the treatment of other closed spaces, such as cold abscesses, containing tubercle-infected fluids.

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AETIOLOGY OF HODGKIN'S DISEASE WITH SPECIAL REFERENCE TO B. TUBERCULOSIS AVIS

BY

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The relation of Hodgkin's disease to tuberculosis has been the subject of extensive inquiry, and many workers, such as Sternberg (1898), Ewing (1927), and others, have repeatedly drawn attention to the similarity of tissue changes produced in both conditions. Opinion, however, is divided on the incidence of tuberculosis in patients suffering from lymphadenoma. Ewing says that "tuberculosis follows Hodgkin's disease like a shadow"; Lemon (1924) reports, to the contrary, that out of 191 cases of Hodgkin's disease under observation in the Mayo Clinic only eight showed evidence of tuberculosis. The latter worker further states that out of twenty-six cases of the disease in which the mediastinal glands were involved there was definite evidence of tuberculosis in only one.

Infective agents other than the tubercle bacillus, such as the diphtheroid organism (Bunting and Yates, 1913), certain moniliae (Dias, 1918) and amoebae (Kofoid, Swezy, and Boyers, 1922), have been described in Hodgkin's disease, but such work has lacked confirmation. Stewart and Dobson (1924) attempted to reproduce the disease in monkeys (*rhesus* and *bonnet*), but without results. Twort in 1930 published the results of six years' research into the causation of the condition, and arrived at the conclusion that the disease was probably of neoplastic origin, since he was unable to isolate any one organism with constancy or to reproduce the disease in laboratory animals with pathological material.

More recently American workers have advanced two fresh views on the aetiology of the condition. Medlar (1931) maintains that the disease is one primarily affecting the bone marrow, for which he proposes the name "megakaryoblastoma" in view of the particular type of cell involved. L'Esperance (1929-31) claims to have reproduced Hodgkin's disease in birds and "treated" guinea-pigs, from whose tissues he recovered the avian tubercle bacillus. This investigator therefore states that Hodgkin's disease is produced by infection with *B. tuberculosis avis*. This view has been further elaborated by Utz and Keatinge (1932), who claim to have treated successfully several cases of lymphadenoma by the use of serums obtained from chickens previously immunized with lymphadenomatous tissue. I have investigated the claims of L'Esperance by the inoculation of chickens and other laboratory animals with material obtained at biopsy from three cases clinically and histologically characteristic of Hodgkin's disease, and also with material removed at necropsy from three other cases of the disease, two of which showed mediastinal involvement.

The following brief extracts of case and post-mortem notes describe the subjects from which material was obtained.

CASE HISTORIES

1. *Case of Professor Fraser's.*—A male, aged 52, had swelling in left axilla of eleven months' duration, with later ulceration and secondary infection lasting three months. There was slight enlargement of the inguinal and infraclavicular glands, with no evidence of mediastinal involvement. Ten per cent. eosinophils were present. Histological diagnosis: Hodgkin's disease.

2. *Case of Dr. Comrie's.*—A female, aged 28, had a swelling of the glands of the neck for eight months, with later involvement of abdominal glands and spleen. These changes were accompanied by extensive bronzing of the skin and intolerable itching. Throughout her illness a fever conforming to the Pel-Ebstein type was present, and the blood picture showed an eosinophilia. At post-mortem the cervical, mediastinal, bronchial, and abdominal para-aortic glands were grossly enlarged, together with slight enlargement of the lymph nodes of the lesser omentum. The spleen was enlarged to about three times its normal size, and contained numerous nodules throughout. The heart, liver, and lungs also showed involvement with lymphadenomatous tissue.

3. *Case of Professor D. Murray Lyon's.*—A male, aged 46, complained of vague symptoms of general illness lasting three months, with loss of appetite and weight, diarrhoea, colic, and dyspnoea. Temperature reaction of the Pel-Ebstein type was present, accompanied by enlargement of liver and spleen. At post-mortem there was considerable enlargement of para-aortic, abdominal, and mediastinal lymph glands, with commencing enlargement of the cervical and inguinal groups. The bone marrow revealed red patches suggestive of erythroblastic reaction, and microscopically proliferation of bone marrow cells affecting the red cell series was found to be present.

4. *Case of Professor Bramwell's.*—A male, aged 27, gave a three months' history of loss of weight and appetite, accompanied by distension of the abdomen and bronzing of the skin. On admission the patient was found to have an enlarged spleen, dullness over the apex of the right lobe, with crepitations and vesicular breathing. Pel-Ebstein type of fever was present. Red blood cells were 4,200,000 per c.mm., and white cells 3,800: differential count was normal, and haemoglobin 70 per cent. Post-mortem revealed typical lymphadenoma of spleen, liver, and para-aortic and cervical glands. Brown atrophy of the heart. No evidence of tuberculosis demonstrable.

5. *Case of Professor Fraser's.*—A female, aged 31, first noticed lumps on her neck two years before examination, initially confined to the left side, but later involving the right. These painless swellings rapidly increased in size, and later gave rise to pressure symptoms in that region. There was no palpable enlargement of spleen, liver, or lymph glands in inguinal or axillary regions. An intermittent fever accompanied her illness. Red blood cells were 4,540,000 per c.mm., and white cells 9,200: polymorphs, 75 per cent.; lymphocytes, small, 11 per cent.; large, 9 per cent.; eosinophils, 4 per cent.; transitionals 1 per cent. Haemoglobin was 70 per cent.; colour index, 0.08. Histological diagnosis: Hodgkin's disease. Deep x-ray therapy and subcutaneous injections of Coley's fluid over the affected area were employed, which resulted in marked diminution in the size of the glands and considerable general improvement.

6. *Case of Dr. Chalmers Watson's.*—A schoolboy, aged 8, gave a five years' history of progressive enlargement of submental, supraclavicular, axillary, and inguinal glands, and of the spleen. Increasing weakness and cachexia, severe secondary anaemia, accompanied by cardiac haemic murmurs, commencing integumentary dryness and pigmentation were present. During the last two years patient exhibited a typical Pel-Ebstein pyrexia. The histological diagnosis, clinical manifestations, course of the disease, and reaction to deep x-ray therapy have shown this case to be almost a textbook picture of the disease.

EXPERIMENTAL WORK

Enlarged lymph glands removed at biopsy, together with liver, spleen, and bone marrow obtained in necropsy, were examined for the presence of avian tubercle bacilli by direct attempts at cultivation on Dorset's egg media, but no such organisms were isolated. It is of interest, however, to state that in both Cases 1 and 6 a small, typical, Gram-positive, aerobic diphtheroid organism was isolated after about ten days' incubation. Both strains subsequently proved to be non-

pathogenic to laboratory animals, and so further investigations were discontinued. About 300 histological sections of affected glands and viscera were stained for acid-fast organisms, but none were found.

Animal Inoculation

Four bantam chickens and four street pigeons were inoculated both intravenously (through the wing vein) and intraperitoneally with 2 to 3 c.cm. of a dense emulsion of affected material, comprising enlarged lymph glands, spleen, and bone marrow. Animals were kept under observation for a period of seven to ten months, but no signs of illness were noticed. Two chickens which had been inoculated with emulsions of spleen and lymph gland by the two routes were examined post mortem ten months later, but found to be perfectly healthy.

Grafting Experiments

Five healthy chickens (three buff orpingtons and two white leghorns) were used for these experiments. With strict aseptic precautions small fragments of an enlarged lymph gland (removed at biopsy by Professor Fraser, from Case 5) were implanted into the birds as follows. (1) *Extraperitoneally*. (2) *Intraperitoneally*. (3) *Intrahepatically*: This was carried out by making a V-shaped incision into the free margin of the left lobe of the liver, and inserting into this a wedge-shaped portion of gland, which was then secured by means of catgut sutures. (4) *Into shaft of femur*: This was done after the manner of an intramedullary graft, and performed by exposing the femur, removing a U-shaped fragment of bone with the aid of bone-nibbling forceps, and then inserting small fragments of lymphadenomatous tissue into the proximal and distal ends of the medullary canal. (5) *Intramuscularly*: Implantation was in the pectoral muscles. All five birds made a good recovery from the operation, and at the end of a week appeared to be in good health.

Animal No. 1 died after three months, succumbing to accidental injury. Necropsy revealed that the attempted graft had undergone necrosis and subsequent extrusion into the superficial tissues, while the surrounding tissues showed extensive fibrosis and cicatricial contracture, presumably in the nature of a reaction towards a foreign body. No evidence of tuberculous ulceration or caseation was to be found in the underlying tissues, peritoneum, or viscera. Animal No. 3 was killed after six months and the site of the attempted graft examined both macroscopically and microscopically, but no changes indicative of tuberculosis were evident and no bacterial growth was obtained on culture. The remaining animals are still under observation, and appear to be healthy after seven months.

DISCUSSION

In the experiments described above no evidence of infection with *B. tuberculosis avis* was found in material taken from six accurately diagnosed cases of Hodgkin's disease.

Cases of human infection due to the avian tubercle bacillus have already been described by several European workers. Löwenstein (1913) obtained the organism from cases of pulmonary, renal, and dermal tuberculosis. Rabinowitsch (1907) succeeded in isolating the organism from the spleen of a case of generalized miliary tuberculosis, and Janscö and Elfer (1910) also demonstrated organisms of a similar type in the mesenteric glands of a child. It would thus appear that the occurrence of human infection by the avian tubercle bacillus has been proved, and isolation of the causative organisms seems to have been achieved by the usual well-recognized methods. With reference to the claims made by L'Esperance, I have not only failed to produce tuberculosis in chickens by inoculation with lymphadenomatous material, but I have also been unable to demonstrate the presence of avian tuberculosis in affected material, either by direct cultural methods or by examination of a large number of stained histological preparations.

It is noteworthy that in the literature of the cases of human tuberculosis due to avian tubercle bacillus there is no mention that the clinical manifestations of these cases in any way differed from the syndrome produced by infec-

tion with the ordinary human or bovine types. Indeed, it is questionable whether the true nature of the causative agent would have been determined had a special search not been made for it.

The feeble pathogenicity of the avian tubercle bacillus to the guinea-pig and its more pronounced effect on the rabbit are well-recognized characteristics (Medlar, 1931) that cannot be lost sight of when one also remembers that the non-pathogenicity of lymphadenomatous material to rabbits and guinea-pigs is a fact of wide acceptance. A notable exception to this is found in the results obtained by M. H. Gordon and co-workers of the Rose Research on Lymphadenoma (1932), who have demonstrated that the intracerebral injection of lymphadenomatous tissue into rabbits is followed by ataxia, muscular spasms, and paralysis. Such effects are not produced, however, by the injection of leukaemic, sarcomatous, and carcinomatous tissue. L'Esperance nevertheless claims to have reproduced avian tuberculosis in birds by the injection of lymphadenomatous material into them, without having simultaneously done so in rabbits. The same worker's claim to have reproduced Hodgkin's disease in guinea-pigs which had previously been inoculated with killed cultures of *B. tuberculosis hominis* is also unconvincing.

It should also be pointed out that, according to Griffith (1930), under domestic conditions poultry exposed to infection readily develop tuberculosis, frequently following the ingestion of contaminated food. Organs most commonly involved are the intestine, liver, and bone marrow, but the writer has been unable to reproduce avian tuberculosis by the introduction of lymphadenomatous tissue directly into these areas.

SUMMARY AND CONCLUSION

Pathological material obtained from six accurately diagnosed cases of Hodgkin's disease have been examined by direct cultural methods for the presence of the avian tubercle bacillus, and histological sections examined for acid-fast organisms, but both with negative results. Tissue emulsions have proved to be non-infective to rabbits, guinea-pigs, pigeons, and chickens on intravenous, intraperitoneal, and intramuscular administration. Attempts to graft lymphadenomatous material obtained from an acute case of Hodgkin's disease into the bone marrow, peritoneum, liver, and muscles of chickens have likewise failed.

No evidence of *B. tuberculosis avis* can be found in cases of Hodgkin's disease.

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