previous pilot experiments it was found that the effect of a given dose of x rays was by no means uniform or predictable even in a uniform group of animals. Ulceration sometimes occurred early or occasionally was delayed; an ulcer which had healed sometimes broke down again. Late effects of irradiation on the skin are being studied in this and other groups of animals, both with and without cortisone. It seems probable that the changes which we have observed in previous experiments, occurring after as long as eighteen months, are part of a different phenomenon. A dose of 6,000 r was chosen as likely to produce early deep ulceration in 100% of control animals.

Cortisone is known to inhibit inflammatory reaction of tissues to irritants of all kinds, and the suppression of this initial inflammatory reaction to radiation may prevent subsequent ulceration. It has been suggested by Järvinen (1951), however, that the suppression of the initial inflammatory response to ultra-violet light by cortisone is in fact a spurious protection, resulting in the end in increased tissue damage. A drug which occasionally produces severe irritation and presumably inflammation of the gastric and intestinal mucosa (P.A.S.) can be administered for long periods under the suppressive action of corticotrophin without resulting in damage to the mucosa (Houghton, 1954). If the protective action of cortisone to x-ray damage is in fact due to inhibition of inflammation, the hormone should be effective if given only during the time that these changes are taking place. The work of Marshall has indicated that this may be true in mice, in which he found that cortisone was most effective if started shortly before the appearance of the lesions. It is possible, however, that cortisone produces a protective action during the actual exposure to radiation. The hormone is claimed to inhibit mitoses in epidermal cells (Green and Ghadially, 1951), but it seems unlikely that this effect could produce the degree of protection that has been demonstrated in this experiment. Whether the protective action of cortisone is a direct effect upon the cells or whether the effects are through some indirect action is not known. Cholesterol is known to undergo chemical change when exposed to ionizing radiation, and it is possible that this is also true of cortisone. Experiments are proceeding, using hydrocortisone ointment locally, to ascertain whether the protective action is a purely local one.

The use of systemic cortisone in radiotherapy is limited by our lack of knowledge of whether or not the protective action is extended to malignant tissues. If it can be shown that tumour cells are not protected, then the administration of cortisone will have a twofold advantage: the undesirable and sometimes severe general effects of radiation are reduced if not altogether abolished; and, secondly, it would be possible to administer larger x-ray doses or to increase the volume of tissue irradiated without fear of excessive damage to normal tissues. On the other hand, the dangers of uncontrolled infection during cortisone therapy cannot be overlooked.

Quite apart from any clinical applications, the demonstration of the protective action of cortisone is of importance in that it shows one method of blocking x-ray damage. Since the fundamental mechanism of the destructive action of x rays is not clearly understood, a study of the protective action of cortisone may well lead to a better understanding of the biological effects of radiation.

It is believed that tissue damage resulting from exposure to nuclear-fission products does not differ essentially from that produced by x-radiation. It is possible, therefore, that the protective action of cortisone might be extended to this field.

Summary

A dose of 6,000 r was delivered to a circular area of skin in 38 guinea-pigs. The 19 control animals showed severe persistent ulceration and cicatrization, whilst the 19 animals receiving parenteral cortisone showed complete absence of such ulceration. Under cortisone the early erythema was reduced and the epilation delayed;

the irradiated areas showed no shrinkage, although this was marked in the control animals. The possible mechanism of the protective action of cortisone is discussed.

We wish to thank Professor B. W. Windeyer and the Cancer Research Committee of Mount Vernon Hospital for their co-operation, and Professor R. W. Scarff and Mr. T. Holmes Sellors for advice and criticism. We are indebted to Dr. K. R. Stokes and Dr. E. Nassau for facilities at Harefield. We wish to thank the Medical Research Council and Roussel Laboratories for supplies of cortisone, and Dr. A. Gremaux and Dr. D. Davies for technical advice.

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HODGKIN'S DISEASE

BY

RALSTON PATERSON, C.B.E., F.R.C.S., F.F.R.

AND

EDITH PATERSON, M.B., F.R.C.P.Ed.

From the Christie Hospital and Holt Radium Institute,
Manchester

Hodgkin's disease, or lymphadenoma, is a fairly well defined clinical and pathological entity when it presents in its classical form. It is, however, only one of a group of less well defined diseases of the lympho-reticular system, although a very distinctive one. Many borderline cases occur in which a crisp diagnosis of lymphadenoma cannot be made with certainty. According to the Registrar-General the annual death rate in England and Wales from Hodgkin's disease is 17 per million population. This is about one-hundredth of the death rate from all types of cancer taken together, or approximately equal to that from cancer of the tongue. Looked at from the point of view of general practice, Hodgkin's disease is therefore a relatively rare disease but common enough to need being kept in mind, in particular when a patient presents with otherwise unexplained lymph-node enlargement. Males are more often affected than females in the ratio of about 2 to 1. The disease predominantly affects persons of middle adult life at the time of their greatest working capacity, as shown in Fig. 1. This graph also demonstrates that childhood and old age are not exempt; we have, however, not seen a case in a subject younger than 2 years.

Pathological Features

The aetiology of Hodgkin's disease is still unknown. It is thought by many to be a generalizing neoplasm. Histologically the appearances sometimes resemble the sarcomas

of reticular tissue, and occasionally the disease terminates as a reticulosarcoma. Others have doubted the neoplastic nature because of the multiplicity of cell types found, and have sought an infective agent. The tubercle bacillus, *Brucella abortus*, and viruses have been considered, but so far there is no accepted evidence of an infective origin.

The enlarged lymph nodes show a loss of the normal architecture; there is a proliferation of reticulum cells in the medullary tissue, and in most cases the presence of the characteristic multinucleate giant cells. Lymphoid cells and fibrous strands are present to a variable degree, and in the chronic case the fibrosis may become very extensive. Other cells such as granulocytes, particularly eosinophils, and plasma cells are present. These last two types are regarded by Willis as a reaction to the presence of tumour cells, not as part of them. Hodgkin's masses in tissues other than lymph nodes show essentially the same pattern. Such masses may arise by direct extension from lymph nodes, but in the lung and bone marrow the very numerous foci sometimes found suggest a blood-stream dissemination.

The pathological features of the disease often merge into

FIG. 1.—Age distribution of 404 treated cases.

the spectrum of other reticuloses just as do the clinical features. Thus atypical cases are seen which resemble reticulum-cell sarcoma or eosinophil granuloma. Some cases are acute with lesions mainly in the viscera; others are relatively benign—the so-called Hodgkin's granuloma.

Clinical Picture

The commonest presenting symptom in the early case is a painless enlargement of the nodes of the neck, usually more marked on one side; the patient may have no other symptoms and may be in excellent general health. Examination will often reveal slight enlargement of lymph nodes elsewhere and the spleen is sometimes palpable. At this stage fever is rarely present. Unlike tuberculosis, the nodes in Hodgkin's disease remain discrete and movable for a long time; they are painless and neither inflamed nor fluctuating.

Although the neck nodes are the commonest group to be found enlarged in the early case, other groups of superficial nodes—for example, in the axilla or groin—may show first. Enlarged nodes in the thorax or the abdomen may be found radiographically or on examination, but only occasionally are the earliest symptoms due to such enlargement, when dyspnoea or gastro-intestinal symptoms become the key complaints. A curious but common manifestation is intolerable itching associated with invasion of retroperitoneal nodes.

As the disease advances the involvement of lymph nodes becomes more generalized or other organs become involved. Splenic enlargement to a variable degree is usual; liver enlargement is less common. The central nervous system, particularly the spinal cord, may be invaded, with resulting paralyses. Skin and subcutaneous tissue, lung, bone, or bone marrow may be affected. Lung involvement is usually

associated with pleural effusion, and bone foci produce pain even before visible destruction can be seen radiographically.

In the terminal phase the essential systemic features or effects become dominant, with obvious general ill-health. Loss of weight and energy occurs. The patient is pale and feverish and perspires freely. The raised temperature may be low-grade and continuous or may be intermittent. A polymorphonuclear leucocytosis is usual, the red-cell count and the haemoglobin fall, and the erythrocyte sedimentation rate is raised. The disease terminates with progressive anaemia which is only temporarily relieved by blood transfusions.

It is, of course, very easy to describe the "average case" in this way, but many individuals fail to conform to this average pattern. In practice, deviation from the picture outlined occurs in two main ways. The course after the typical onset in the cervical nodes may show only one or two of the features described—apart from the terminal one. For example, involvement of one group of nodes after another, but none of great size, may become the whole story and yet lead on to a slow systemic deterioration with anaemia as the only really definite feature. Alternatively, the case may present from the beginning with only one of the less common features—for example, in the spinal cord or in bone—and without enlargement of superficial nodes. Not only so, but many cases which ultimately can only be labelled Hodgkin's disease overlap into the other forms of reticulosis and show in addition to their Hodgkin's features some features of the leukaemias, of the lympho-reticulosarcoma group of tumours, or of other reticuloses.

The clinical picture is therefore variable, but the common picture is that of multiple and generalized lymph-node enlargement leading on to haemopoietic aplasia.

Diagnosis

The diagnosis is practically always made from biopsy of a lymph node or other focus. No other tests are exclusive to this disease. A positive Mantoux test is of no value in differential diagnosis as it is positive in many cases of Hodgkin's disease. The E.S.R. tends to be raised as it is in other conditions. The blood count is not characteristic. A recent article describes pain in bone after a glass of sherry as pathognomonic of bone invasion, but this delightful suggestion awaits confirmation. Owing to the number of atypical cases accurate assessment of the stage of the disease is not easy. It depends but little on the site or extent of actual involvement. However, the presence of fever and a falling haemoglobin level are reliable indications of advancing disease.

Treatment

Hodgkin's disease is, in the end, always fatal. Treatment policy is therefore primarily directed towards particular manifestations of the disease or to the relief of symptoms rather than to the unknown root cause. Its main aim is to maintain the patient in the best possible condition for the longest possible time. This aim is achieved by employing the whole gamut of treatment methods now available, but using each appropriately and conservatively. Each of what will become a series of separate treatments has to be carried out in hospital or in the out-patient department; but the intervals between treatments should be as long as they can be made, and essential sojourns in hospital should be as short as is compatible with effective treatment.

Three methods of treatment are available—surgery, radiotherapy, and chemotherapy.

Surgery

Surgery is usually required in some form even if only for biopsy. Where masses are single or localized to one lymphatic region surgical excision provides one method of removing a mass. It has been claimed that, for masses limited to the neck, surgical dissection gives more enduring local results than radiotherapy, but this is doubtful.

Radiotherapy

Radiotherapy has for many years been the mainstay of treatment, and remains so, as the characteristic foci of lymphadenoma are radiosensitive. Once the diagnosis is made, treatment is directed towards securing resolution of all affected individual lymph-node groups. Before initiating this scheme in cases presenting with only a single focus it is important that any probability or possibility of a curable lymphosarcoma or reticulosarcoma be excluded. Detail of radiotherapy technique and dosage is not relevant to this article, as it is a matter for the radiotherapist. Only a brief outline, therefore, is given of the broad principles underlying any approach. Treatment methods are essentially simple and only moderate radiation dosage is used. The extent of treatment varies with the extent of node involvement. It ranges from a single treatment of nodes in one side

of 0.2 mg. per kg. at twenty-four-hour intervals. Great care must be taken that none of the injection escapes into the subcutaneous tissues, where it is extremely irritating. Thrombosis of the injected vein may occur; this can be prevented by making the injection through the rubber tubing of a saline drip. The immediate side-effects of nitrogen mustard are distressing but are of short duration. Vomiting generally occurs within an hour or two of the injection and diarrhoea may follow. A later side-effect which occurs at about two weeks is leucopenia, which should be limited to a reduction of neutrophils. A reduction in platelets or of haemoglobin is not usual at the doses suggested, but if it occurs it should be transient. The benefits of nitrogen mustard become apparent within a day or two. An elevated temperature which has not responded to antibiotics becomes normal, appetite is improved, and the patient gains a great sense of well-being. Enlarged nodes diminish in size and itching is relieved. The duration of improvement is variable; two to three months can be regarded as a good response.

Triethylene melamine (T.E.M.) has been described more recently, and is likely to supplant nitrogen mustard because of the milder side-effects. This can be given orally as enteric-coated tablets with less gastrointestinal disturbance than occurs after nitrogen mustard. The improvement is less rapid and hence less dramatic, but is equally well maintained. The total dose of T.E.M. is 0.25 mg. per kg., which is given in fractions over two or three days. Thus for a patient weighing 65 kg. a dose of 5 mg. a day may be given daily for three days. The tendency to leucopenia is just as great, however, as with nitrogen mustards, and this dose should rarely be exceeded.

Treatment with either NH_2 or T.E.M. is given as courses spread well apart. With either T.E.M. or the nitrogen mustards repeated courses of treatment may be given so long as the bone marrow is not aplastic. It is dangerous to repeat the dose in the presence of a leucopenia or if the bone marrow shows a diminishing cellularity, and it is unwise to repeat a course of treatment at an interval shorter than about six weeks to two months. Thus the treatment requires careful and repeated blood counts as a means of control. The response to the earlier courses is almost always good. Later courses of treatment produce a less good and a less lasting effect.

If no response is obtained to one of these forms of chemotherapy, it is unlikely that the other will be beneficial. Fig. 2 illustrates the haemopoietic response to chemotherapy.

Recently, cortisone or A.C.T.H. has been suggested as beneficial in the otherwise terminal case; and there are indications that this approach may have a temporary value.

Relationship Between Radiotherapy and Chemotherapy

This relationship merits analysis at this point. Chemotherapy can unquestionably yield resolution of masses even in the early case and is therefore in one sense entirely applicable. Such resolution is, however, shorter than that achieved by localized x-ray treatment, while the employment of chemotherapy at this early stage uses up tolerance, particularly haemopoietic tolerance, which will be needed later. We are therefore definitely of the opinion that radiotherapy should be used first, except for the case which is already very advanced when first seen. It should be maintained as long as possible as a series of courses. Chemotherapy is kept in reserve for application in the later phases, when the disease is becoming less responsive to radiotherapy, is generalizing, or presents in such a systemic form as to make x-ray therapy impracticable because too extensive. In some cases it is found beneficial to give one of these chemo-

FIG. 2.—Showing typical response of white blood cells and haemoglobin to triethylene melamine and later, after a remission, to nitrogen mustard.

of the neck to a whole sequence of treatments to all the external lymph-node areas, neck, groins, axillae, to the mediastinum, and to the retroperitoneal chain of nodes which require a course of treatment extending to several weeks. Treated masses almost invariably resolve and any pressure symptoms are relieved.

Skin itching is nearly always relieved after radiotherapy of the retroperitoneal nodes. In all but the most advanced cases some improvement of the systemic symptoms can be expected. Reaction to the treatment is seldom distressing. Where large volumes have to be irradiated there may be some radiation sickness. Skin reaction is rarely carried further than a brisk erythema requiring no special care other than keeping dry. Mucosal reactions in the mouth, pharynx, or intestine may occasion temporary discomfort, but are transient and require little attention.

After each course of treatment as long an interval as possible is allowed before repeating treatment either to new foci or, though this is rare after adequate treatment, to recurrent masses. In the end, however, radiation becomes increasingly ineffective in controlling the disease, as general deterioration sets in.

Chemotherapy

Chemotherapy has, by the use of systemic drugs discovered in the last decade, established an important place for itself in relation to the treatment of Hodgkin's disease. The first drug found effective was nitrogen mustard (methyl-bis(beta-chloroethyl)-amine hydrochloride) (NH_2), and it is still commonly used.

Nitrogen mustard in one or other of its forms will effect a satisfactory remission in many cases at a total dose of 0.4 mg. per kg., given as two intravenous injections each

therapeutic agents for a case which is generalized and at the same time to use irradiation locally for an obvious mass. It has not been shown, however, that the simultaneous routine combination of chemotherapy with radiotherapy in the early case improved the average survival time of patients compared with that of patients treated with radiotherapy alone.

Pregnancy occurring during Hodgkin's disease is a complication which may prejudice treatment. This possibility should be excluded before embarking on treatment, as it is inadmissible to irradiate the foetus or to subject it to chemotherapy. Depending on the condition of the patient, it may be advisable to terminate the pregnancy and thereafter institute treatment. If termination is not possible or desired, treatment should be limited to radiotherapy which excludes the abdomen and groins until after the birth of the child. Further radiotherapy or chemotherapy may then be used.

Home Care

Both these treatments, chemotherapy and radiotherapy, are better carried out by those with specialized experience. In spite of this the general practitioner undoubtedly carries the heavier burden. On him lies the responsibility of keeping the patient comfortable for the intervals between courses of treatment, and in keeping clearly in his mind that his purpose should be to try to prolong each interval to the maximum and not have the patient go running back to hospital for each new minor symptom or new lump. Expectant treatment of symptoms becomes, therefore, the keynote; this may include the aspiration of pleural fluid. Great attention should be paid to maintaining the general health of the patient. Fresh air and rest are important, and some form of iron should be prescribed. While skin irritation is alleviated either by x-radiation of abdominal nodes or by chemotherapeutic means, the relief in severe cases is sometimes disappointingly brief. In these circumstances local applications of calamine with phenol may be of value; the antihistamine preparations are not. In the terminal case with a rapidly falling haemoglobin a temporary improvement may be obtained by a transfusion of whole blood, or by the use of A.C.T.H. or cortisone.

Prognosis

Academically it is true that Hodgkin's disease is incurable, but the statement must be read with due regard to the prolongation of life now possible, using modern treatment to the full. The Table gives the five-year survival of a num-

Hodgkin's Disease: Five-year Survival Rate (Crude) of 256 Treated Cases (1934-47)

Clinical Findings	Male	Female	Total
Disease initially localized	44%	64%	51%
" " generalized	12%	21%	15%
All cases together	21%	34%	25%

ber of cases treated at this hospital. As will be seen, it compares reasonably with the five-year survival of some of the more treatable cancers. A useful fraction of cases can be kept going for anything from five to ten years, most of them in a tolerable state of health for the greater part of the time. Clinically, both the extremes of short survival and long survival are found. Acute cases are usually atypical in having the distribution of lesions mainly in the viscera. There is almost from the beginning a high temperature and severe prostration. In such cases, which occur generally in young people, the duration may be only a few months, and response to chemotherapy is slight. The really chronic type of case, on the other hand, may be kept in reasonable health for periods of up to and exceeding ten years, during most of which time the patient remains able to attend to his business.

OBSERVATIONS ON THE AETIOLOGY OF IDIOPATHIC STEATORRHOEA

JEJUNAL AND LYMPH-NODE BIOPSIES

BY

J. W. PAULLEY, M.D., M.R.C.P.

Physician to the Ipswich Hospitals

I have previously reported the finding of emotional factors influencing the onset and relapses of idiopathic steatorrhoea, and of personality traits much like those found in ulcerative colitis and Crohn's disease (Paulley, 1949a, 1949b, 1950, 1952a, 1952b, 1952c). This was unexpected, and led me to wonder how these factors might cause such a disturbance of small-bowel function. With colitis and ileitis in mind, the most likely possibility was a form of jejunitis. That there might be mucosal oedema seemed probable from a study of small-bowel meals, which usually show broadening of the valvulae conniventes in idiopathic steatorrhoea. The interesting observation by French (1949, 1950-1) and Frazer *et al.* (1949) that the cause of the phenomenon of "clumping" in small-bowel barium examinations was flocculation of the barium by excess mucus seemed to lend support to the idea of a low-grade chronic inflammation or irritation of the small gut. The chief difficulty about this theory was that since Thaysen's (1932) monograph it had been, and still is, accepted that the jejunal mucosa is normal in sprue and idiopathic steatorrhoea, and that any abnormality found should be attributed to post-mortem change. As a result, for twenty years those interested in this field have ignored the possibility of a mechanical hindrance to absorption and have sought, without success, for causes ranging from vitamin deficiency to adrenal dysfunction. However, on studying Thaysen's evidence carefully I was unconvinced by it (Paulley, 1949a), based as it was on necropsy studies of two cases of his own—one sprue and one non-tropical sprue—and a rather one-sided view of the literature.

The only certain way of testing the jejunitis hypothesis was to obtain biopsy material, and in the past five years I have been present at five laparotomies on patients with steatorrhoea. One was found to have Whipple's disease (Paulley, 1952a) and is still alive and well; the other four are described in this paper. The series is not large, but the indications for laparotomy in steatorrhoea are limited, though the finding of a case of Whipple's disease and an x-ray negative case of Crohn's disease in so small a series may suggest that it should be done more often.

Review of the Literature

Thaysen's monograph also dealt extensively with sprue, and it will also be necessary to refer to some of the old ideas about that disease here. Thaysen's observations led him to the conclusion that there were no characteristic morbid histological changes in the intestinal wall in either condition. He dismissed much strong evidence to the contrary advanced by previous workers (Faber, 1904; Beneke, 1910; Justi, 1913; Manson-Bahr, 1915, 1924) of inflammation and ulceration of the intestinal mucosa, because they had not been found constantly or were autolytic. Elsewhere, however, he was less downright, and said: "It must be correct to interpret these intestinal changes as being of secondary nature, either produced by relatively low virulent micro-organisms that have nothing to do with the aetiology of sprue, or resulting from irritation of the mucous membrane owing to abnormal acidity of the intestinal content, or as a result of both agents."