In My Own Time

Hodgkin's disease

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I first learnt of Hodgkin's disease in 1940 as a medical student at Cambridge, when the father of one fellow student, and shortly afterwards the brother of another became victims. I did not meet either of them, and it was some years before I saw the full extent of the protracted misery endured by patients with this disease. One of the excellent features of preclinical medical education at Cambridge was the Part I course in general pathology, but Hodgkin's disease was considered too exotic for inclusion: "We don't bother you with Hodgkin's disease in the Part I class," was the reply to my question about the nature of the characteristic giant cells. In the Part II class, the disease was considered in some detail: we examined much pathological material and learnt that a good description of the giant cells had been published by W S Greenfield long before those of either Sternberg or Reed, by whose names the cells are now known. On anatomical grounds, the polymorphic cellular infiltrate was generally included with the "reticulososes" or "lymphomas," but its nature was obscure; the prevailing opinion favoured a granulomatous process resulting from an unknown infectious agent. No similar disease was known in any other species of wild or domestic animal, and all attempts to induce it in laboratory animals failed—as they have to this day.

Distressing symptoms

Sadly, I first saw Hodgkin's disease in a fellow student at University College Hospital Medical School during the war. This brave young man continued his work without fuss almost until the moment when he was forced to his death bed, but it was pitiful to watch the progressive deterioration as his life ebbed away. The horrifying feature of the clinical course of Hodgkin's disease was the near inevitability of its progression to a toxic state dominated by malaise, sweats, fevers, and cachexia.

In varying degree, patients also suffered from the effects of tumour masses that compressed or infiltrated organs and vital structures, while, for some, the crowning misfortune was the onset of intractable generalised pruritus which deprived the patient of sleep and led to frenzied, almost continuous, scratching with excoriation and tearing of the skin. One or more attacks of herpes zoster, sometimes including several adjacent dermatomes and followed by protracted pain, added greatly to barely

endurable suffering. The numerous tranquillisers and sedatives of today were not then available.

Good palliation

Although the disease was often advanced when first recognised, it was sometimes diagnosed—without symptoms—when apparently confined to the site where the first mass of lymph nodes was discovered by the patient, usually in the neck. Nevertheless, opinions were divided whether the presenting focus was primary, or an outlier from an inaccessible deep-seated node mass; whether spread occurred from one group of nodes to another, or whether the disease was multicentric from the beginning. It was known that the enlarged lymph nodes would regress and become impalpable when exposed to x-rays to a total dose of about 1500 rad. In most of the cases so treated, the disease recurred after a few months at the treated site, or at an adjacent or more distant site as well. Occasionally, however, the patients remained well for some years, and successive recurrences at several sites could be treated successfully in the same way until the disease became generalised. The existence of these cases did not alter the general view that the disease was multicentric, and that there was no justification for attempting to eradicate it by high-dose treatment to an apparently primary focus. The corollary was that the mere presence of lumps that were causing no trouble was not an indication for treatment. The aim of treatment was to palliate, and nothing must be done that might harm the patient unless the proposed treatment was likely to relieve otherwise intolerable symptoms. At that time, radiotherapy was administered by orthovoltage machines at 250 kilovolts, and it was not possible to avoid damage to the skin that resulted in permanent telangiectasia, atrophy of the epidermis, and fixation to the structures beneath the irradiated area. If recurrences at a site were treated several times, the skin beneath the irradiated area would sometimes ulcerate, and, because of the devascularised state of the underlying tissue, skin grafts could not survive.

This was the position when, late in 1947, I started work at the then Royal Cancer Hospital. I had the privilege of following the progress of many patients—in Sir David Smithers's department, patients in the asymptomatic phase, whose disease was still thought controllable by radiotherapy; and those with toxic manifestations and largely beyond control by radiotherapy in the medical clinics of Dr P E Thompson Hancock and Dr J B Harman. My task was to assess the place of the recently introduced chloroethylamine drugs in treatment. One of these nitrogen mustard compounds had been used during the previous five years at several centres in the United States and in England—notably by the group at the Chester Beatty Research Institute and the Royal Cancer Hospital, and, in Manchester, by Dr J F Wilkinson—but for "security" reasons the first publications had been postponed until 1946. It seemed a near miracle to observe the rapid subsidence of severe toxæmia after a single

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injection of nitrogen mustard; a high temperature would sometimes fall to normal within 24 hours. Because of bone-marrow depression the difficulty was to sustain the advantage gained. A dose high enough to be effective could not always be repeated soon enough to maintain control, but the toxic state of a few patients was well controlled for several years by treatment with chloroethylamines alone. It was sometimes difficult to use nitrogen mustard itself, because the venous thrombosis it caused gradually exhausted the supply of accessible veins, but several orally administered aromatic chloroethylamines that were synthesised at the Chester Beatty Research Institute—of which chlorambucil is now the best known—were equally effective and did not cause the repeated vomiting that nitrogen mustard did.

In the next two decades two quite different types of cytotoxic drugs were found to be effective, even when the chloroethylamines had lost their value: they were the vinca alkaloids (vinblastine and vincristine were the most useful ones) and the methylhydrazine derivative, procarbazine. Until the late 1960s it was customary to use each group of agents singly, usually in the order of their introduction, changing from one to another when control was lost. Some patients proved highly resistant to chemotherapy, and responded little or not at all to any of the agents: occasionally, after failure with a chloroethylamine and vinblastine—each used for three months—a dramatic, though sometimes short-lived, response followed treatment with procarbazine. Other patients were kept reasonably healthy for several years by treatment with a member of each of the three groups of drugs in succession.

New approaches

In the early 1960s Vincent de Vita at the National Cancer Institute, Bethesda, applied to advanced Hodgkin's disease the idea of multiple-drug therapy—already used with some success in treating childhood leukaemia. Six short courses of nitrogen mustard, vincristine, and procarbazine were administered monthly in combination, and prednisone was added in two. It was soon obvious that the results were far superior to those obtained by the old single-drug method. More patients responded to this treatment, but most impressive was the duration of the benefit conferred: about one-third of the original group of patients reported on by de Vita remain apparently free of disease to this day, having received no further treatment. Nowadays, de Vita's combination (or similar ones) is routinely used in treating advanced Hodgkin's disease.

Two equally important advances took place in the 1960s. The radiological technique of lymphography made visualisation of the lymph nodes in the pelvic and para-aortic chains possible. Unsuspected sites of disease could now be ascertained in cases of Hodgkin's disease initially thought to be confined to one site, usually the neck. The systematic search for occult lesions in other organs by biopsy examination of the liver and bone marrow, and by detailed inspection of thin slices through the whole excised spleen, soon showed that Hodgkin's disease indeed originated in a focus and spread in the course of time in a regular manner along contiguous lymph-node chains. The spleen was found to be the take-off site for further dissemination, because the liver and bone marrow were rarely found to be infiltrated unless the spleen was concerned.

These exhaustive studies, pioneered by Vera Peters of Toronto, and Henry Kaplan at Stanford University, vindicated the views of the minority who, several decades earlier, had maintained that if the disease could be shown to be localised to a site, the correct treatment would be to irradiate that site at tumoricidal dosage. If the focus were sterilised, and no other lesion was present, the disease would be cured. Some believed that spread occurred from one group of nodes to the next because of the frequency with which recurrence took place at sites adjacent to a focus that had been successfully treated by irradiation. These workers had even begun treating adjacent

areas "prophylactically" in the hope of retarding or even preventing the spread of the disease.

The second major advance was the technical improvement of radiation facilities which made possible the irradiation to high dosage of large volumes of tissue without damaging the skin. Knowledge of the mode of spread of the disease paved the way for an internationally agreed staging system which could be applied to every patient by carrying out a systematic series of investigations. The treatment appropriate to each stage could now be precisely defined—essentially irradiation for disease still confined to the lymph nodes—and multiple-drug treatment for patients with extranodal disease as well. The aim was now to cure, not to palliate.

Results at all the major centres now suggest that Hodgkin's disease in the early stages is being cured in a high proportion of cases, and that at least some late-stage patients are being cured. It is therefore sad to report that, even now—when so much has been taught and written about the disease—patients are occasionally referred with advanced disease who were mis-handled when diagnosed. These patients, often teenagers or young adults, usually present with painless lumps in the neck, are treated unsuccessfully for some weeks with antibiotics, and then referred to a hospital where, after variable delay, a biopsy is arranged. Contrary to general belief, the histological diagnosis of Hodgkin's disease is occasionally very difficult, and a pathologist who rarely sees it should, when in doubt, seek expert advice. It is inadmissible to say "a granulomatous process, probably inflammatory; Hodgkin's disease is a possibility," and take no further action. It is tragic when the clinician reading the report also takes no further action until, months later, more nodes have appeared, the patient has night sweats, and has begun to lose weight. It is scarcely credible that in one such case the only treatment then administered was local irradiation at low dosage to two sites. When I first saw the patient she had extensive disease of the lungs, bones, and bone marrow, but she could probably have been cured had appropriate action been taken earlier. Painless non-tender lumps in the neck in young adults should be excised for biopsy without delay.

New problems

Within the last 20 years the outlook for patients, many of them teenagers or young adults, diagnosed as suffering from Hodgkin's disease has been transformed. For the earlier stages, the chance of cure is very high, and it is not negligible even in the most advanced stage, but what is the cost? The development of the elaborate staging procedure in the past decade—often including laparotomy and splenectomy—was linked to the evidence that, in most cases, radiotherapy could eradicate disease confined to the lymph nodes, whereas chemotherapy could eradicate extranodal disease in only about one-third. This meant that the treatment appropriate for each patient could not be specified until the extent of the disease had been ascertained. The staging procedure could undoubtedly be simplified if the type of treatment did not depend on what was found.

Disease of the spleen is sometimes confined to a few infiltrates 2 or 3 mm in diameter, too small to be detected by the most refined non-invasive techniques. Why not irradiate the spleen routinely on the assumption that it is always diseased, instead of removing it? Splenectomy carries risks of its own both in the short and long term, especially in younger patients. Unfortunately, irradiation of the spleen to the high dosage necessary to be sure of sterilising any deposits, however small, is generally considered difficult to accomplish without causing irreparable damage to part of the left kidney and lung. Attempts to follow wide-field nodal irradiation by intensive chemotherapy have led to a small but definite increase in the incidence of other malignant diseases in patients apparently cured of Hodgkin's disease. Does the cured patient come through the ordeal of staging and treatment unscathed? There is growing evidence of a high incidence of psychological disturbance—even in cases

where the whole process of referral, diagnosis, staging, and treatment appears to have been accomplished smoothly. Many patients experience loss of libido, and a worrying incidence of profound hormonal disturbances and associated sterility is being found. There is no room at all for complacency, and every aspect of current procedure is under critical scrutiny by those engaged in managing Hodgkin's disease. This is definitely not a disease to be handled by a "loner." Accurate diagnosis, a planned routine of investigation and treatment are more than ever necessary now that the main problem has been solved—namely, whether Hodgkin's disease is curable.

MATERIA NON MEDICA

X-raying mummies

As a radiologist whose spare time occupation is archaeology I find that my lay colleagues have a touching faith in the magic x rays. I was recently invited to the preview of a travelling exhibition of Egyptian papyri. At a loss to explain why my name had been included in the guest list, as my interests tend towards the Roman period, I discovered that the eminent papyrologist had suggested that a mummified crocodile in the local museum might be stuffed with papyri. The authorities were not keen on a laparotomy and had suggested that all might be revealed by means of x rays. So the sleek black body was carefully loaded into an estate car, driven to the department, and ceremoniously carried under the arm of the curator to the examination room.

As I pondered over the radiographs, it seemed as though the reptile was filled with all the pebbles and gravel from the bed of the Nile. Suddenly my son, following in father's footsteps, leant over my shoulder exclaiming, "Dad, there's a fish in it." Sure enough, we made out the characteristic outline of a fish vertebra hidden among the shadows of the skeleton and gravel. By alternately standing the reptile on its head and then on its tail between radiographs the gravel slid down and then up revealing the "middle cut" of a fish we provisionally identified as *Eutropius niloticus*. There were some 17½ vertebral bodies out of a possible 48. Our registrar, who had lived in Egypt, assured us that the head end would have been cut off soon after catching to limit putrefaction, and the tail end would not have been appropriate as an offering to the Gods. We further observed that some of the gravel did not move about and from the outline of this we concluded that the part fish had been packed in wrappings with gravel to make it look like a complete fish.

One problem remains: the eyeless barbed hook among the movable gravel—did it catch the crocodile, its last meal, or was this the entrapped tool of a delving papyrologist?—JOHN COLE (consultant radiologist, Birmingham).

Refuge in Scotland

It was 10 pm on 29 August 1939 on the Polish luxury liner *MS Pilsudski*, and we were passing north of the Hebrides. I was with a group of Polish doctors and students returning home after a six-week trip in the USA. The passengers were dancing in the lounge when suddenly the orchestra stopped and the Captain announced through a loudspeaker: "We are heading for the nearest port."

"War" flushed through our minds. The dancing was over, and we talked anxiously. Since our departure from the USA on 23 August we had been haunted by the dramatic headlines of the latest news in the New York papers: "Hitler Stalin Pact," "Doom of Poland," "Fourth partition of Poland" and predicting imminent war.

Very few went to bed that night. Unable to sleep myself I went at dawn on the deck for a refreshing stroll. In the first glimmer of the rising sun I saw on the horizon the misty shore of Scotland with contours of green hills in the far distance. We were sailing to the safety of Nigg Bay on the peaceful Moray Firth. Two days of anxious waiting followed.

The German invasion of Poland started on 1 September followed on 17 September by the Russian invasion from the east, which ended after one month's hopeless fighting in the total occupation and partition of the country. Honouring the mutual aid agreement with Poland Great Britain and France declared war on 3 September.

The problems now are to increase the proportion of patients cured at all stages, and to reduce morbidity. To accomplish this it is important that the patients are managed at properly equipped centres where work on the disease is a major commitment. There are several groups in the United Kingdom working on different approaches to the problem. The largest is the British National Lymphoma Investigation—created almost single-handed a decade ago by Dr A M Jelliffe, whose enthusiasm has secured the collaboration of his colleagues at some 30 centres. Other major groups are those at Manchester, Oxford, the Royal Marsden Hospital, and St Bartholomew's Hospital.

The passengers were disembarked. The liner was directed to Newcastle upon Tyne and made into a troopship with mounted anti-aircraft guns, only to be torpedoed near Hull a few hours after leaving South Shields in November 1939 to join a convoy destined for New Zealand. I had been offered the post of the ship's doctor but I had luckily declined because I suffered badly from seasickness.

I headed south to enlist in a Polish army which had been forming in France. I was half way through a training course at a military medical centre near Rennes when the German invasion of France in May 1940 and the subsequent collapse of the French resistance necessitated the evacuation of the British and Polish troops. The British managed splendidly at Dunkirk. The widely dispersed Polish units were hurriedly collected by the British Navy from various French ports on the Atlantic coast. Our Polish Medical Corps Centre was evacuated together with other units in five collier ships—1000 soldiers per deck—from St Jean de Luz on the Spanish border. Escorted by a destroyer, we sailed in a wide circle in the Atlantic, heading north-west.

For the second time in the war I landed in Great Britain, and again found refuge in Scotland—this time for good.—W TOMASZEWSKI (general practitioner, Edinburgh).

Bob Graham round

Recently, after many months of hard training and planning, I fulfilled a longstanding ambition in qualifying for membership of the Bob Graham 24-hour Club. I would not recommend the attempt to many, but there can be few pastimes more guaranteed to take one's mind off the following Monday morning surgery.

The only qualification for membership is to complete, within 24 hours, the round of 42 Lakeland summits initially traversed by Bob Graham in 1932. This is a distance of about 72 miles with an ascent and descent of some 27 000 feet and includes most of the major summits—Helvellyn, Gable, Skiddaw, the Scafells, and Pillar to name but a few. Though a very elite club until four or five years ago the round has become very popular in recent years with probably some 20 to 30 attempts at this time of the year.

My round, which started at 2.30 am on 30 June, was about the 120th successfully completed attempt, and demanded nearly 20 hours of running and walking with an hour's rest. My neurotic interest in the weather satellite pictures before my attempt was blessed by a cool fine day with a high cloud base—though the first few hours had been run in mist. This was obviously a great help in navigating, and facilitating much more rapid progress; indeed many previous attempts had foundered because of bad weather.

I enjoyed the many days on the mountains spent in reconnoitring the individual sections, and the unremitting grind on the day was amply offset by the satisfaction of completing the round. A certain amount of discomfort plagued the day such as a sprained ankle coming off the first fell and blurred vision from corneal oedema caused by excessive contact lens wear. These were compensated by the magic moments of the day—floating up the initial road section on a surge of adrenaline, sitting on Blencathra in the cool of the evening, and embracing the summit cairn of Skiddaw, the 42nd top, in the gathering mist.

But, oh the relief of trotting into Keswick to the enthusiastic welcome of wife, friends, and pacers and the luxury of sitting down in the pub to a pint of beer.—TONY DEALL (general practitioner, Penrith, Cumbria).