The ratio between the mortality and the incidence rates shows marked variation with age. Mortality is low compared with incidence at ages under 15 years (5%) and at ages 15 to 24 years (4%), but subsequently it increases with age. This corresponds with the pathological finding that papillary carcinoma is the predominant type in childhood and anaplastic carcinoma the predominant type in old age. Follow-up of patients reported under the national cancer registration scheme confirms that the early prognosis is good in youth and becomes progressively worse in adult life.

Data obtained from three studies in the U.S.A. show a similar change with age in the ratio between mortality and incidence. The ratio is somewhat lower at ages 20 to 69 years in the U.S.A., suggesting that the incidence in England and Wales may be slightly underestimated.

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POST-CRICOID CARCINOMA: REGIONAL INCIDENCE IN ENGLAND AND WALES

BY

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This report on the regional incidence of post-cricoid carcinoma in England and Wales was stimulated by the observation of Scott (1960) and Payne (1961) that the incidence of pernicious anaemia varies in different parts of the country, and the occurrence, in a few patients, of both post-cricoid carcinoma and pernicious anaemia (Jacobs, 1962). It was made possible by the fact that since 1957 the Registrar-General has placed deaths from post-cricoid carcinoma in a class of their own (I.S.C. No. 147.2) instead of including them under the general class of "malignant neoplasms of the hypopharynx" (I.S.C. No. 147).

Material.—The numbers of deaths due to post-cricoid carcinoma occurring in England and Wales during the five years 1957-61 were obtained from the Registrar-General. These were subdivided into the standard regions of England and the two subregions of Wales (Registrar-General, 1963). Separate figures were given for the two sexes. For the years 1959-61 details of age and social class were also obtained. An assessment was made of regional differences for each sex separately and of possible differences due to age or social class.

Results

Post-cricoid carcinoma is not a common disease. The total number of deaths due to this cause in the whole of England and Wales did not exceed 250 in any of the years under review. Deaths occurring during the whole period 1957-61 in each region, together with the average crude death rate for those years, are shown in Table I. Death rate in this disease probably reflects the true incidence fairly accurately, and the greater mortality in females agrees with clinical impressions. In both sexes the death rate is higher in Wales than elsewhere, and highest in North and West Wales (Wales II). The χ^2 test was applied to these mortality figures, and the results are highly significant in females. Comparing all the regions, $\chi^2=117.9$, $P<0.001$. When Wales II is excluded the other regions compared give $\chi^2=48.1$, $P<0.001$, and for England alone $\chi^2=31.8$,

$P<0.001$, indicating that the regional variations in England are also significant. When applied to male deaths in the whole of England and Wales $\chi^2=25.7$, $P<0.01$; but when Wales II, the area of high mortality, is excluded the other regions compared show no significant difference.

TABLE I.—Deaths and Average Crude Death Rate Due to Post-cricoid Carcinoma in England and Wales, 1957-61

Region	Male		Female	
	No. of Deaths	Average Death Rate (per Million Population)	No. of Deaths	Average Death Rate (per Million Population)
Wales I	12	2.6	51	10.7
" II	12	6.7	41	21.4
North-Western ..	35	2.6	137	8.0
South-Western ..	17	2.1	67	7.9
Northern	21	2.6	44	5.4
East and West Ridings	16	1.6	74	6.9
North Midlands ..	22	2.5	60	6.6
Midlands	29	2.6	63	5.3
Eastern	12	1.4	49	5.4
London and South-Eastern	41	1.6	140	4.8
Southern	13	1.9	26	3.6

Death rates were calculated for both sexes in 10-year age-groups from 35 years upwards in the two Welsh regions and in England. The increased mortality in Wales was apparent in all groups except men of 75 years and older (Table II). Social class could be established in only 329 cases, but so far as could be seen from these limited data deaths were distributed proportionately between classes (Table III).

TABLE II.—Total Death Rate from Post-cricoid Carcinoma in Different Age-groups, 1959-61 (Per Thousand Population)

Sex	Region	35-44	45-54	55-64	65-74	75+
Male	Wales II	0.022	—	0.019	0.111	0.071
	" I	—	0.030	0.018	0.050	—
	England	0.001	0.002	0.039	0.029	0.074
Female	Wales II	0.062	0.037	0.104	0.270	0.250
	" I	0.016	0.030	0.035	0.093	0.095
	England	0.008	0.027	0.042	0.056	0.049

TABLE III.—*Proportion of Occupied Population Age 35 and Over (1951 Census) and Deaths from Post-cricoid Carcinoma in Each Social Class*

	Total No.	Percentage of Population/Deaths in Social Class				
		I	II	III	IV	V
Population	18,627,716	3	19	48	17	13
Deaths	329	2	18	43	24	13

Discussion

The regional differences in deaths from post-cricoid carcinoma are particularly marked in females, in whom the disease is most common. The high incidence in Wales and the North-west and the low incidence in the Home Counties are similar to the pattern seen in both pernicious anaemia and gastric carcinoma (Payne, 1961). The similarity to carcinoma of the stomach is particularly close. The area of highest incidence of post-cricoid carcinoma (see Map) coincides closely to that of gastric carcinoma,

which comprises Caernarvon, Anglesey, Merioneth, Denbigh, and Cardigan (Stocks, 1958). The area of lowest incidence (see Map) includes Kent, Surrey, Sussex, Southampton, and the Isle of Wight, which are among the areas of lowest mortality from gastric growths (Stocks, 1958). Comparison between the crude death rates for the two types of carcinoma in females in the standard regions shows a significant rank correlation ($r = +0.90$; $P < 0.01$). Post-cricoid mortality is, however, also correlated with the general crude death rate in the standard regions ($r = +0.76$).

In males only, the number of deaths in the Wales II region is significantly higher than in the rest of the country. The lack of significant variation between other regions may be a consequence of the small numbers of deaths recorded, or it might reflect a difference in aetiology of the growth in the two sexes. The Paterson-Kelly syndrome, which is thought by many to be a precursor of post-cricoid carcinoma (Ahlbom, 1936; Owen, 1950), occurs predominantly in women, and its infrequency in men may account for the small number of male deaths.

There is no satisfactory explanation for the geographical variation in incidence of gastric and post-cricoid carcinoma or of pernicious anaemia in England and Wales. Stocks (1958) noted that those populations living in mountainous areas, where impervious rock was covered by only a thin layer of soil, had a high rate of gastric carcinoma, while "chalk" areas collected at the bottom of the scale. This

seemed to suggest that soil drainage might be an important aetiological factor, although the type of soil itself also tended to be of a specific character in the high cancer regions. Scott (1960) similarly noted a high incidence of pernicious anaemia in areas of volcanic rock. The suggestion that the high incidence of post-cricoid and gastric carcinoma in North Wales might be a racial trait is not supported by the observation that gastric carcinoma is as common among people of English parentage as those of Welsh parentage living in the same districts (Stocks, 1957).

Similarly, the varying incidence of gastric carcinoma and pernicious anaemia, both of which tend to be associated with blood group A, cannot be ascribed to regional variations in blood-group frequency (Payne, 1961).

Witts (cited by Scott, 1960) has suggested that the prevalence of pernicious anaemia might be related to the prevalence of unemployment during the 1930's with its consequent malnutrition, and Stocks (1958) has shown that carcinoma of the stomach increases in frequency from social class I (professional) to V (unskilled). The present small numbers of cases of post-cricoid carcinoma show no difference between the social classes.

There are many clinical associations within this group of conditions. The increased incidence of gastric carcinoma in patients with pernicious anaemia has been demonstrated by Kaplan and Rigler (1947), Mosbech and Videbaek (1950), and others. The occurrence of the Paterson-Kelly syndrome and post-cricoid carcinoma in patients with pernicious anaemia has also been noted (Jones and Owen, 1928; Brown, 1946; Jacobs, 1962). Out of 52 cases of the Paterson-Kelly syndrome examined in Cardiff in the last year two had gastric carcinomas and one had had a total gastrectomy for carcinoma 10 years previously.

A familial tendency is found in pernicious anaemia (Callender and Denborough, 1957; McIntyre *et al.*, 1959) and in gastric carcinoma (Koller, 1958). In the case of post-cricoid carcinoma evidence of familial predisposition is difficult to obtain because of the rarity of the growth, but Simpson (1939) recorded an interesting family of three sisters, one of whom had post-cricoid carcinoma, the second had a similar growth together with pernicious anaemia, and the third exhibited the Paterson-Kelly syndrome. Kruisinga and Huizinga (1959) reported two pairs of twins suffering from the "Plummer-Vinson" syndrome. It seems likely that a genetic factor plays some part in the onset of these conditions.

The clinical association of post-cricoid carcinoma with pernicious anaemia and gastric cancer is not obvious, because of its relative rarity. The present evidence of a similar geographical distribution of cases in England and Wales may indicate a common factor in their aetiology.

Summary

The mortality due to post-cricoid carcinoma in England and Wales during the years 1957-61 has been examined. Analysis into region, sex, age, and social class shows a high incidence in North and West Wales in both sexes and some regional variations in England in women. These variations are not apparently related to age or social class but are similar to the variations found in the incidence of pernicious anaemia and gastric carcinoma. Some clinical associations between these conditions are discussed.

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DETECTION OF INCOMPLETE ABLATION AFTER YTTRIUM-90 IMPLANTATION OF PITUITARY

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Now that implantation of the pituitary with radioactive material is being widely used, it is of interest and value to have some simple method of determining whether or not pituitary destruction has been complete. Until recently, estimation of urinary gonadotrophins has been considered to be the most reliable test of pituitary destruction (Notter, 1959), but unfortunately it is too sensitive a test of pituitary damage. As little as 50% destruction of the gland can result in failure of significant gonadotrophin secretion.

The experimental work of Ganong and Hume (1956) has demonstrated that secretion of thyrotrophin and corticotrophin continues even although a considerable proportion of the pituitary has been destroyed, and corticotrophin secretion may continue with as little as 5% of the gland left intact. Unfortunately neither of these hormones can be readily assayed direct nor are the methods very sensitive. An indirect estimate of thyrotrophin activity can be obtained by determining the 24- or 48-hour uptake of ^{131}I by the thyroid or by estimating the urinary excretion of ^{131}I and calculating the "T" index. Forrest *et al.* (1960) found that while the values for the T index correlated fairly well with the degree of pituitary destruction, values in the hypothyroid range could be obtained after necrosis of only 50% of the pituitary gland.

Impairment of adrenal function follows deficient secretion of corticotrophin. This may be detected clinically by finding that the patient has become cortisone-dependent, or on cessation of corticosteroids that the patient fails to excrete a water load adequately. The former is not objective enough, the latter non-specific; neither test separates the completely from the incompletely hypophysectomized patient sharply enough, and both put an undue strain on the patient. The latter criticism also applies to the measurement of urinary or plasma steroids after withdrawal of corticosteroid for at least 72 hours. In this test a rise in plasma or urinary steroid level at that time indicates a reserve of corticotrophin. This test can be shortened and the sensitivity possibly increased by administering metyrapone ("metopirone"; SU 4885), the adrenal 11β -hydroxylase inhibitor (Liddle *et al.*, 1959). The purpose of this paper is to show that the metyrapone test

is a satisfactory although indirect method of detecting residual pituitary activity, and that it is much more sensitive in this respect than the best direct means (Loraine, 1962), the estimation of human pituitary gonadotrophin.

Methods

The patients under investigation were admitted one week prior to ^{90}Y implantation of the pituitary. Twenty-four-hour specimens of urine were collected for three days, each collection starting at 6 a.m. On the second day metyrapone was administered every six hours in a dose of 750 mg. Four to six weeks after the implant had been done the patient was readmitted to hospital, 24-hour urine collections being made as before for a period of seven days. On the first day the patient generally continued with cortisone 37.5 mg. and in addition received 80 units of "cortrophin-Zn" intramuscularly in divided doses. Cortisone was discontinued on the second day and a further 80 units of cortrophin-Zn given. Three days were allowed to elapse between the administration of the corticotrophin and the metyrapone, which was given on the sixth day in the same dose as on the previous admission.

A second group of patients, who received no corticotrophin prior to the metyrapone test, were studied. Beta-methasone was given in a dose of 0.5 mg. b.d. for at least two days, then in a dose of 0.5 mg. the day before metyrapone, and stopped completely the day of, and the day after, metyrapone.

The urinary excretion of 17-hydroxycorticosteroids (17-OH-CS) was measured, using a modification of the method described by Appleby *et al.* (1955). In this method urinary 17-OH-CS are finally determined as 17-oxosteroids using the Zimmermann colour reaction. We feel that it is essential to do all the Zimmermann reactions from any one patient at the one time if small changes in steroid excretion are to be detected. Urinary gonadotrophins were measured by the method described by Loraine and Brown (1954).

Results

Patients with breast carcinoma (18), diabetic retinopathy (4), and acromegaly (2) have had pituitary function assessed before and after ^{90}Y implantation of the pituitary.

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