The later development in the patient's serum of possible weak activity against normal kidney from herself, the antigen donor, and the other individuals suggests either chemical similarity between the kidney and cancer microsomal antigens or persistence in the cancer of kidney-specific material in reduced amount; complete identity between the kidney and cancer microsomal antigens is excluded by the failure of fusion of the gel lines and the results of differential absorptions. The absence of activity against other human tissues or tumours, necrotic or otherwise, indicates that the precipitin to the renal cancer is tissue-specific and not a general isoantibody.

Despite the lack of evidence of a cytotoxic effect on the tumour by the antibody, the fact that globulin, possibly antibody, had localized *in vivo* on the surface of viable tumour cells is an encouraging observation. It suggests that such antibody could conceivably be used as a specific localizing carrier for radiotherapeutic or chemotherapeutic agents. However, the possible cross-reactivity with normal kidney, in which globulin localization was also demonstrated in the post-mortem histological preparations, is a warning that damage to normal organs might result from attempts at active cancer immunization unless complete cancer specificity of the antigen could be assured. On the other hand, we have shown that the anti-kidney activity of the anti-cancer serum was removable by kidney absorptions, which left the anti-cancer activity largely unaffected. Such an absorbed serum should be non-toxic to normal organs and the possibility of its *in vivo* localization in the renal cancer of a passively immunized patient is an obvious subject for future study.

Summary

A patient with advanced renal cancer was immunized with a microsomal fraction in Freund's adjuvant of a homologous tumour with similar morphology.

A precipitin against human renal cancer was first demonstrated by gel-diffusion studies of the patient's serum four weeks after immunization. Immunohistological examination of the tumour *post mortem* showed localization of globulin on the surface of the cancer cells. There was no indication that the immunization procedure had any effect on the tumour growth or the clinical course.

This research programme has been supported by grants from the Medical Research Council and the Scottish Hospital Endowments Research Trust. Lederle Laboratories kindly supplied the methotrexate. We are indebted to Mr. N. Logie for providing surgical specimens of kidneys and kidney cancers, and to Dr. T. A. J. Ogunbiyi, Sister Lawson, and Mr. J. Urquhart for medical, nursing, and technical assistance respectively.

REFERENCES

Brit. med. J., 1959, **2**, 750.
Finney, J. W., Byers, E. H., and Wilson, R. H. (1960). *Cancer Res.*, **20**, 351.
Goldman, L. (1961). *Arch. Derm.*, **84**, 948.
Mansi, W. (1958). *Nature (Lond.)*, **181**, 1289.
Mellors, R. C. (1962). *Bull. N.Y. Acad. Med.*, **38**, 75.
Mihich, E (1962). *Cancer Res.*, **22**, 218.
Nairn, R. C. (1962). *Fluorescent Protein Tracing*, p. 111. Livingstone, Edinburgh.
—— Fothergill, J. E., McEntegart, M. G., and Porteous, I. B. (1962). *Brit. med. J.*, **1**, 1788.
—— Richmond, H. G., and Fothergill, J. E. (1960a). Ibid., **2**, 1341.
—— —— McEntegart, M. G., and Fothergill, J. E. (1960b). Ibid., **2**, 1335.
Southam, C. M. (1961). *Med. Clin. N. Amer.*, **45**, 733.

THE CURE OF HODGKIN'S DISEASE

BY

ERIC C. EASSON, M.D., D.M.R.T., F.F.R. **MARION H. RUSSELL, A.I.S., F.S.S.**

Christie Hospital and Holt Radium Institute, Manchester

The title of this paper has been deliberately phrased because we feel it is time that the pessimism of the past was challenged. This challenge has already been made, for example, by Peters and Middlemiss (1958), but a new generation of medical men is still being taught that this disease is "invariably fatal" (Davidson, 1960). We present here an analysis of data collected at the Christie Hospital, Manchester, which further confirms the conclusion that Hodgkin's is indeed a curable disease. Whatever else it may mean, the word "cure" inspires a sense of comfort and reassurance in the lay mind. In medical writing it is a word not commonly employed, and attempts at definition are always open to criticism. A realistic meaning, however, can be given to the word if cure of a disease is taken to connote that in time—probably a decade or two after treatment—there remains a group of disease-free survivors whose annual death rate from all causes is similar to that of a normal population group of the same sex and age distribution.

It is not easy, in the light of present-day knowledge, to understand how Hodgkin's disease acquired its sinister reputation. It is true, as we shall show, that once the disease is generalized the prognosis is poor. But many patients present themselves at hospital with a lymphadenopathy which is still localized, and it is at this stage that the opportunity for cure should not be lost.

Clinical Material and Mode of Management

During the years 1934–56 1,189 patients diagnosed as having Hodgkin's disease were examined for the first time in the clinics of the Christie Hospital, Manchester. Of these, 85% received treatment. The remaining 15% consisted of patients for whom radiotherapy was withheld because of advanced disease, and who were referred to their local hospitals for terminal care.

Of 926 treated cases, 822 had the clinical diagnosis confirmed by unequivocal histological reports of Hodgkin's disease. This clearly defined group of cases has been used to determine the prognosis. (A large group of cases with equivocal reports will be discussed later.) The whole of the reported series has a minimal after-treatment period of five years; 446 cases have matured to 10 years, and 191 are capable of yielding 15-year results.

The term "localized" implies that the lymphadenopathy was at the time of treatment clinically confined to one lymph-node region and was amenable to radical irradiation in one undivided volume of tissue. Thus enlarged lymph nodes were confined to one or both

sides of the neck ; to one axilla ; to one supraclavicular fossa and the related axilla ; to one groin ; or to the mediastinum and supraclavicular fossa (but not extending above the lower deep cervical level). The term "generalized" means that the lymphadenopathy had extended beyond the separate categories already described and was not therefore treatable in one localized volume. Examples are: neck and groin ; both axillae ; both sides of the neck plus one or both axillae. Systemic features of Hodgkin's disease (pyrexia, pruritus, and anaemia) were also interpreted as indicating generalized disease.

X-ray treatment, when radical, was carried out with 250 kV machines. During the period surveyed the technique most commonly employed aimed at irradiating the entire lymph-node region affected by the use of the four-field trunk bridge (Easson *et al.*, 1957): when this was not suitable (as in the case of axillary involvement) large parallel opposed fields were used. The radiation dosage to the involved area was in the region of 2,500–2,750 rads ; the total duration of treatment was three weeks, with five fractions each week.

For patients with a generalized lymphadenopathy comparatively simple *x*-ray treatments of shorter duration were given. Alkylating agents such as nitrogen mustard were also prescribed for cases with systemic disease.

Results of an Analysis of Hodgkin's Disease

In the tables which follow, survival at the fifth, tenth, and fifteenth years is expressed as age-corrected rates %, to conform to the presentation of results adopted at the Christie Hospital (Paterson, Tod, and Russell, 1950). As the majority of the treated patients suffering from Hodgkin's disease are under 65 years of age, the difference between crude and age-corrected rates is very small at the fifth year and does not exceed 5% at the fifteenth year.

The ratio of generalized to localized lymphadenopathy for the analysed series is approximately 2:1. Table I shows how poor are the survival rates after *x*-ray and/or nitrogen mustard therapy in patients whose Hodgkin's disease was already generalized by the time they were first examined at the Christie Hospital. Nevertheless, though poor, these results are by no means negligible. The similarity of the survival rates at the fifth and tenth years indicates that there is good reason to expect the eventual 15-year results on the entire series to follow suit.

It is, however, in studying the survival rates of patients with localized Hodgkin's disease (Table II) that more active optimism in prognosis finds justification. Again the potential long-term prognosis of the 277 patients treated in 1934–56 can be anticipated by the stability of the fifth- and tenth-year results in the three subgroups reported.

To assess the potential curability of localized Hodgkin's disease the crude survival curve to the fifteenth year is, in Fig. 1, compared with the *expected* survival trend for a normal population similarly distributed by sex and age. The shape of the curve for the Hodgkin's group indicates that the *rate* of mortality progressively decreases after about the fifth year, until between the tenth and fifteenth years the death rate no longer exceeds that of the comparable normal population group. Moreover, as none of the survivors who had full radical treatment showed any evidence of disease there is no obvious reason why clinically localized Hodgkin's disease should not be regarded as about 40% curable.

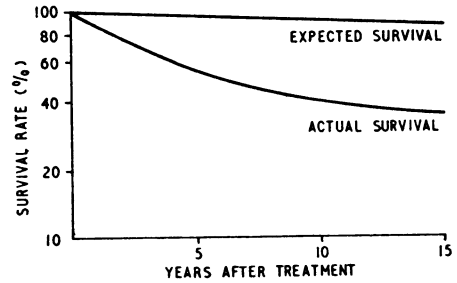

FIG. 1.—Localized Hodgkin's disease: comparison of crude survival rate with the expected survival rate in a normal population.

One aspect of prognosis to which attention should be drawn is that the outlook is substantially better for females than for males. In our series the ratio of males to females is 2:1 ; the survival rates are roughly in inverse ratio. Thus of the 127 patients with generalized disease with a 15-year age-corrected survival rate of 11.6% the respective rates for 87 males and 40 females are 9.2% and 16.9%. For localized lymphadenopathy (Table II) the 64 patients with a 15-year survival rate of 39.7% consist of 40 males and 24 females with rates of 32.1% and 52.0% respectively. Differences of a similar order exist at the five-year and 10-year points. These sex differences in prognosis have been shown for certain other forms of malignant disease treated at the Christie Hospital (Russell, 1954).

Although it is now difficult from these data to sustain the belief that Hodgkin's is a disease of multifocal origin it was on this commonly held hypothesis that a series of patients with localized lymphadenopathy were treated several years ago by a combination of radical *x*-ray therapy and full dosage of nitrogen mustard (Paterson, 1958). Table III shows that the five-year and 10-year survival rates are almost identical with those of a similar series of patients treated by irradiation alone, thereby adding further evidence against the supposed multifocal nature of this disease—a belief

TABLE I.—*Hodgkin's Disease—Generalized Lymphadenopathy*

Years	No. Treated	Age-corrected Survival Rate (%)		
		5 Years	10 Years	15 Years
1934–46	127	16·2	13·5	11·6
1934–51	309	17·2	11·0	
1934–56	545	17·8		

TABLE II.—*Hodgkin's Disease—Localized Lymphadenopathy*

Years	No. Treated	Age-corrected Survival Rate (%)		
		5 Years	10 Years	15 Years
1934–46	64	50·1	42·3	39·7
1934–51	137	56·0	45·2	
1934–56	277	56·8		

TABLE III.—*Hodgkin's Disease—Localized Lymphadenopathy*

Treatment Technique	Years	No. Treated	Age-corrected Survival Rate (%)	
			5 Years	10 Years
X-ray plus nitrogen mustard ..	1949–52	35	55·2	47·5
X-ray only ..	1942–48	32	60·9	46·6

which has too long engendered an attitude of hopelessness and helplessness and which has encouraged a palliative approach to therapy where cure ought to have been the therapeutic object.

Since the work of Jackson and Parker (1947) there has developed a general belief that Hodgkin's disease may vary from a highly malignant and rapidly fatal illness to an almost benign variety described as Hodgkin's paragranuloma. It has also come to be assumed that only patients with the paragranulomatous type of lesion could possibly survive more than a few years. Histological review of the biopsy material from our long-surviving patients has produced no confirmation that these patients conform exclusively to the histological picture of the paragranuloma. Furthermore, it has been pointed out by Symmers (1958) that the paragranulomatous form of Hodgkin's disease is more than eight times as common in males as in females. Since males outnumber females by 2 to 1 in our series, and since their prognosis is also found to be significantly poorer than that in females, the contention that survival depends on "benign" Hodgkin's disease is untenable.

Comparison of Hodgkin's Disease with Lymphosarcoma and Reticulosarcoma

In order to put the prognosis of Hodgkin's disease into perspective it is of interest to make a comparison with the group of diseases sometimes described as the sensitive sarcomas. This group consists of lymphosarcoma and reticulum-cell sarcoma. The distinction between these two is often difficult both clinically and histologically, and for this reason they have been analysed here as one group. Table IV shows the results of *x*-ray treatment of generalized disease. In common with generalized Hodgkin's lymphadenopathy the prognosis is poor and is, in this series, rather worse than is the case for Hodgkin's disease. However, the survival rates after irradiation of localized disease (Table V) show similar gratifying results.

TABLE IV.—*Lymphosarcoma and Reticulosarcoma—Generalized*

Years	No. Treated	Age-corrected Survival Rate (%)		
		5 Years	10 Years	15 Years
1933–46	64	10·3	8·2	7·4
1933–51	113	13·5	10·7	
1933–56	169	13·6		

TABLE V.—*Lymphosarcoma and Reticulosarcoma—Localized*

Years	No. Treated	Age-corrected Survival Rate (%)		
		5 Years	10 Years	15 Years
1933–46	69	47·7	43·4	42·6
1933–51	129	50·5	42·5	
1933–56	174	48·1		

The *crude* rates to the fifteenth year are shown in Fig. 2. Compared with the curve of *expected* survival for the appropriate normal population, here again it is clear, as with Hodgkin's disease, that the two curves become parallel between the tenth and fifteenth years. No patients were reported as showing evidence of disease at the latter point.

In this sarcoma group also the prognosis is different for males and females. The ratio of male to female cases in the generalized group is, like Hodgkin's disease, 2 : 1, and the 15-year survival rates are again in inverse ratio, there being a rate of 6.5% for 44 males and 11.7% for 20 females. There is an interesting and

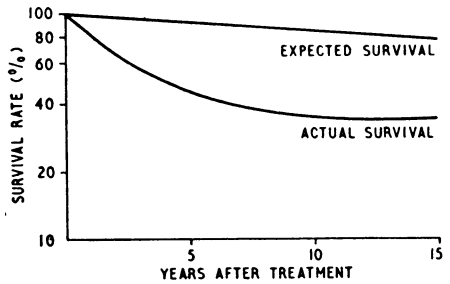

FIG. 2.—Localized lymphosarcoma and reticulosarcoma: comparison of crude survival rate with the expected survival rate in a normal population.

statistically significant difference (P=0.05) in the localized group where the sex ratio of male to female is 1:1. The difference in long-term prognosis, whilst again better for females, is less striking than in localized Hodgkin's disease, being 34.1% for 35 males and 51.2% for 34 females.

Comparison of the survival rates for localized Hodgkin's disease and localized lymphosarcoma and reticulosarcoma on a comparatively short-term (five years) and long-term (15 years) basis is made more effectively in one table (Table VI), showing striking evidence of the similarity in their response to radiation therapy.

TABLE VI.—*Comparison of 15-Year Survival Rates of Hodgkin's Disease and Lymphosarcoma and Reticulosarcoma*

Clinical Stage	No. Treated		Age-corrected Survival Rate (%)	
	Hodgkin's Disease	Lympho- and Reticulo-sarcoma	Hodgkin's Disease	Lympho- and Reticulo-sarcoma
Localized	64	69	39·7	42·6
Generalized ..	127	64	11·6	7·4

It is true that the two disease groups are not exactly comparable in one respect: the Hodgkin's series relates solely to lymphadenopathies, there being only a negligible incidence of this disease in other sites, whereas in the lymphosarcoma and reticulosarcoma series the lymph-node group amounts to only 39.7% of the localized cases. This variable factor in anatomical distribution does not, however, invalidate comparison of the reported survival rates, because, as an essential part of the study, such differences were investigated to ensure that comparison was not fallacious. It was found that the survival rates for the disease in anatomical subgroups were almost identical.

Although, as previously indicated, the results so far have related to cases in which unanimity of opinion was expressed by clinicians' diagnoses and pathologists' reports, there exists a substantial group of equivocal cases (194, 131, and 94 cases at 5, 10, and 15 years respectively) which it was impossible to allocate to either of the defined groups. Examples of such cases are: (*a*) clinical diagnosis Hodgkin's disease, pathological report indefinite—suggestive of Hodgkin's disease or lymphosarcoma ; (*b*) clinical diagnosis reticulosarcoma, pathological report Hodgkin's disease. It is of interest to compare the survival rates of this group of cases with

the summated Hodgkin's and lymphosarcoma and reticulosarcoma results previously shown separately. This is done in Table VII. The differences between the survival rates for the equivocal and unequivocal groups are not significant at the fifth, tenth, or fifteenth years.

TABLE VII.—*Comparison of Unequivocal and Equivocal Groups*

Clinical Stage	Group	Age-corrected Survival Rate (%)		
		5 Years	10 Years	15 Years
Localized	Unequivocal	53·6	44·0	41·0
	Equivocal	49·3	38·1	36·7
Generalized	Unequivocal	16·8	11·0	10·5
	Equivocal	15·1	8·2	8·2

Conclusions

According to the criteria of cure defined above there is evidence from the series of cases here reported that the two major groups of lympho-reticular disease—Hodgkin's disease and lymphosarcoma and reticulosarcoma—are equally curable. Nearly 40% of patients who present with clinically localized disease are curable, while the outlook is certainly not hopeless even for those who have generalized disease at the time of treatment. In both of these categories the prognosis is more favourable for women than for men.

It is interesting to note that, whether the clinical diagnosis or the histological report be equivocal or not, the prognosis is remarkably consistent both for localized and for generalized lymphadenopathies. It would seem, therefore, that whatever the type of lympho-reticular disease, and despite clinical and histological disputation, the urgent need is for radical *x*-ray therapy with curative intent, especially in those cases with localized disease.

What is needed is the opportunity to give radical treatment to the majority rather than the minority of patients suffering from these diseases. Early recognition of this complex group of diseases, coupled with appropriate action, would improve still further the overall cure rates already achieved.

Summary

The customary caution inherent in published survival rates for malignant disease obscures the very possibility of permanent cure. When the expectation of life of a group of patients free of disease becomes similar to that of the general population of the same sex and age constitution we are entitled to speak then of cure.

Survival studies of substantial numbers of patients 5, 10, and 15 years after treatment indicate that nearly 40% of those suffering from localized Hodgkin's disease are indeed cured. Since almost identical cure rates are obtained for patients with lymphosarcoma and reticulosarcoma, it is urged that, whatever the histological disputation, all these lympho-reticular lymphadenopathies require immediate radical *x*-ray therapy while they are still localized if the opportunity for cure is not to be lost.

We are indebted to Dr. J. P. Smith, consultant pathologist, for much helpful advice and criticism in the preparation of this paper.

REFERENCES

Davidson, L. S. P. (1960). *The Principles and Practice of Medicine: A Textbook for Students and Doctors*, 5th ed. Livingstone, Edinburgh.

Easson, E. C., Massey, J. B., Jones, B. E., and Pointon, R. S. (1957). *Brit. J Radiol.*, **30**, 354, 311.

Jackson, H., jun., and Parker, F., jun. (1947). *Hodgkin's Disease and Allied Disorders*. Oxford Univ. Press, New York.

Paterson, E (1958). *Brit. J Cancer*, **12**, 332.

Paterson, Ralston, Tod, M. C., and Russell, M. H. (1950). *The Results of Radium and X-ray Therapy in Malignant Disease* (Third Statistical Report). Livingstone, Edinburgh.

Peters, M. V., and Middlemiss, K. C. H. (1958). *Amer. J. Roentgenol.*, **79**, 114.

Russell, M. H. (1954). *Brit. med. J.*, **1**, 430.

Symmers, W. St. C. (1958). In *Cancer*, edited by R. W. Raven, vol. 2, Part II, Ch. 24. Butterworth, London.

LONG-TERM TREATMENT OF CHRONIC PYELONEPHRITIS IN CHILDREN

BY

LIBUSE HRADCOVA, M.D.

IVth Paediatric Clinic, Faculty of Medicine, Charles University, Prague, Czechoslovakia

In the past the majority of patients with chronic pyelonephritis were treated by means of short-term administration of antibiotics and sulphonamides whenever there was an acute flare-up of infection. No treatment was given between acute attacks. In this way permanent sterilization of urine was achieved in only approximately 10% of all patients (Orsten, 1960). Helmholz (1941) was the first to recommend the protracted administration of small doses of sulphathiazole for chronic urinary infection. Addis (1948) used this method for the treatment of chronic pyelonephritis with remarkable success. Stansfield and Webb (1954) were among the first paediatricians to report on the advantages of long-term therapy. They used sulphadimidine for the treatment of chronic pyelonephritis in children, and recommended that it should be administered for at least two months ; when the disease had been present longer than two months they recommended that treatment should be for at least six months. Marshall and Johnson (1946) discussed the effect of nitrofurantoin on chronic infections of the urinary tract in children. Good results were claimed after several months of treatment.

In spite of these promising results, long-term treatment did not at first become generally accepted. This was probably due to a justified apprehension of secondary reactions if full doses were given over a long period, or of bacterial resistance if only small maintenance doses were used. These problems have been the subject of several papers, especially those by Haschek (1959) and Dumittan (1960), who agree that long-term administration of small amounts of antibacterial agents is only rarely associated with the appearance of resistance in urinary bacteria.

Present Series.—The series comprised 20 children, of whom 11 were girls. They were under observation from 1954 to 1959. At the time of their first admission to hospital they were aged 3 to 14 years. Judging from the history, the disease had lasted from three months to 10 years. Seven had had the disease for less than one year, another seven from one to three years, and the remainder from 5 to 11 years. All but three—those with short histories of only three to six months—had first been treated elsewhere, some of them only as outpatients. Eleven had been wrongly diagnosed—four as