fact that in the past so much has been written with regard to the treatment of the fixed structural type of spinal lateral curvature, it has generally been conceded that little progress has been made and that the results obtained have been far from satisfactory. It has been generally recognized, indeed, that patients with bony rotation could not be anatomically straightened, and in selected cases only could they be improved.

Many theories concerning the mechanism of the spine have been advanced at different times, but with little or no result so far as the correction of the spine is concerned, and not more than a year or so ago it was generally recognized by all who tried to treat the fixed types of scoliosis that little or no headway toward remedying the condition could be made. Even though the contour of the trunk had been changed after a number of years of constant treatment, the radiograph still showed not only

* Read in the Section on Orthopedic Surgery of the American Medical Association, at the Sixty-Fourth Annual Session, held at Minneapolis, June, 1913.

* Because of lack of space, this article is abbreviated in THE JOURNAL. The complete article appears in the Transactions of the Section and in the author's reprints.