Today's Treatment

Blood and Neoplastic Diseases

Treatment of the Lymphomas

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The term lymphoma is used to describe those primary malignant diseases of lymphoreticular tissue which usually arise in lymph nodes, the diagnosis being made by microscopic examination of biopsy material. The precise histological type is important and a simple classification on which treatment is based is shown in table I. Several diseases have been omitted, such as macroglobulinaemia, because they are discussed in other articles in this series, and the problem of the relationship between these diseases and leukaemia will not be discussed. The importance of this simple scheme is that it enables the patients to be grouped into those likely to have a good prognosis and those in whom the prognosis is very poor—which in turn has a bearing on the type of treatment to be used. Hodgkin's disease will be discussed first because the situation here is more clearly understood than with the other lymphomas.

TABLE I—*The Lymphomas*

	New Nomenclature	Old Nomenclature
<i>Hodgkin's Disease</i>	Lymphocytic Predominant	(a) Paragranuloma
	Nodular Sclerosis Mixed Cellularity	(b) Granuloma
	Lymphocytic Depletion	(c) Sarcoma
<i>Non-Hodgkin's Lymphoma</i>	Group 1 {	(a) Follicular Lymphoma
	Group 2 {	(b) Lymphosarcoma
		(c) Reticulum Cell Sarcoma

Hodgkin's Disease

The principles of treatment are easy to state, and apply equally to the other lymphomas: localized disease is treated with radiotherapy and generalized disease with chemotherapy. The best treatment for this disease is radiotherapy and all the complicated staging classifications are designed to answer the simple question whether it is technically possible to irradiate all the known disease, or whether there has been spread to other organs such as the liver, lung, bone marrow, etc. making this impos-

sible—in which case chemotherapy must be used. The problem with Hodgkin's disease is how to determine the exact anatomical extent of disease and this raises the vexed question of how extensively these patients should be investigated and, in particular, whether they should have liver biopsies, peritoneoscopies, laparotomy, splenectomy, and bone-marrow trephines. The answer lies in determining the aim of treatment. If the aim is palliation then clearly subjecting patients to such intensive, and possibly hazardous, investigation is unjustified, but if the aim is to attempt to eradicate all disease with a view to obtaining a cure then such procedures become essential. One of the purposes of this article is to emphasize that in many patients Hodgkin's disease can be "cured" provided the correct treatment is given from the beginning.

Radiotherapy

Radiotherapy is the best treatment for Hodgkin's disease when localized to lymph node groups and limited in extent, and a high proportion of such patients can now be cured when appropriately treated with modern radiotherapy techniques.

Basically, treatment involves the irradiation of the lymph node chains in the upper or lower half of the body, or both, so that all sites of known disease are generously covered, and some adjacent and clinically uninvolved regions are also included. The success of such regional or wide-field irradiation depends on:

TABLE II—*Clinical Staging - Ann Arbor Classification.*

<i>Stage I</i>	Involvement of a single lymph node region (I) or of a single extra-lymphatic organ or site (IE).
<i>Stage II</i>	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localised involvement of extra-lymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (IIE).
<i>Stage III</i>	Involvement of lymph node regions on both sides of the diaphragm (III) ± involvement of the spleen (IIIS) or localised extra-lymphatic organ or site (IIIE).
<i>Stage IV</i>	Diffuse or disseminated involvement of one or more extra-lymphatic organs or tissues, e.g. liver, marrow, pleura, lung, bone and skin.

Systemic Symptoms—Weight loss, fever, sweating.
If absent = 'A'. If present = 'B'.

Cancer Research, 1971, 31, 1860.

(1) An accurate assessment of the extent of disease—that is, the staging of the disease (table II).

(2) A correct assessment of the risk that clinically undetected disease is present. This requires knowledge of the influence and the inter-relationship of sex, age, histological type, and the presence of systemic symptoms on the behaviour of the disease. In general, being male, elderly, or having mixed cellularity or lymphocytic depletion means that the disease is often more widespread and the prognosis worse than in women, younger

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patients, and those with lymphocytic predominant or nodular sclerosis.

(3) The treatment of all involved node regions in continuity by irradiation dose of 3,500-4,000 rads over four weeks, which is sufficient to destroy all tumour tissue yet well tolerated by the large volumes of normal tissues inevitably included.

With the advent of supervoltage equipment in the 1950s, particularly the linear accelerator, powerfully penetrating and accurately directed beams of x-rays became available which could be precisely shaped to cover the lymph-node regions above or below the diaphragm en bloc with better shielding of normal tissues from the main radiation beam. Thus, when disease involves supradiaphragmatic or infra-diaphragmatic node groups, the so-called "mantle" or "inverted-Y" techniques are used, respectively. The "mantle" technique, first used by Professor Henry Kaplan at Stanford, encompasses cervical, supra-clavicular, axillary, and mediastinal node areas, and the mantle fields are applied anteriorly and posteriorly, and precisely opposed, with as much protection of lungs and other normal tissues as possible. The anterior and posterior "inverted-Y" fields encompass inguinal, iliac, and para-aortic node groups, with shielding of the kidneys and protection of the gonads. With nodal disease above and below the diaphragm, both techniques can be used sequentially with precise joining of the mantle and inverted-Y fields, to provide what is sometimes termed "total nodal irradiation."

Importance of Disease Staging

Though accurate and effective radiotherapy is now available at many centres, the outstanding problem is one of correctly staging the disease in terms of anatomical sites of disease, to ensure that radiotherapy is used only in well-localized disease, and chemotherapy for generalized disease. Such is the importance of correct staging, therefore, that many special diagnostic procedures are employed, including mediastinal and hilar tomography, isotope scanning, and trephine bone biopsy. Leg lymphography is now routinely used to help in the assessment of retroperitoneal node involvement in the iliac and para-aortic regions, to follow the response of involved nodes to the radiotherapy, and to help in detecting possible subsequent reactivation of disease in nodes that remain opacified. In certain special centres exploratory laparotomy and splenectomy have been carried out, principally to detect disease of the spleen and liver, and also to perform an excision biopsy of selected lymph nodes from different sites. Laparotomy thus supplements lymphographic examination by enabling the lymphographic assessment of disease to be compared with the precise histological status of those nodes.

Nevertheless, the major benefit from laparotomy lies in detecting occult disease in small spleens, and the absence of disease in moderately enlarged spleens. In fact, whether the spleen is palpable cannot be used as an index of disease activity. Several large series have shown that if the spleen is palpable there is only a 70% chance that it will be involved, and that conversely if the spleen is impalpable (or of normal or small size as determined by scanning) it nevertheless is involved in half the patients. The practical importance of this is that if a patient is assumed not to have splenic disease because the spleen is small, then this will not be included in the field of abdominal radiotherapy and the patient will relapse because of undetected occult disease. Alternatively if the spleen is wrongly thought to be involved because it is palpable the patient may be staged as having generalized disease and given chemotherapy when in fact he should be treated for localized disease with radiotherapy. In most large series the stage has been changed in one-third of the patients after laparotomy with splenectomy. There is a small post operative morbidity after this procedure, usually from chest or wound infection, but the mortality is very low in experienced hands. The procedure is therefore best selectively applied to fit patients with apparently localized disease.

It is our policy to carry out this procedure on all patients with Stage I, II, and IIIA disease, provided, of course, that the patient is fit for operation, but not with Stage IIIB or IV disease

as these will be treated with chemotherapy regardless of the abdominal findings.

In young women found to have abdominal or pelvic node disease at laparotomy and therefore likely to require pelvic irradiation, the opportunity is taken of transposing the ovaries to the mid-line, where they can be shielded from the direct beam of radiation.

The recent great advances that have been made in the radiotherapy of Hodgkin's disease have resulted not only from improvements in radiotherapy technique, but by these more certain methods of patient selection. Thus, over 80% of patients with early stages of disease now survive five years. In the less favourable groups of patients current investigations may show whether the addition of chemotherapy can improve the results of radiotherapy alone.

CHEMOTHERAPY

Chemotherapy may be used for two different purposes in Hodgkin's disease. Firstly, as an adjuvant to radiotherapy, where this is the definitive treatment but rapid shrinkage of tumour is required as an emergency. Examples of this include spinal cord compression and obstruction of major airways, where one course of chemotherapy may rapidly alleviate the situation allowing radiotherapy to be given with greater ease and safety, subsequently. Conversely, patients receiving chemotherapy occasionally require radiotherapy to relieve troublesome focal disease, such as refractory painful bone infiltration, or obstructive jaundice caused by enlarged lymph nodes at the porta hepatis. Secondly, chemotherapy may be used as the primary treatment if the disease is generalized.

Modern chemotherapy began at the end of the second world war with the introduction of nitrogen mustard, and since then several agents with differing actions have been shown to be effective in Hodgkin's disease. The most useful group of drugs are the nitrogen mustards, either mustine hydrochloride or cyclophosphamide; the vinca alkaloids, vincristine, or vinblastine; procarbazine; and, finally, corticosteroids such as prednisone. In the past these were used consecutively, often giving single agents for long periods without any respite from treatment, and they were changed only when the disease had clearly escaped from the effect of the drug. The results were certainly encouraging but far from satisfactory—with 25% of the patients obtaining a complete remission and a further 50% having objective improvement (partial remission)—and only 25% remaining alive five years after starting chemotherapy.

A major advance was made when workers at the National Cancer Institute, Bethesda, introduced a regimen in which four drugs were used together (mustine, vincristine, procarbazine, and prednisone—MOPP). They obtained complete remissions in 80% of patients with a further 10% partial remissions, and 75% were still alive at five years, many having been free from all disease for this period. At St Bartholomew's Hospital and the Royal Marsden Hospital, Sutton, a modification of this regimen has been used (MVPP), in which the timing is slightly different and vinblastine is used instead of vincristine. The results are very similar but the toxicity is slightly different, as will be discussed later. The two regimens are shown in tables III and IV. They incorporate two of the fundamental principles

TABLE III—The MVPP Combination

Drug	Dosage
Nitrogen mustard	6 mg/sq m i.v. on days 1 and 8
Vinblastine*	6 mg/sq m i.v. on days 1 and 8
Procarbazine	100 mg/sq m orally daily on days 1 to 14 inclusive
Prednisone†	40 mg/adult orally daily on days 1 to 14 inclusive 4 week gap between courses

* The original MVPP regimen included an injection of vinblastine on day 14. This has been abandoned due to the development of transient leukopenia in many patients on day 14.

† A total dose of 40 mg per adult patient is given. This dose is never exceeded but may be reduced in children.

TABLE IV—The MOPP Combination

Drug	Dosage
Nitrogen mustard	6 mg/sq m i. v. daily on days 1 and 8
Vincristine	1.4 mg/sq m i. v. daily on days 1 and 8
Procarbazine	100 mg/sq m orally daily on days 1 to 14 inclusive
Prednisone†	40 mg/sq m orally daily on days 1 to 14 inclusive
	Six courses are given with two weeks rest between the end of one course and the beginning of the next one

† Prednisone is only given with the first and fourth courses

of modern chemotherapy; firstly, to use the drugs in combinations adding to their efficiency and lessening the likelihood of the development of resistance; and, secondly, to leave periods without any treatment so that the normal tissues of the body can recover from the toxic effects of treatment.

A recent analysis of patients treated at St Bartholomew's Hospital with the MVPP regimen showed that if the patients had never received chemotherapy in the past, complete remissions were obtained in 84%, and 78% would be alive at five years. Nevertheless, with patients who had previously been given "old-fashioned" treatment using single drugs continuously, 43% obtained a complete remission and only 36% would be alive at five years. The reason for this is that continuous treatment damages the bone marrow, making it impossible to give adequate combination chemotherapy. It is essential that when the decision to use chemotherapy is made quadruple therapy should be given from the start, and continuous single-drug treatment should not be tried first.

An additional problem is what to do with the small percentage of patients who do not respond to treatment and those who relapse. Unfortunately, other drugs are not very effective, but combinations of bleomycin with BCNU (a drug produced by the N.C.I., Bethesda), may produce transient improvement, though rarely complete remission of the disease.

Non-Hodgkin's Lymphoma

The principles of treatment of non-Hodgkin's lymphoma are the same as for Hodgkin's disease, with radiotherapy for localized, and chemotherapy for generalized disease. There are, however, considerable practical differences for two reasons; firstly, the behaviour and prognosis vary with the different histological types; secondly, the pattern of recurrence is not predictable as it is in Hodgkin's disease, making it difficult to know how extensive fields of radiotherapy should be.

RADIOTHERAPY

In general, this group of diseases is very responsive to radiotherapy, but treatment policies are determined principally by the histological variety of the particular disease, its site, and extent of involvement.

Group 1—Follicular Lymphoma and Well-differentiated Lymphocytic Lymphoma

In this more favourable histological group (table I), the diseases have a slow rate of growth and the prognosis in many patients is good. As with Hodgkin's disease, localized disease is appropriately treated by radiotherapy, which can be curative, or may at least defer the onset of disseminated disease. Radiation doses of 3,500 rads in four weeks can eradicate disease, provided that its full extent is adequately covered. Localized disease within this group is often found in certain sites within the head and neck, such as the orbit, paranasal sinuses, nasopharynx, tonsil, or base of tongue, and regional radiotherapy at these sites including the adjacent uninvolved lymph-node groups can cure a substantial proportion of such patients, over half at some sites.

In certain less common sites such as the stomach or testicle, a major surgical procedure is first required to establish the diagnosis and with the help of lymphography to assess the presence and extent of regional node disease; wide-field radio-

therapy may then be planned with the intent to cure. Follicular lymphoma confined to the lymph nodes may often be controlled for many years with irradiation of the lymph-node groups in continuity, even with involvement above and below the diaphragm by using wide-field radiotherapy as in Hodgkin's disease.

Group 2—Poorly Differentiated Lymphocytic Lymphoma and Histiocytic Lymphoma

This group of diseases often presents with widespread disease, clearly beyond the scope of radiotherapy. Even when the disease is apparently well localized, however, radiotherapy commonly fails because of early relapse at distant sites or the development of generalized disease. The role of radiotherapy in this group is thus much less well defined. The combination of local radiotherapy followed by chemotherapy is a rational approach which is under investigation. In patients with widespread disease radiotherapy may best be used as an adjuvant to chemotherapy, by producing rapid shrinkage of bulky and distressing local tumour masses, or relieving local discomfort at sites of relapse if the disease becomes refractory to chemotherapy.

With the use of more effective combination chemotherapy regimens in this group of diseases, more patients are being rendered disease free, but a high incidence of later central nervous system relapse is now being seen, similar to earlier experience in acute lymphoblastic leukaemia. The value of prophylaxis with cranial irradiation and concurrent intrathecal injections of methotrexate in preventing or delaying this development is currently under investigation. Therapeutic craniospinal irradiation and concurrent intrathecal chemotherapy is being given to patients in an attempt to eradicate established central nervous system disease.

CHEMOTHERAPY

As with radiotherapy, chemotherapy for generalized lymphoma depends on the histological variety. Obviously one could have many different regimens for each type but it is probably best to have a simple approach and limit the number of groups. In practice we have only two (table I). Follicular lymphomas and well-differentiated lymphocytic lymphoma form one group with a "good" prognosis; poorly differentiated lymphocytic and histiocytic lymphomas form the second group with a "poor" prognosis.

Group 1

Follicular lymphoma and well-differentiated lymphocytic lymphoma (table I) frequently run a benign course and it may be many years between their presentation as localized disease and the onset of generalized involvement. Other patients present with generalized disease, and there is a special, though small, group who have only splenomegaly and they may have prolonged remissions; some may even be cured by splenectomy.

The conventional treatment for this group of patients is to give an alkylating agent such as chlorambucil or cyclophosphamide, either continuously or intermittently. The indications for this are large glandular masses too disseminated for radiotherapy to be feasible, or involvement of other organs. The doses tend to be low—for example, chlorambucil 5-10 mg daily or 10-15mg for short periods with periods without treatment between the courses (one regimen consists of two weeks' treatment with 10-15mg daily followed by two weeks with no treatment, but many other dose schedules exist). In general the concept of intermittent treatment is more acceptable at present for reasons already stated. Once all evidence of disease has been removed, treatment may be discontinued because of the long interval before relapse which occurs in some patients.

Steroids are also of use in these patients, and play a much more important part in management than in Hodgkin's disease. They have at least two specific actions: they frequently cause regression of lymph-node masses and organ infiltration (the so-called lympholytic effect); and they are of great value in the presence of anaemia and thrombocytopenia, probably because there is nearly always reduced survival of red blood cells and platelets. Our policy is to start with a dose of prednisolone at 40mg/day/adult, and reduce this as rapidly as possible, stopping whenever this is feasible.

The alternative is to take a more aggressive approach to treatment, giving one of the combinations mentioned in the next section, such as cyclophosphamide, vincristine, and prednisolone—but the value of this is still being investigated.

Group 2

The prognosis in poorly differentiated lymphocytic lymphoma and histiocytic lymphoma (table I) is very poor, particularly with histiocytic lymphoma, and an aggressive attack on the disease is the only chance of restoring normal health for any significant time. The regimens which have been used include MOPP (table IV), combinations of cyclophosphamide, vincristine and prednisolone (such as CVP—table V), and more complicated regimens involving the use of cytosine arabinoside, doxorubicin, asparaginase, and other experimental drugs.

TABLE V—Intensive Cyclical Combination Chemotherapy for Lymphoma

N.I.H. Regimen—"CVP"	
Cyclophosphamide tablets Vincristine injection	400mg/m ² daily orally for 5 days 1.5mg/m ² i.v. day 1 only (upper limit of 2mg for adults)
Prednisolone tablets	100mg/m ² daily orally for 5 days

This is given every three weeks, usually for a total of six courses before reassessing the patient.

There is little value in an article such as this for giving details of the combinations under investigation because they change all the time depending on the results of the preliminary studies. It is better to recommend that when doctors are faced with such patients they should contact their nearest centre specifically interested in such problems for the latest information. Indeed, there is an argument for all such patients to be referred to special centres because only in this way will enough be learnt to improve the progress of the diseases.

Complications of Treatment

RADIOTHERAPY

Like surgery, curative radiotherapy always damages some normal tissue, but in Hodgkin's disease the immediate effects are usually mild and so well tolerated that many patients can be treated as outpatients.

Epilation of the occipital scalp, soreness, and pigmentation of the axillary and cervical skin, and mild oesophagitis usually develop during "mantle" irradiation, but the cutaneous and mucosal reactions recover quickly and full re-growth of scalp hair is seen within four to six months.

The "inverted-Y" technique may cause mild gastrointestinal symptoms, such as loss of appetite, nausea, and occasionally diarrhoea but can usually be easily controlled. Appreciable bone-marrow suppression may occur when the mantle and inverted-Y techniques are applied consecutively, but a rest of three to four weeks between courses of treatment permits marrow recovery and reduces the risk

of low blood counts interfering with the second course of treatment.

The later potential complications of radiotherapy are particularly important, because many patients can now be cured. Their incidence and severity are reduced by scrupulous planning and protection of sensitive tissues. After mantle irradiation, apical and paramediastinal pulmonary fibrosis may be detected radiologically, but this rarely causes symptoms. A syndrome of acute transient radiation myelopathy may follow irradiation of the cervical spinal cord after a variable latent interval—with electrical paraesthesiae on neck flexion in the lumbosacral segments, upper limbs, or trunk—but always completely recovers.

Whenever inguinal and pelvic nodes are treated, the gonads of both sexes can be shielded from the direct radiation beam, but appreciable gonad doses from scattered radiation are unavoidable and may lead to infertility and amenorrhoea in about half of young women. The lower testicular doses received rarely interfere with sexual function, though the risk of congenital abnormalities in the offspring is thus theoretically increased.

CHEMOTHERAPY

Nearly all drugs used in the treatment of the lymphomas are toxic to the bone marrow, the exceptions being prednisone, bleomycin, and to some extent asparaginase. In addition they have individual specific effects which are of considerable importance.

Bone marrow toxicity is undoubtedly the major worry, being most definite in patients who have received much treatment, whether it be total nodal radiotherapy, or continuous drug chemotherapy, in the past. All patients must have regular blood counts, including platelet counts, but this group must be followed with special care, because it is a tragedy to lose a patient from the effects of treatment which has successfully eradicated the disease.

Uric-acid nephropathy is a potential hazard whenever malignant tissue is being destroyed and the use of allopurinol as a routine starting 24-48 hours before treatment is a wise precaution against this complication. The only thing which must be remembered is that this drug potentiates the action of 6-mercaptopurine, whose dose may have to be modified if allopurinol is being given.

Space precludes a detailed analysis of all the complications of the drugs used for chemotherapy, but table VI lists some of the major systems of the body which may be affected. Since many of the diseases can also give rise to similar syndromes it is sometimes difficult to elucidate whether they are due to disease or cytotoxic therapy—for example, jaundice, renal failure, etc.

TABLE VI—Some Complications of Cancer Chemotherapy

Bone marrow suppression	Most anticancer agents except Hormones and Enzymes
Gastrointestinal complications	Many anticancer agents
Neurotoxicity	Vinca alkaloids
Cardiotoxicity	Daunorubicin
Bladder	Cyclophosphamide
Hepatotoxicity	6-mercaptopurine, methotrexate
Nephrotoxicity	Many drugs can produce hyper- uricaemia
Salt and water retention	Steroid hormones
Lung, skin	Busulphan, bleomycin
Diabetes	Steroid hormones, asparaginase

A few practical points are worth mentioning. With the nitrogen mustard group, mustine hydrochloride (which must be given into a fast-running intravenous drip) invariably causes nausea and vomiting, which may be prevented to some extent by giving chlorpromazine half and hour before the injection. The most serious complication of treatment with cyclophosphamide is haemorrhagic cystitis, which may be prevented by ensuring a high fluid intake before and during its administration.

The vinca alkaloids are neurotoxic, vincristine being more so than vinblastine, which is why in the MVPP regimen (table III) vinblastine was used instead of vincristine. Nevertheless, vincristine is less toxic to the bone marrow than vinblastine so that the MOPP regimen (table IV) may have less effect on normal haemopoiesis than MVPP.

Alopecia is common with modern combination chemotherapy, particularly when doxorubicin (adriamycin), cyclophosphamide, vin-

cristine, and 5-fluorouracil are used. Because alopecia affects the patients' appearance it has been regarded as a serious side effect and has inhibited some people from using these drugs, particularly in combination. Nevertheless, the situation must be seen in true perspective. Firstly, if patients are warned that they will go bald and a suitable wig ordered before they lose their hair, most will accept the situation. Conversely, if they are *not* warned confidence may be lost and great distress caused. Secondly, alopecia is a small price to pay for successful chemotherapy leading to a return to normal health, but a high price if the chemotherapy is unsuccessful. Probably the most difficult decision in the management of the lymphomas is to know when to stop treatment.

Finally, it is important to realize that when doses are published in combination regimens these represent what it is aimed to give—that is, it is the *maximum* that is given. Frequently one

gives less, usually because of marrow toxicity, and individual idiosyncratic reactions.

Conclusion

The treatment of the lymphomas, together with the leukaemias, represents one of the most exciting areas in cancer today. Improvements in radiotherapy and chemotherapy have created a situation where a significant percentage of patients, whether they present with localized or generalized disease, may be restored to health for many years—if not cured. Others are less fortunate but the situation is challenging and it is hoped that present research will not only improve the progress for these patients but the lessons learnt in these diseases may benefit patients suffering from other forms of malignant disease.

Any Questions?

We publish below a selection of questions and answers of general interest

Amphetamines and Intellectual Ability

Is there any evidence that the long-term use of amphetamines reduces intellectual ability?

There is no clear evidence that the long-term use of amphetamines reduces intellectual ability, but in one study of individuals taking high doses of amphetamines, one third said that their memory or their ability to concentrate had been impaired. No testing was done in this study to determine the possibility of permanent brain damage.¹ Several investigators have suggested that recovery from the major effects of chronic use of large amounts of amphetamines taken intravenously is slow but complete, requiring perhaps six to 12 months of abstinence.¹⁻³ One study with monkeys employing high doses within the range consumed by some chronic human users produced evidence of significant cardiovascular change and permanent neurological damage after only a few weeks of daily drug administration.⁴ Further research will be needed before a definitive answer could be given to this question.

¹ Kramer, J. C., Fischman, V. S., and Littlefield, D. C., *Journal of the American Medical Association*, 1967, 201, 305.

² Kramer, J. C., in *Drug Abuse: Proceedings of the International Conference*, ed. C. J. F. Zarafonitis, p. 253. Philadelphia, Lea & Febiger, 1972.

³ Commission of Enquiry into the Non-Medical Use of Drugs, *Final Report*, Appendix A.3, p. 342. Ottawa, Information Canada, 1973.

⁴ Rumbaugh, C. L., *et al.*, *Radiology*, 1971, 101, 345.

Weber-Christian Disease

What is Weber-Christian disease and how should it be treated?

Relapsing febrile nodular non-suppurative panniculitis is eponymously referred to as Weber-Christian panniculitis after their separate descriptions of the syndrome.^{1,2} Rarely, visceral rather than pannicular (superficial fascial) fat is involved and the title Weber-Christian disease or syndrome may then be used. Whatever title is used the syndrome is best considered as a reaction pattern.³ The primary abnormality is probably a vasculitis causing fat necrosis. Histologically acute inflammatory cells are replaced by histiocytes laden with fat and a lipophagic granuloma is formed. Healing

then takes place with fibroblastic invasion and the inflammatory reaction may obscure the vasculitis originally responsible for it. Typically the condition is characterized by the spontaneous appearance of multiple subcutaneous tender nodules, usually on the thighs and lower trunk. The lesions resolve over a period of a few weeks leaving a saucer-like depression, but recurrent bouts are common. During eruptive phases the patient is frequently pyrexial and other systemic features such as joint pains may occur. Liquefying panniculitis is probably a clinical variant in which the nodules liquefy and an oily yellow or brown liquid is discharged.

Investigations should be directed towards identifying a possible cause of the primary vasculitis—just as, for instance, in the investigation of erythema nodosum. The syndrome may follow a bacterial infection such as tonsillitis, be induced by drugs, or be part of an autoimmune disorder such as lupus erythematosus. The underlying vascular pathology might, however, be associated with other disease processes, for example, diabetes. The differential diagnosis involves other nodular lesions on the legs such as nodular vasculitis and polyarteritis nodosa. Subcutaneous granulomas including tuberculosis, sarcoidosis, gummatous, deep mycoses, foreign body granulomata, deep granuloma annulare, and even dermatitis artefacta should also be thought of. The panniculitis associated with pancreatic disease may be indistinguishable clinically and, in patients over 50, pancreatic malignancy should be excluded. In patients under 50 estimation of the serum amylase and the use of other pancreatic function tests may be more helpful.

Treatment should if possible be directed against any underlying cause. If none is detectable, then it can only be symptomatic. Systemic corticosteroids may be helpful in some patients but must be used in high dosage (for example, prednisone, 80 mg daily) during the eruptive phase. As soon as lesions cease appearing the dose should be reduced slowly. Long-term treatment is contraindicated. Beneficial effects have also been attributed to a variety of other agents, including antimalarials, phenylbutazone, and salicylates, but, because of the episodic nature of the condition, their efficacy is hard to assess.

¹ Weber, F. P., *British Journal of Dermatology*, 1925, 37, 301.

² Christian, H. A., *Archives of Internal Medicine*, 1928, 42, 338.

³ MacDonald, A., and Feiwel, M., *British Journal of Dermatology*, 1968, 80, 355.