organisms colonising the wound and also, perhaps, with the natural defences.

Clinical sensitivity tests are required to give information on the possible effectiveness of treatment with an antibiotic, and for this purpose 18-hour diffusion tests with flucloxacillin at 37°C might be adequate. These would also detect the emergence of strains of *Staph aureus* highly resistant to flucloxacillin at 37°C—a type of resistance which we have not yet encountered but for which the microbiologist must be vigilant. Benner and Kayser¹¹ found an increasing proportion of clinical isolates of *Staph aureus* in which most cells in the culture were resistant to methicillin and its analogues, and infection with such strains was less responsive to treatment with these antibiotics. The heteroresistant state is best shown by parallel sensitivity tests with methicillin at 30°C and at 37°C, or by 18- and 42-hour methicillin sensitivity tests at 37°C, which would also show the reduced sensitivity of these strains at 37°C and detect the emergence of a strain highly resistant at 37°C. Methicillin sensitivity tests done only at 30°C would fail to detect the emergence of such highly resistant strains, as well as failing to recognise the potential value of flucloxacillin and its analogues in treatment of infections by heteroresistant strains of *Staph aureus*.

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A small cluster of Hodgkin's disease

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Summary

Nine cases of Hodgkin's disease and one of acute lymphoblastic leukaemia occurred in 1972-5 in an area of less than 1 km². Clinical, social, and drug histories provided no relevant information, and definite patient-to-patient contacts before the onset of disease were not established. There was a higher incidence of malignant neoplasms in first-degree relatives of the patients than in those of a small control group living in the same area. There was no apparent reason for this cluster of cases, but geographical, climatic, and entomological studies are being carried out.

Introduction

Reports of cases of Hodgkin's disease¹⁻⁴ and leukaemia⁵⁻⁷ occurring in a pattern similar to that seen in infectious disease have stimulated interest in space-time clustering in all types of

lymphoreticular and haematological malignancies. We recently heard about a cluster of five patients with Hodgkin's disease living close to each other, and further investigation disclosed a further four cases of Hodgkin's disease and one of leukaemia within an area of less than 1 km² (population about 2800). All these patients presented within a period of four years. We describe here the clinical and epidemiological findings.

Patients and methods

Full clinical and histological details were available for all 10 patients. All were interviewed and epidemiological inquiries made. The immune status of four patients was assessed by in-vivo and in-vitro techniques.

Results

The incidence of Hodgkin's disease in the area studied was greater than 70 cases per 100 000 population per year, although the expected incidence (for the Sheffield metropolitan area) was 4-5 cases per 100 000 per year. The clinical and epidemiological details of the patients are summarised in the table and their homes are marked on the map. For reasons of confidentiality we have not given precise details of roadways.

The patients had no common features in their medical histories, and the incidence of glandular fever, tonsillectomy, and appendicectomy was not increased. The drug and social histories of the patients were unremarkable but the incidence of malignant neoplasms among first-degree relatives seemed to be higher than in a group of 30 patients matched for age and sex who were attending the local general practitioner's surgery. Among first-degree relatives of the controls there were seven malignant neoplasms (three gastrointestinal, two lung, one haematological, and one where the primary site was undetermined), while among those of the 10 patients studied there were six (four gastrointestinal, one lung, and one haematological).

No definite patient-to-patient contacts were elicited, despite the fact that several of the patients lived very near to one another. No

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Summary of clinical findings in cluster of cases

Case No	Age and sex	Occupation	Date of arrival in area	Date of presentation	Medical history	Family history of malignancy	Lymph node site of presentation	Ann Arbor stage	Type of Hodgkin's disease	Immunity	Fate
1	10 M	Schoolboy	1969	Jan 1972	Tonsillectomy 1969	Leukaemia (grandmother)			(Acute lymphocytic leukaemia)		Remission
2	29 M	Milkman	1971	Nov 1972	Scarlet fever in childhood	Stomach carcinoma (father)	Axilla	3B	Nodular sclerosing		Remission
3	54 F	Clerk	1969	Aug 1973	Herpes zoster 1973	Rectal carcinoma (father)	Cervical	4A	Mixed cell		Died 1973
4	22 M	Electrician	1969	Nov 1973	Glandular fever 1967, eczema and hay fever in childhood		Cervical	1A	Mixed cell	Normal	Remission
5	60 M	Labourer	1960	July 1974	Eczema in youth, chronic parotitis 1956 (radiotherapy), duodenal ulcer 1958		Cervical	3A	Mixed cell	Normal	Died 1975
6	27 F	Housewife	1974	Jan 1975		Eye tumour (mother)	Cervical	4B	Lymphocyte depleted		Alive in relapse
7	24 F	Computer programmer	1971	Jan 1975	Recurrent tonsillitis over previous 5 years		Cervical	2A	Lymphocyte depleted	Normal	Remission
8	45 F	Canteen assistant	1958	April 1975	Duodenal ulcer 1960, dermatitis 1971	Abdominal neoplasm (father)	Groin	3B	Lymphocyte predominant		Remission
9	38 M	Driving instructor	1970	Oct 1975	Tonsillectomy 1944		Mediastinal	2A	Mixed cell	Normal	Remission
10	64 M	Excavator driver	1936	Dec 1975	Appendicectomy in childhood	Stomach carcinoma (grandmother)	Abdominal	2B	Lymphocyte predominant		Remission

contacts common to the patients before the onset of disease—for example, tradesmen, clergymen, medical practitioners—were detected. Six of the patients lived in houses built within the last seven years on old farm land. All but one patient lived on one side of a valley, along which runs a brook (see map). On the other side of the brook is a small factory but no definite pollution from this has been detected in the past 10 years. The brook is polluted mainly from surface drains, as are many other streams, and it has been known for several years that sewage overflows into the brook in wet weather. The main sewerage services to the new estate have recently been found to be inadequate.

Map showing homes of the 10 patients in the cluster with relevant geographical and environmental features.

Raw sewage from an old farm runs directly into the small reservoir of the brook, a fact only recently discovered during a predemolition survey of the farm buildings.

Climatic indices from official meteorological office statistics show that the area had a wet spring and prolonged dry summer in 1969 and 1970. These years may be important in the history of the cluster, because most of the patients arrived in the area during or shortly after that time. The local incidence of notifiable disease for the period of study was unremarkable.

Discussion

The problem in establishing the statistical significance of clusters has been discussed elsewhere.⁸ Nevertheless, the patients we studied lived in a very small area and the incidence during the period of observation was about 15 times that seen in the rest of the city.

Unlike previous investigators,^{4 9 10} we were unable to establish any definite prior contact between the patients in our study. Clinical, social, and drug histories did not seem to be relevant, but the geographical, climatic, and entomological features of the

area are being investigated further. A medical history of glandular fever¹¹ and tonsillectomy¹² or appendicectomy¹³ may be associated with an increased incidence of Hodgkin's disease, but these antecedent factors were not found in most of our patients.

A possible genetic role in leukaemia and lymphoma is suggested by (a) the familial clustering of some cases,¹⁴⁻¹⁶ (b) the finding of an increased prevalence of certain HLA antigens,¹⁷ and (c) an association with genetically determined immunological abnormalities.¹⁸ None of our patients were related and immune status was normal in those patients tested. There was, however, an increased incidence of malignant neoplasms in the close relatives of the patients when compared with that in the relatives of a small group of age- and sex-matched controls on the same general practice list and living in the same area.

The "incubation period" in Hodgkin's disease has been variously calculated as being from a few months¹⁹ to several years.^{1 2 4} Our study gives no definite information on this point, but if we are dealing with an infectious agent and assuming the earliest date of possible contact within the cluster to be 1971 the incubation period here seems to be less than five years.

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