ATYPICAL HODGKIN'S DISEASE

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The following case of Hodgkin's disease seems worthy of publication on account of certain difficulties in diagnosis due to unusual signs and symptoms and because of uncommon post-mortem findings.

CASE RECORD

History.—A married woman, V.T., aged 31, was admitted to the National Temperance Hospital on January 5th, 1931. Twenty-one months previously she had, for no apparent reason, been suddenly seized for the first time with a severe lancinating pain in the lumbar region. Aspirin gave relief in one and a half hours. Since then backache, varying in intensity, had been present daily. She had gradually lost strength, and shortly before admission had lost weight rapidly—"almost four stone in about as many months." There was nothing of interest in the previous history—no injury to the spine, no pneumococcal, typhoid, staphylococcal, or other infection. Family history was of no interest.

On admission the patient was very ill-looking, with anaemia, manifest wasting, and great weakness. Temperature 99.8° F., pulse 94, respiration 22. Mentally clear. Tongue whitish, with dry fur; bowels, open; micturition and

(b) Thorax: "Some thickening of the hilar shadows on each side. Lung tissue clear. Diaphragm moves well. No radiological evidence of tuberculosis."

The blood Wassermann reaction was negative, while the blood culture, at the height of the fever (January 15th, 1931) was also negative.

Blood Counts.—Twelve counts were done (H. H. S.) in hospital. Space precludes giving these in detail; the main features of most are shown on the temperature chart. In the differential count the percentages of white corpuscles were as follows:

Polymorphs, 80-91 (average 85); lymphocytes, 6-20 (average 12); large mononuclears, 1-5 (average 3); eosinophils, 0-3 (average 0.5); basophils, 0-1 (average 0.4); myelocytes, 0-2 (average 0.25).

It will be noted that the secondary anaemia that was in progress remained more or less stationary to the end, also that the degree of leucocytosis did not correspond with the degree of fever, the highest counts, indeed, being obtained when the temperature was normal or nearly so.

Fever.—As will be seen from the chart there were, in hospital, three bouts of fever. The first was the most marked, and lasted three weeks. High and intermittent during the second week, the fever disappeared at the end of the third week in a surprising and unaccountable manner. The spinal defect and the indefinite abdominal mass already mentioned—the only lesions found—remained apparently *in statu quo*, and the blood culture was negative. The subsequent afebrile period, broken occasionally by evening rises to 99° F., lasted five weeks. The second spell of fever was much less than the first, and of only a week's duration. It was succeeded by an afebrile period of seven weeks, and then by twelve days of

urine, normal. There was no complaint of sensory disturbance or special weakness in legs. Considerable tenderness and muscle-guarding was found over the region of the second, third, and fourth lumbar spines, but the spines could not be felt—otherwise nothing abnormal was found here. In the dorsal region there was a pronounced scoliosis, convex to the right, which apparently had not been noticed until admission to hospital. It was thought that the deformity was compensatory to distortion from vertebral destruction in the mid-lumbar region. For about an inch or two to the right and left of the middle line, and extending roughly from 3 inches above to 1 inch below the umbilicus, was felt an ill-defined mass, tender and seemingly firm in consistency. Bowel distension and inability of the patient to relax properly made palpation very imperfect. Though there was a possibility of this being glandular in nature no glandular enlargement was discovered. Liver, spleen, heart, lungs, nervous system, mediastinum, skin, fauces, and gums gave no sign of disease. A few shotty lymphatic glands were noticed in both groins and one moderately enlarged gland at the root of the right side of the neck. Pelvic examination showed "tenderness on pressure high up in the right vaginal fornix, and on moving the cervix. No mass felt." (Mr. D. Denham Pinnock.)

Pathological and X-Ray Examination.—Microscopical examination of the excised lymphatic gland in the neck showed "extensive fibrosis obliterating glandular structure, but areas of lymphocytes remaining intermingled with numerous endothelial cells, some of these being so large as to suggest mononuclear giant cells. Structure not definitely lymphadenomatous, but might represent the fibrous stage of a lymphadenomatous gland." (H. H. S.) The x-ray reports were as follows:

(a) Lumbar and lumbosacral regions: "Much absorption of body of third lumbar vertebra. Some absorption along the superior surface of fourth lumbar vertebra. Probably a tuberculous lesion."

more or less intermittent fever terminating in death. In view of the extensive suppurative changes found post mortem the long afebrile periods (mentioned again later) are of considerable interest, especially after the fierce initial bout of fever and the seemingly moribund condition of the patient. The pulse rate remained throughout in the region of 80-90, except when the temperature was high, when it went up to 100-115, and, just before death, to 132.

Appearance and Nutrition.—The changes undergone by the patient in this respect were remarkable. On admission a pale, emaciated woman, obviously suffering great pain, she began to gain in strength and put on weight rapidly as soon as she reached the afebrile stage. Even the short febrile period in March did not greatly impede her progress, and from April 13th to 17th she actually had a menstrual period, the first for eight months. The subsequent rapid downhill progress, terminating in death, was therefore both surprising and disappointing.

Post-Mortem Examination

Nothing abnormal was found in the cranial cavity or brain. In the thorax there were present greatly enlarged mediastinal and peribronchial glands, while in the right lung two nodules could be felt, one in the upper and the other in the lower lobe, the larger being the size of a walnut. Some nodules, not easily palpable, were present in the left lung. On section the nodules were seen to project beyond the level of the surrounding lung tissue, and looked like secondary deposits of new growth. No abnormality was found in the alimentary tract. There was a chain of greatly enlarged lymphatic glands extending from both inguinal regions along the iliac arteries and aorta up to the pancreas and spleen. Those on the left side were suppurating, and there was a large abscess in front and on the left side of the third and fourth lumbar vertebrae, burrowing into and destroying the left psoas muscle and eroding the bodies of the vertebrae, so that a finger could be passed into the spinal canal, although the

abscess was outside the theca. The affected third and fourth vertebrae had undergone considerable rotation, being twisted so that their spines pointed to the left instead of posteriorly—hence the reason for their not being felt on clinical examination. The liver was normal, and macroscopically there appeared to be only moderate simple hypertrophy of the spleen. Nothing abnormal was detected in kidneys, uterus, or ovaries.

Microscopical Appearances.—The following tissues were examined: abdominal and thoracic lymphatic glands, periosteum and fibro-cartilage from the lumbar vertebrae, and one of the nodules from the lung. The general histological plan was the same in all, so that on cursory examination one might easily mistake a section of the lung nodule for one of a lymphatic gland. In the lymphatic gland the lymphocytes are diminished and their place partly taken by proliferating endothelial cells, including many characteristic mono- and multi-nuclear giant cells with centrally placed nuclei—the so-called Sternberg giant cells. The reticulum is much hypertrophied, and large strands replace the lymphocytes, some of which remain as islands surrounded by fibrous tissue. Where suppuration has occurred polymorph cells abound in the pus and in the abscess wall. Granulomatous changes involve the periosteum of the invaded vertebrae and the intervertebral disk. In the lung nodule, except at the periphery, the pulmonary alveolar structure has been obliterated. The tissue is very vascular and blood has been extravasated. There is, for the most part, nothing particular about the granulomatous structure except the presence of many neutrophilic polymorph leucocytes, while in one or two areas a considerable number of giant cells of the Langhans type are present. A few such cells are the centres of islands of tissue having the appearance of a tubercle, others are interspersed with the cells of the granuloma. There is no sign of caseation.

Hirschfeld,¹ describing similar cells present in lymphadenoma, regards them as tuberculous, but the presence of other cells showing an apparent transition from the Sternberg type of giant cell to the Langhans type suggests that in this case these cells constitute a rather unusual form of granulomatous change, a view strengthened by the absence of signs of tuberculous disease elsewhere in the lung.

DISCUSSION

The signs and symptoms exhibited by the patient were: anaemia, with marked and rapid emaciation; severe pain in the back and sides, with lateral curvature of the spine and tenderness over the lumbar vertebrae; attacks of remittent or intermittent fever separated by lengthy afebrile, or nearly afebrile, periods, and a high leucocytosis of inflammatory type. The patient's extraordinarily rapid improvement during the afebrile period should also be regarded as a symptom.

Reference to Ziegler's excellent monograph² shows that all these symptoms, with the possible exception of the spinal curvature, may be met with in cases of Hodgkin's disease, yet one would submit that not all of them are commonly present in, or generally recognized as associated with, the disorder. Mention is here made of the severe pains and the leucocytosis, and although the existence of the inflammatory type of leucocytosis in the latter stages of lymphadenoma is now more generally recognized, figures as high as 240,000 have been reported (Schur). Of bone involvement and pain, Ziegler² says: "Involvements of bone are relatively common in Hodgkin's disease; generally they do not betray themselves clinically"; and, again: "In connexion with bone involvement severe pains can arise." The same author's masked, or typhoid, form of the disease, in which the retroperitoneal glands are affected almost exclusively, corresponds very closely with this case, for from the results of *x-ray* examination one may reasonably assume that the involvement of the mediastinal glands and lungs was a late manifestation. However, some of the usual symptoms of these masked cases, such as oedema of the feet and abdominal wall, and diarrhoea, were absent, also the leucopenia of this type of lymphadenoma was replaced by

a leucocytosis. Finally, there was no clinical enlargement of the spleen. The rapid but highly deceptive improvement in the patient's general condition—so apt to encourage belief in any form of treatment—is worth further consideration. "These patients, brought desperately low in the fever periods, can actually swell up—that is, put on flesh—during the afebrile periods, though anatomically the disease continues to spread" (Ziegler²). This reaction is diagnostically useful only in the presence of enlarged glands of doubtful nature. This feature of the disease appears not to be widely recognized.

The post-mortem and microscopical findings exhibit further points of interest, differentiating this case from the average case of Hodgkin's disease. Thus the formation of pus in the iliac glands and the large abscess surrounding the bodies of the affected vertebrae and extending into the left psoas muscle is quite an unusual occurrence in lymphadenoma, as is also the associated marked erosion of the bodies of the third and fourth lumbar vertebrae with consequent spinal curvature. However, involvement of the vertebrae is by no means so uncommon as Ziegler would lead one to suppose. Thus, examining the lumbar vertebral bodies in twenty-two cases, Professor H. M. Turnbull found them implicated in eight (36.4 per cent.), and examination of the dorsal vertebrae in two cases revealed similar involvement in each. In all cases the areas of disease were macroscopic in the sawn-through vertebrae. In our case the changes were more profound. Commenting on the case described by Drs. Hare and Lepper,³ Dr. Parkes Weber suggests direct extension from glands to the vertebral periosteum, a view also expressed by Professor Turnbull.⁴ The extraordinarily firm adhesion of some of the glands to the vertebrae in our case supports this view.

The breaking down of the glands and the formation of the perivertebral abscess may be ascribed to a secondary infection. It is unfortunate that this probability was not explored when the post-mortem examination was made. The polymorph pus in the walls of the abscesses certainly suggests a secondary invading organism. Professor Turnbull, whom we desire to thank for his kindly help, states that "while firm caseation is common in Hodgkin's granuloma, we have never at the London Hospital seen an abscess in an uncomplicated case of Hodgkin's disease." The absence of obvious enlargement of liver and spleen is unusual in this type of case, and it is regretted that these organs were not examined microscopically. As to the lung, Ziegler's² estimate of involvement in 8 per cent. of cases probably exaggerates the frequency. The absence of pulmonary symptoms would be remarkable were it not that a mild bronchitis, easily overlooked in the presence of more serious symptoms, is usually the only manifestation of the granulomatous changes.

The diagnostic difficulties in the case were, in the first place, due to the absence of any mass ascribable with certainty to enlargement of lymphatic glands, to the leucocytosis of an inflammatory type, but above all to evidence of disease of the vertebral column accompanied by severe pain. As has been stated, the *x-ray* report suggested tuberculous disease of the spine, but the age of the patient, the high fever, and the inflammatory type of leucocytosis suggested as a more likely diagnosis infective osteomyelitis of the spine, though no focus of infection was found, and no history of such or of a general infection was obtained. According to H. W. Carson⁵ deformity is rare in this disease, but lancinating pain unrelieved by rest—such as occurred in this case—is characteristic, whereas in Pott's disease pain is usually relieved by rest. The same writer refers to the frequency of abscess in osteomyelitis, but in our case abscess formation was a post-mortem finding. Carson obtained in blood culture a pure growth of *Staphylococcus aureus* in all his cases, whereas blood

culture in our case was negative. Nevertheless, as suppurative changes are unknown in Hodgkin's disease, apart from secondary infection, the osteomyelitic nature of the infection taking part in the extensive erosion of the vertebral bodies and development of the abscess may be regarded as the correct explanation.

The case here reported is further proof of the extraordinary difficulties that may have to be overcome in order to arrive at the correct diagnosis of Hodgkin's disease.

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THE PHYSIOLOGICAL AND CLINICAL RESULTS OF DIVISION OF THE VAS DEFERENS*

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The vas deferens, or spermatic duct, is the tube which carries the mature spermatozoon from the testicle to the seminal vesicle. It is lined by ciliated epithelium, and the lumen in comparison to the thickness of the wall of this duct is extremely small. The vas deferens has very little contractile power, the reason for which is obvious when it is remembered that the spermatozoon is mobile and is assisted towards its destination by cilia. It is only when it has entered the seminal vesicle that muscular effort is required to urge it further forward on its final journey. There must be some correlation between the vesicles, when they are fully distended with spermatozoa, and the migration of these sperm cells from the seat of their development. The capacity of the seminal vesicle is limited, and thus some control must be exercised over the number of spermatozoa which may travel in any given time along the vas deferens. It is pure surmise how this comes about, but in all likelihood a distended vesicle has an inhibitory effect upon the movements of the cells from the testicle. Coitus has but an indirect relation to these activities.

When the vas deferens is divided or ligated it is necessary to consider the effect upon the testicle, the seminal vesicle, and the prostate gland. As regards the latter, it should be obvious that no change, either physiological or anatomical, will take place, and yet in the days before prostatectomy was introduced it was a common practice to divide both vasa in the belief that the operation would result in a decrease in the size of the enlarged prostate. It is probable that this procedure was intended as a substitute for castration, which was the treatment in vogue during the nineteenth century. The removal of the testicle was discarded on account of the mental complications which it produced, but though it had no effect upon the adenomatous growth of the gland, the latter eventually underwent atrophy, due, of course, to disuse.

Division of the vas deferens *per se* has no effect upon either the function or size of the prostate gland. The quantity of the secretion is unaltered. It thus comes about that the man who has had both vasa divided is unaware of any change in the act of coitus. The quantity of fluid ejaculated is normal, but there are no spermatozoa present. With the knowledge that the vesiculæ seminales merely function as reservoirs for the mature spermatozoa

it is clear that any interference with the flow of cells into these small pouches must lead to their gradual shrinkage and complete atrophy. This is exactly what happens after a dissolution of the continuity of the vasa deferentia. The vesicles, at first palpable through the wall of the rectum, slowly shrivel until they are no longer to be felt by rectal examination.

A much more difficult study is the effect of duct division upon the testicle. There is one definite negative finding—namely, that there is no change in the shape and size of the gland. On the other hand, little is known as to the life history of the spermatozoon when it is imprisoned within the tubules of the epididymis. One can only surmise that the adult cell dies of inanition, unemployed and unwanted. Is the process of development of the sperm cell interfered with by the inability of its mature relatives to escape from the nest and migrate, as nature intends them to? Here again, in another but less important form, is the problem of the unemployed and its effect upon control of the birth of the unwanted. The urge to further formation of spermatozoa must remain, even after division of the vas, so long as sexual desire persists. One can visualize the overcrowding of the tubules of the epididymis with adult cells and the final squeezing out of existence of those that have not reached maturity. The final phase, in all probability, is the testicle's impotence to produce any sperm cells at all.

Such, in brief, are the physiological results of division or ligation of the vasa deferentia. Equally interesting and instructive are the clinical results of this simple surgical procedure.

OPERATIVE TECHNIQUE AND COMPLICATIONS

The operation can be carried out by any medical practitioner with a knowledge of minor surgery, but it must be stressed that this operation, if not performed efficiently, may lead to serious complications.

By far the easiest method of exposing the vas is as follows:

After the skin of the scrotum has been sterilized with iodine, picric acid, or methyl violet the vas is felt for immediately below the external abdominal ring. On the right side it is easily isolated with finger and thumb from the other constituents of the cord, but the left one is not so readily picked out on account of the multiplicity of veins which surround it. As soon as the duct is firmly gripped and fixed an incision is made in the scrotal skin between the operator's finger and thumb. With a pair of toothed forceps the vas is held while the tissues surrounding it are dissected away. It is then cut across and each end crushed between artery forceps. Should the surgeon desire to inject the vesiculæ seminales with an antiseptic or sclerosing solution in order to prevent subsequent vesiculitis the proximal end of the vas must not be crushed until the injection has been made. The procedure is: the proximal end of the cut vas is lightly held with forceps while a blunted hypodermic needle is passed down its lumen. (A sharp-pointed needle is found to catch in the wall of the duct and prevent the flow of fluid along the correct channel.) As soon as the surgeon is satisfied that the needle is in the right position 4 c.cm. of 1 in 10 carbolic acid—or any other antiseptic and sclerosing solution which may be preferred—is injected by means of a glass syringe. By this technique the vesiculæ seminales are sterilized, and, if the correct solution is used, also sclerosed. The divided ends of the vas are now pushed back into the scrotum and the skin wound sutured with catgut.

The complications which may arise from division of the vas are, in the main, the result of errors of technique. Thus, failure to maintain perfect asepsis will lead to scrotal cellulitis and the surrounding of the testicle by a hard mass, which has been mistaken for epididymo-orchitis. Again, particularly on the left side, a vein may be punctured during dissection and the error not recognized. The result is the formation of a scrotal haematoma.

* A post-graduate lecture delivered at the Hampstead General Hospital, November 9th, 1932.