PAPERS AND ORIGINALS

Paget's disease of bone in 14 British towns

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Summary

The radiological prevalence of Paget's disease was studied in 14 towns. Routine radiographs showed that the disease was present in 5.4% of people aged 55 years and over. The disease was more prevalent in men than in women at all ages, and the prevalence increased with age. The three Lancashire towns studied (Preston, Bolton, and Blackburn) had higher rates than elsewhere. This probably reflects a real geographical variation in the prevalence of Paget's disease in England and Wales.

Introduction

Within England, Wales, and Scotland there are regional variations in hospital discharge rates for Paget's disease of bone,¹ with rates being generally higher in the north and west than in the south and east. A similar variation is shown by mortality rates for the disease.^{2,3} Discharge and mortality statistics are, however, imperfect indicators of the prevalence of a chronic disease with low mortality; and investigation of Paget's disease is further complicated by the relative infrequency of clinical as opposed to subclinical forms. To establish whether or not there are regional variations in the prevalence of Paget's disease in England and Wales more accurate data are needed. To this end a survey was carried out in which the prevalence of subclinical Paget's disease in 14 towns was determined from routine radiographs of elderly people.

Methods

Twelve towns in England and Wales were initially selected: Bath, Bradford, Cardiff, Hull, Ipswich, Leicester, Plymouth, Preston,

Reading, Southampton, Stoke, and York. These towns were selected to ensure a wide geographical spread and to represent the range of hospital discharge rates. They encompassed a range of socioeconomic characteristics. Towns known to have high migration rates were avoided. As a result of the findings in these 12 towns Blackburn and Bolton were added to the survey.

In each town a sample of abdominal x-ray films of people aged 55 and over was taken from the stored films within the x-ray department of a general hospital. The selected films showed the entire pelvis and sacrum, the femoral heads, and all lumbar vertebrae. Ninety-five per cent of patients with Paget's disease have the disease in these sites.⁴ The films included those taken specifically to show the skeleton and others taken during intravenous pyelography, barium studies, and plain abdominal examinations. Depending on the records system in use at each hospital the films were extracted sequentially either in order of the x-ray department number or by searching through the current x-ray request cards for the relevant film numbers.

Samples of about 1000 x-ray films were drawn for each of the first 12 towns studied, and in the remaining two the sample size was about 600. In each town similar numbers of radiographs were drawn for men and women. The films were initially classified by one observer (PWLC) into three groups: positive (unequivocal signs of Paget's disease), doubtful, and negative. A second observer (PBG, a radiologist) then examined all the positive and doubtful films and a one-in-10 sample of the negative ones. The doubtful group made up about 3-4% of the total films examined, and all were subsequently classified as either positive or negative. Standardised criteria for the radiological diagnosis of Paget's disease were established in a pilot study and were similar to those of Murray and Jacobson⁵ and Campbell-Golding.⁶ After completing the survey a selected sample of 144 films from 10 of the towns was re-examined to determine the extent of within-observer variation.

Results

The figure shows the combined age-sex specific prevalence rates for the 14 towns. The findings accord with previous observations on the frequency of Paget's disease. In both sexes there is a progressive increase in prevalence with age and rates for men are consistently higher than those for women.^{7,8}

Table I shows the prevalence of Paget's disease in each of the 14 towns. The prevalence rates for each sex were directly standardised to allow comparisons corrected for the differing age distributions of the subjects in the various towns. In table I the towns are listed in descending order of overall age- and sex-standardised prevalence (final column), which varied from 7.5% in Preston to 4.2% in York. Because the prevalence in Preston was much higher than that in any other of the original 12 towns the two nearby towns of Bolton and

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Prevalence of Paget's disease of bone according to age and sex.

TABLE I—Prevalence of Paget's disease among hospital patients aged 55 years and over in 14 towns

Town	No of patients	No with Paget's disease	Prevalence (%) of Paget's disease		
			Men*	Women*	Both sexes†
Preston	1000	82	8.6	6.3	7.5
Bolton	602	42	7.7	6.4	7.1
Blackburn	595	39	8.8	3.8	6.3
Bradford	1000	59	7.9	3.6	5.8
Leicester	1021	57	7.8	3.1	5.5
Hull	1000	53	7.6	3.1	5.3
Ipswich	997	50	6.5	3.8	5.1
Southampton	1000	53	6.6	3.6	5.1
Reading	989	56	7.3	2.7	5.0
Bath	998	52	5.3	4.7	5.0
Cardiff	999	41	6.6	3.3	4.9
Plymouth	959	48	6.8	2.7	4.7
Stoke	1000	40	4.7	4.2	4.5
York	1000	41	5.8	2.5	4.2
All towns	13 160	713	7.0	3.8	5.4

Total number of men: 6626. Total number of women: 6534.

*Age-standardised rates. †Age- and sex-standardised rates.

Blackburn were added to the survey. Their prevalences of 7.1% and 6.3% respectively ranked immediately below that of Preston, giving a concentration of the highest prevalences in the three Lancashire towns.

In each town the rate for men was higher than that for women; the overall male rate was 7.0% compared with 3.8% for women. The highest prevalences among men were in Blackburn (8.8%) and Preston (8.6%), while the highest female rates were in Bolton and Preston (6.4% and 6.3% respectively). In some towns, however, there was a discordance between the ranking of sex-specific prevalences, possibly because of the small numbers of cases. In Bath and Stoke, for example, the low male rates of 5.3% and 4.7% were associated with female rates of 4.7% and 4.2% respectively, which were above the mean value for females (3.8%).

Table II shows the variation in prevalence according to type of radiological examination. Among the 2738 skeletal x-ray films the

overall rate was 7.2% compared with a rate of 4.9% among the remaining x-ray films, which were plain abdominal films, barium studies, or intravenous pyelograms. The non-skeletal radiographs were combined into one group as there were no important differences in prevalence between the different types. The final column of the table gives an overall prevalence rate corrected for the varying proportions of skeletal radiographs sampled in the different towns. The ranking of towns according to prevalence standardised in this manner was similar to that when no correction was made for the types of x-ray examination: in particular the position of the three Lancashire towns was unchanged. (In table II the towns are listed in the same order as in table I.)

The radiographs of patients with Paget's disease were grouped according to the extent of the disease, as indicated by the number of bones affected, there being 10 possible bones (two femora, two sides of the pelvis, sacrum, and five lumbar vertebrae). When the percentage prevalences were calculated according to the number of sites affected (table III) those for the seven towns with the highest prevalences (from the final column of table I) were consistently higher than those for the other seven towns.

TABLE III—Percentage prevalence according to extent of disease. Numbers of positive cases are given in parentheses

No of sites affected:	1	2	3	4-10	All patients
7 Towns with highest prevalence (n = 6215)	3.3 (204)	1.3 (81)	0.7 (44)	0.9 (53)	6.2 (382)
7 Towns with lowest prevalence (n = 6945)	3.0 (211)	0.9 (60)	0.2 (12)	0.7 (48)	4.8 (331)

The extent of between- and within-observer variation in interpreting the x-ray films was assessed. In each town at the time of the survey the radiologist examined a 10% sample of all films initially classified as negative. No reclassification was necessary. He examined all films initially classified as doubtful or positive. One hundred and forty-four of these films, drawn from 10 towns, were re-examined at the end of the survey. Sixty-two of this sample had been initially classified as doubtful, a proportion far greater than that in the main survey. The radiologist's re-examination of the films was carried out in such a way that he was unaware of his earlier report on the films. The agreement between the first and second examinations was 92%, with only 12 radiographs reclassified (table IV). Seven films judged as positive in the first examination were reclassified as negative, and five films judged as negative were reclassified as positive. These 12 films were drawn from nine towns and there was therefore no evidence of a systematic change in the radiologist's diagnostic criteria during the course of the survey. When the results of this observer variability study were put in the context of the mix of radiographs classified in the town survey they indicated an overall within-observer agreement level greater than 99%.

TABLE IV—Results of re-examination of sample of 144 radiographs

	Second examination		
	Paget's disease	No Paget's disease	Total
First examination: Paget's disease	70	7	77
No Paget's disease	5	62	67
Total	75	69	144

Discussion

This survey of the radiological prevalence of Paget's disease in England and Wales has given results which generally agree with hospital discharge and mortality data.¹⁻³ The towns with the highest prevalences were in the north and west of the country. More specifically the finding of a high prevalence in Preston was corroborated by high rates in the nearby towns of Bolton and Blackburn. There is therefore evidence of a concentration of the disease in Lancashire.

Although the prevalence of the disease among patients

TABLE II—Prevalence of Paget's disease by type of radiological examination

Town	Prevalence (%) of Paget's disease		
	Skeletal radiograph to show lumbar spine and pelvis*	Radiographs taken for plain abdominal examinations, IVP, or barium studies*	All types of radiological examination†
Preston	19.0	5.6	8.4
Bolton	7.8	6.8	7.0
Blackburn	16.2	5.1	7.4
Bradford	4.3	6.1	5.7
Leicester	10.1	4.2	5.4
Hull	2.8	6.0	5.3
Ipswich	5.7	4.9	5.1
Southampton	4.3	5.6	5.3
Reading	6.5	4.5	4.9
Bath	7.3	4.5	5.1
Cardiff	7.4	3.9	4.6
Plymouth	9.1	4.8	5.7
Stoke	8.2	3.7	4.6
York	7.6	4.0	4.8
All towns	7.2 (2738)†	4.9 (10 368)†	5.4

†Figures in parentheses are numbers of patients; type of examination not recorded for 54 patients.

*Age-standardised rates.

†Rates standardised for age and type of examination.

attending for routine x-ray investigations is a biased estimate of the true prevalence of the disease in the community, it seems unlikely that comparisons between towns will be affected by these biases. The towns with higher prevalences showed this in both sexes and at all ages. The higher prevalences did not depend on a higher level of clinical suspicion of Paget's disease by doctors referring patients for skeletal x-rays, because they were recorded in both skeletal radiographs and in radiographs taken during barium studies, intravenous pyelography, and other abdominal examinations (table II). A study of x-ray request forms in Southampton, Blackburn, and Bolton has shown that in patients with radiological evidence of Paget's disease this diagnosis is rarely stated on the form. Although the prevalence was higher among patients referred for skeletal x-ray examination, most of whom would presumably have had skeletal symptoms such as backache, standardisation to allow for the differing proportions of skeletal and other types of examination had little influence on the overall prevalence in each town (table II). The towns with higher prevalences showed this independently of the extent of the disease, as indicated by the number of bones affected (table III).

The findings suggest that the differences in radiological prevalence of Paget's disease recorded in this study reflect geographical differences in disease prevalence, the most striking feature of which is the high prevalence in the Lancashire towns. The two obvious characteristics of these Lancashire towns are that they are northern and industrialised. That the prevalence of Paget's disease does not depend on latitude alone is shown by the finding of a low prevalence in York (table I). That it is not only

related to industrialisation is shown by the low prevalence in Stoke. It is hoped that further studies which are being carried out in northern industrial towns will elucidate this. In addition, studies of other Lancashire towns are being undertaken to determine the extent of the apparent focus of high prevalence.

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Diagnosis of invasive candidosis by enzyme immunoassay of serum antigen

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Summary

Enzyme immunoassay was used to measure *Candida albicans*-related antigen in sera of rabbits and mice infected with *C. albicans*. A range of heterologous antigens tested gave no cross reactions. Of the three patients who were investigated and gave positive reactions, two were confirmed as having deep candida infections. Enzyme immunoassay is efficient, simple, and sensitive, and may prove valuable in the early diagnosis of invasive candida infections.

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Introduction

Invasive fungal disease in immunosuppressed or otherwise compromised hosts has been encountered with increasing frequency in those who have undergone transplantation¹ or open heart surgery² and others.³ Diagnosis depends on detecting increasing titres of precipitating and agglutinating antibodies in patients' sera by Ouchterlony double diffusion, counter-immunoelectrophoresis (CIE),⁴ or enzyme immunoassay.^{5, 6} The more direct approach of detecting *Candida albicans* protein antigen in patients' sera has been made by crossed-line electrophoresis,⁷ and cell-wall mannan has been detected by passive haemagglutination.⁸

For routine testing of many serum samples, a method is still required that combines high sensitivity, using small volumes of serum, with unequivocal results at an early stage in the development of the disease. For these reasons we used the microplate double-antibody sandwich method of enzyme immunoassay,⁹ based on the concept of Engvall and Perlmann,¹⁰ for detecting circulating candida antigen.

Methods

Animal inoculations—Mice were injected subcutaneously with 5 mg of cortisone (Cortistab) one day before intravenous challenge with 0.1 ml of 10⁵ blastospores/ml from a 12-hour culture of *C. albicans* strain 6224 (Mycological Reference Laboratory, London) suspended in distilled water. Groups of 10 mice were killed by cervical