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Improving Prognosis of Hodgkin's Disease in Scotland

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Abstract—*Time trends in mortality from Hodgkin's disease have been studied in Great Britain for the 70-year period, 1911–1980, and incidence in Scotland since 1959. In both Scotland and England and Wales, in each sex, mortality from Hodgkin's disease rose steadily from 1911 until 1970 and thereafter dropped substantially; the greatest fall was apparent in Scottish males. While mortality rates continue to decline in Scotland the incidence has remained fairly constant over the last 25 years suggesting a major change in prognosis for this disease. The introduction of effective chemotherapy and improved techniques of radiotherapy appear to have improved prognosis sufficiently, and to have been made adequately widely available, as to influence overall mortality rates at a national level as well as at the level of the clinical trial. No such improvement in prognosis, however, explains the declines observed in mortality rates among children of each sex in both areas which have taken place since the 1930s. In view of the current knowledge of the aetiology of Hodgkin's disease this fall may have been brought about by changes in socio-economic factors.*

INTRODUCTION

ONE HUNDRED AND FIFTY years have passed since Thomas Hodgkin described in detail the disease which now bears his name [1]. In the interval which has elapsed since, Hodgkin's disease has proved intriguing to workers in internal medicine and radiotherapy, chemotherapy, haematology, immunology and epidemiology.

Perhaps current knowledge of the epidemiology of Hodgkin's disease is, as has been suggested [2], out of proportion to its public health impact but this is mainly thought to be due to the persistent possibility that Hodgkin's disease may [3] or may not [4] be related to a transmissible agent. A secondary reason for this great interest lies in the remarkable improvement in survival obtained by therapy in the last two decades.

The majority of epidemiological studies of Hodgkin's disease have been of an analytical rather than a descriptive nature. Studies reporting improvements in survival have generally been from clinical series or clinical trials.

The purpose of this communication is to investigate time trends in both the incidence and mortality of Hodgkin's disease in Scotland to ascertain whether increases in survival reported in clinical series have affected national mortality rates. Spatial and temporal trends of Hodgkin's disease in both Scotland and England and Wales are also presented.

MATERIALS AND METHODS

Mortality data for Hodgkin's disease, together with population denominator information, were available from 1911 to 1970 for Scotland [5] and separately for England and Wales [6]. Data for Scotland until 1985 were obtained from the annual reports of the Registrar General for Scotland [7] and the corresponding data for England and Wales were obtained until 1980 [8]. Throughout the study period data for Scotland and England and Wales have been aggregated over 5-year time periods thus ensuring a degree of statistical stability in the calculated rates of this relatively rare cancer. However, mortality data in Scotland are also pre-

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sented for individual years since 1959 for comparison with Scottish incidence data. Incidence data for Hodgkin's disease in Scotland were available between 1959 and 1984 from the Scottish Cancer Registration Scheme [9] which covers the whole of Scotland with five regional population-based registries from which collected information is transmitted to the Central Registry in Edinburgh.

Incidence data were also available from those areas contributing to *Cancer Incidence in Five Continents* [10], in particular all five Scottish Cancer Registry Regions (East, North-east, North, South-east and West) and six regions of England and Wales (Trent, Oxford, Mersey, South Thames, Birmingham and North-west).

To help adjust for differences in the age structures of populations either from time to time or from place to place, age standardization [11] has been carried out using the World Standard Population as standard. Average annual age-standardized incidence rates per 100,000 person-years, average annual age-standardized mortality rates per 100,000 person years and average annual age-standardized truncated rates per 100,000 person-years have been calculated. For simplicity, future reference to these quantities will be as incidence rates, mortality rates and truncated rates, as appropriate.

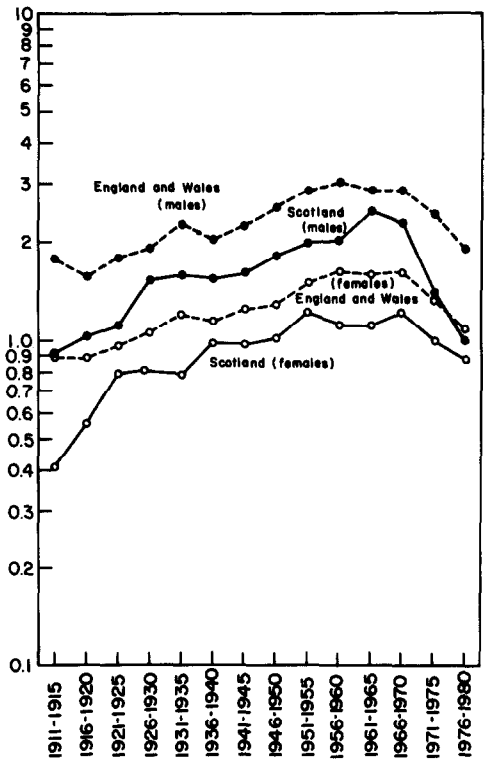

Fig. 1. Mortality from Hodgkin's disease in Great Britain, 1911–1980. Average annual age-standardized mortality rates per 100,000 person-years. Males and females—all ages.

RESULTS

The all-ages mortality rates for Hodgkin's disease rose, in each sex, from 1911 until the late 1960s in both Scotland and England and Wales (Fig. 1). Mortality thereafter fell at similar rates of decline in each sex in England and Wales and in females in Scotland, but mortality rates in Scottish males fell more steeply. Throughout the period, mortality in males was uniformly greater than mortality in females with mortality higher in England and Wales than in Scotland.

The greatest fall in mortality since 1970 has taken place in the 35–64 age group. These truncated rates bear more similarity, among each sex, to one another than the all-ages rates (Fig. 2). Once again the declines in mortality in each sex in England and Wales and in females in Scotland were similar and, once more, the greatest decline was apparent in Scottish males.

When mortality rates in children (0–14) are examined there is an apparent decline in each sex which has taken place since the 1930s in both areas (Fig. 3).

Many factors must be taken into account when interpreting trends in mortality data and, in the first instance, it is important to examine incidence data if available. In Scottish females, while mortality has been declining gradually, incidence has not fallen throughout the same time period (Fig. 4a). Examination of similar data in males, among whom mortality has decreased more remarkably, reveals that until 1969 incidence and mortality were relatively equal. Thereafter, while mortality rates have dropped quickly and continue to drop, the incidence rates has remained fairly stable (Fig. 4b).

In the eleven cancer registry regions of Great Britain included in Volume 4 of *Cancer Incidence in Five Continents* there is little systematic variation in either the all-ages rates or the truncated rates (0–34, 35–64, 65+) in either sex (Table 1).

DISCUSSION

Prior to modern radiation and chemotherapy, a diagnosis of Hodgkin's disease has been described as a 'virtual death pronouncement' [2]. Untreated, Hodgkin's disease is fatal, but if treated properly, is nowadays often curable [12]. This dramatic improvement in prognosis is one of the great advances in cancer therapy [13].

Modern chemotherapy of Hodgkin's disease began with a report on 57 patients treated with nitrogen mustard [14]. However, it was the initial report on 14 patients [15] and subsequent reports from the same group of researchers [16, 17] which led to the development and implementation of MOPP (Mustine, Vincristine, Procarbazine and Prednisone) which has proved so effective in the drug treatment of this condition. Around the same

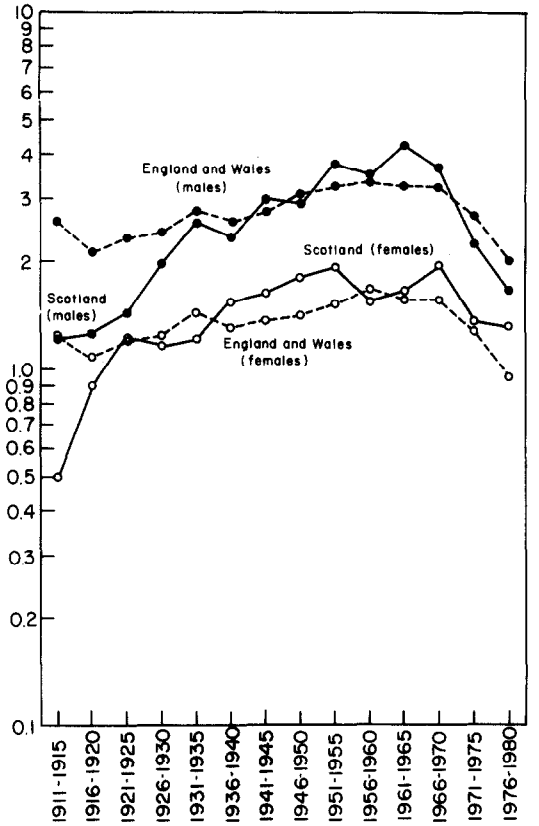

Fig. 2. Mortality from Hodgkin's disease in Great Britain, 1911–1980. *Average annual truncated age-standardized mortality rates per* 100,000 *person-years. Males and females—aged* 35–64.

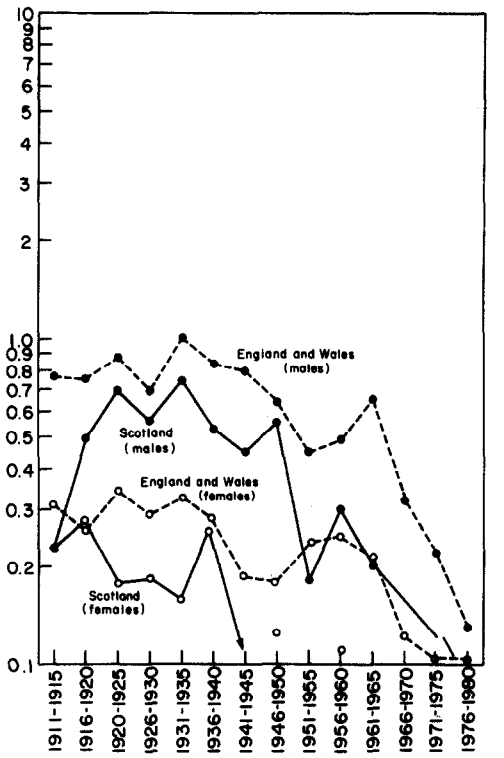

Fig. 3. Mortality from Hodgkin's disease in Great Britain, 1911–1980. *Average annual truncated age-standardized mortality rates per* 100,000 *person-years. Males and females—aged* 0-14.

period, it became apparent that results obtained in Hodgkin's disease were improved using megavoltage X-rays [18].

The coincidence of these two events helped greatly in improving prognosis for patients with Hodgkin's disease whether this was measured by survival rates obtained from clinical series or controlled clinical trials [12, 15, 16, 17, 19–22]. However, use of measures such as the 5-year survival rate to demonstrate improvements in prognosis have several shortcomings [23]. For example, the 5-year survival rate will be raised just as much by advancing the diagnosis by 1 year as by delaying the time of death by 1 year, i.e. earlier diagnosis will produce apparent improvements in survival. Furthermore, clinical trials are generally performed on those highly selected patients referred to specialized cancer treatment centres and the changes in prognosis observed among these patients may not necessarily benefit the general population with the disease. For these, and other reasons, examination of mortality data is preferable as an indicator of changing prognosis.

We have shown here that mortality from Hodgkin's disease in Scotland has declined since 1970, while the incidence has remained fairly constant. The delay between universal recognition of treatment improvements and their implementation in the majority of patients would appear able to explain the (real) drop in mortality which began in Scotland in approximately 1970.

Thus it would appear that treatment has been sufficiently successful and widely implemented to change the levels of mortality from Hodgkin's disease on a national basis. The recent report [24] of a continuation in improvement in the survival rate and disease-free interval of Hodgkin's disease through developments in therapy appears to be substantiated by the continued, downward trend in the death rate among each sex in Scotland at a time when incidence has remained constant.

No such milestone improvement in therapy, however, can alone explain the declines observed in mortality from Hodgkin's disease in children which have taken place in both areas of Great Britain since 1930. Unlike most malignant disease, Hodgkin's disease has the appearance of bimodality in the age-incidence curve. It has been proposed [25] that Hodgkin's disease resulted from two processes with the apparent bi-modality resulting from the superimposition of two disease distributions with different age peaks. It is now speculated that Hodgkin's disease may be one rare consequence of an infection with a common virus and that the probability of its

Fig. 4. Hodgkin's disease in Scotland. Annual age-standardized rates per 100,000. *Incidence and mortality in (a) males—all ages, (b) females—all ages.*

Table 1. *Hodgkin's disease in Great Britain Cancer Registry Regions. Mid-*1970*s. Average annual age-standardized incidence rates per* 100,000 *person-years. Males and females*

	Males				Females			
	All	0–34	35–64	65+	All	0–34	35–64	65+
England								
Trent	3.1	2.2	4.3	5.8	2.1	1.8	2.3	4.2
Oxford	3.1	2.5	3.5	7.1	1.9	1.5	2.3	3.2
Mersey	2.9	2.1	4.1	4.5	1.6	1.2	2.1	3.1
South Thames	2.7	2.4	3.0	4.1	1.6	1.4	1.9	2.8
Birmingham	2.7	1.8	3.9	5.6	1.9	1.6	2.1	3.9
North-west	3.4	2.7	4.1	6.3	1.8	1.2	2.6	3.7
Scotland								
East	3.2	2.1	3.9	9.9	2.5	1.7	3.1	6.5
North-east	3.0	2.1	4.2	5.4	2.5	2.1	2.7	6.0
North	1.9	1.0	2.7	6.0	1.3	0.3	3.3	1.6
South-west	3.9	3.2	5.1	4.5	2.1	1.9	2.1	4.3
West	2.2	1.2	3.8	4.2	2.0	1.4	2.5	5.1

Source: Waterhouse *et al.* [10].

occurrence increases when infection is delayed until adolescence or young adulthood [26, 27]. If correct, then factors in the childhood environment such as family size and general hygiene, which influence age of exposure to infectious agents, should be associated with the risk of Hodgkin's disease in young adulthood. As a corollary to this hypothesis, the general improvement in hygiene and reduction in family size may have brought about this reduction in Hodgkin's disease.

Validity of diagnosis of Hodgkin's disease since 1911

Since this study has utilized data from the early decades of this century, it is natural to question the validity of these data and knowledge of Hodgkin's disease at the time. Hodgkin's disease was well enough known to be accorded an individual rubric in the publication of the *International Statistical Classification of Causes of Death* and to have retained such recognition until the present day [28]. However, the origins of the disease were not understood and the early classifications placed Hodgkin's disease in the infectious disease section, a situation which persisted until the sixth revision [29].

Thomas Hodgkin described seven cases with what he termed '. . . morbid appearance of the absorbent glands and spleen . . .' in 1832 [1]. Although he did not personally carry out any histological studies, some of his specimens were preserved and later some were demonstrated to have the microscopical appearances of Hodgkin's disease [30].

W.S. Greenfield gave a clear account of the microscopical features of Hodgkin's disease to the Pathological Society of London in 1878. He described the destruction of normal glandular

pattern, fibrosis and the presence of multinucleate cells which have subsequently become an important criterion in the identification of the Hodgkin Giant Cell. The Hodgkin giant cell was described again in 1898 [31] and a later report [32] added information to what has become known as the Reed–Sternberg cell and emphasized that Hodgkin's disease was a distinct clinical and pathological entity with its own distinctive histological pictures. Therefore, much was known about Hodgkin's disease when data were first reported in 1911 indicating that this cause would probably be at least as well recorded on death certificates as any other malignancy.

Therefore the increase in Hodgkin's disease seen between 1911 and 1970 is likely to be real as are the differences between the mortality rates between Scotland and England and Wales, seen especially in the over-65s: the reason for such a difference is not, however, obvious.

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REFERENCES

1. Hodgkin T. On some morbid appearances of the absorbent glands and spleen. *Med Chir Trans* 1832, **17**, 68–114.
2. Grufferman S. Hodgkin's disease. In: Schottenfeld D, Fraumeni F, eds. *Cancer Epidemiology and Prevention*. Philadelphia, Saunders, 1982, pp. 739–753.
3. Vianna NJ, Polan AK. Epidemiologic evidence for transmission of Hodgkin's disease. *N Engl J Med* 1973, **10**, 499–502.
4. Grufferman S, Cole P, Levitan TR. Evidence against transmission of Hodgkin's disease in high schools. *N Engl J Med* 1979, **300**, 1006–1011.
5. Case RAM, Coghill C, Davies HM *et al.* Serial mortality tables. *Neoplastic Diseases*, Vol. 4. *Scotland* 1911–1970. London, Institute of Cancer Research, 1976.
6. Case RAM, Coghill C, Davies HM *et al.* Serial mortality tables. *Neoplastic Diseases*, Vol. 1. *England and Wales* 1911–1970. London, Institute of Cancer Reserch, 1976.
7. Registrar General for Scotland. *Annual Report II Mortality Statistics*. Edinburgh, HMSO, 1982.
8. Office of Population Censuses and Surveys. *Mortality Statistics. Review of the Registrar General on Deaths by Cause, Sex and Age, in England and Wales*, 1980. Series DH2, No. 7, London, HMSO, 1982.
9. Department for Health in Scotland. *The Scottish National Cancer Registration Scheme*. Edinburgh, DHS (HMSO), 1961.
10. Waterhouse JAH, Muir CS, Shanmugaratnam K, Powell J, eds. *Cancer Incidence in Five Continents*. Lyon, IARC, 1982, Vol IV.
11. Doll R, Smith P. Age Standardised Incidence Rates. In: Waterhouse JAM, Muir CS, Shanmugaratnam K, Powell J,eds. *Cancer Incidence in Five Continents*. Lyon, IARC, 1982, Vol IV.
12. Dady PH, McElwain TJ, Austin DE, Barrett A, Peckham MJ. Five years experience with ChlVPP: effective low-toxicity combination chemotherapy for Hodgkin's disease. *Br J Cancer* 1982, **45**, 851–859.
13. Frei E. The National Cancer Chemotherapy Program. *Science* 1982, **217**, 600–605.
14. Gilman A, Philips FS. Biological actions and therapeutic application of the data re choroethyl amines and sulphides. *Science* 1946, **103**, 409–414.
15. DeVita VT, Moxley JM, Brace K, Frei E. Intensive combination chemotherapy and X-irradiation in the treatment of Hodgkin's disease. *Proc Am Assoc Cancer Res* 1965, **6**, 15.
16. DeVita VT, Serpick A, Carbone PP. Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med* 1970, **73**, 881–895.
17. DeVita VT, Simon RM, Hubbard SM *et al.* Curability of advanced Hodgkin's disease with chemotherapy. Long term follow up of M.O.P.P. treated patients at the National Cancer Institute. *Ann Intern Med* 1980, **92**, 587–595.
18. Hoppe RT. Radiation therapy in the treatment of Hodgkin's disease. *Semin Oncol* 1980, **I**, 144–154.
19. Hunter A, Crowther D, Malpas JS, Peckham MJ, Smithers DW, Hamilton Fairley G. Combination chemotherapy in advanced and recurrent Hodgkin's disease. *Natl Cancer Inst Monogr* 1973, **36**, 395–402.
20. McElwain TJ, Toy J, Smith IE, Peckham MJ, Austin DE. A combination of chlorambucil, vinblastine, procarbazine and prednisolone for treatment of Hodgkin's disease. *Br J Cancer* 1977, **36**, 276–280.
21. Sutcliffe SB, Wrigley PFM, Peto J *et al.* M.V.P.P. chemotherapy regimen for advanced Hodgkin's disease. *Br Med J* 1978, **i**, 679–683.
22. Kaye SB, Juttner CA, Smith IE *et al.* Three years experience with ChlVPP (a combination of drugs of low toxicity) for the treatment of Hodgkin's disease. *Br J Cancer* 1979, **39**, 168–174.

23. Enstrom JE, Austin DF. Interpreting cancer survival rates. *Science* 1977, **195**, 847–851.
24. Tura S, Mazza P, Zinzani PL *et al.* Hodgkin's disease (HD): a historical perspective. *Eur J Cancer Clin Oncol* 1986, **22**, 1315–1323.
25. MacMahon B. Epidemiologic evidence on the nature of Hodgkin's disease. *Cancer* 1957, **10**, 1045–1054.
26. Gutensohn N, Cole P. Epidemiology of Hodgkin's disease in the young. *Int J Cancer* 1977, **19**, 595–604.
27. Gutensohn N, Cole P. Epidemiology of Hodgkin's disease. *Seminars in Oncology Reprint*. New York, Grune and Stratton, 1980.
28. Smith P. Current assessment of 'case cluttering' of lymphomas and leukaemias. *Cancer* 1978, **42**, 1026–1034.
29. WHO (World Health Organization). *Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death*, Sixth Revision. Geneva, WHO, 1948.
30. Fox H. Remarks on microscopical preparations made from some of the original tissue described by Thomas Hodgkin. *Ann Med Hist* 1926, **8**, 370–374.
31. Sternberg C. Uber eine Eigenartige unter dem Bilde der Pseudoleukamie verlaufende Tuberculose des lymphatischen Apparates. *Zetischr Heilkunder* 1893, **19**, 21.
32. Reed DM. On the pathological changes in Hodgkin's disease with special reference to its relation to tuberculosis. *John Hopkins' Hosp Rep* 1902, **10**, 133.