THE AETIOLOGICAL SIGNIFICANCE OF GEOGRAPHICAL VARIATIONS IN CANCER MORTALITY

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In a previous communication (Legon, 1951) it has been suggested that the areas of heaviest total cancer mortality in England and Wales are the areas of soils richest in organic matter, and that these heavy mortalities may be related to the micronutrient deficiencies that sometimes appear in crops grown on peat soils. The purpose of the present paper is to examine this hypothesis in the light of quantitative data on soils and of recently published work on plant copper metabolism.

Regions of Abnormal Total Cancer Mortality in England and Wales

Fig. 1 depicts the counties and groups of counties in which total cancer mortality is almost certainly abnormal. They are the counties that showed consistently high or consistently low mortalities for all cancer in the analyses of Stocks (1928) and Stocks and Karn (1931). It does not follow that the rest of England and Wales has a normal mortality, nor that the counties shown on the map have abnormal mortalities over the whole of their areas. All that can be deduced with certainty is that abnormal total cancer mortalities must prevail among a large proportion of the populations resident in the counties shown here, and that true regions of abnormal total cancer mortality exist in the general areas of these counties, but are almost certainly not coextensive with them.

FIG. 1.—The areas of abnormal total cancer mortality in England and Wales (see text). Small figures refer to soil samples (see Table I); these were obtained from the most populous agricultural parts of the areas when possible.

The areas may be described as follows, with details of mortality from cancer of particular sites based on the detailed studies of Stocks (1936, 1937, 1939):

High-mortality Areas.—H1: The high-mortality areas of the north-west. H1a: North Wales, including the counties of Anglesey, Caernarvon, Denbigh, Flint, Merioneth, and Montgomery. The total excess in this area results from a huge excess for gastric cancer and a smaller excess for intestinal cancer. Most other sites show deficiencies. H1b: Cheshire shows a large excess for gastric cancer, but several other sites have excesses. H1c: Cumberland shows markedly excessive mortality from intestinal cancer. H2: The high-mortality area of the Fenlands includes the counties of Ely, Huntingdon, Peterborough, and Lincoln (Holland). In this area all sites show excessive mortalities except the lung, the larynx, and the tongue, mouth, and jaw (as one site). H3: The London area of high mortality consists of the counties of London and Middlesex. Respiratory sites show marked excesses, while the stomach does not.

Low-mortality Areas.—L1: The low-mortality area of the south-west includes the counties of Radnor, Brecon, Hereford, Worcester, Gloucester, Glamorgan, Devon, and Dorset, and the Isle of Wight. Many sites show deficiencies. L2: The low-mortality areas of eastern England include the counties of (a) the North Riding, (b) Lincoln (Kesteven), (c) Norfolk and East Suffolk, and (d) Kent. Many sites show deficiencies.

Grouped under these two broad headings are areas of the most diverse physical and cultural landscapes; and this, together with the variations of site distribution, discourages the idea that common conditioning factors may underlie the variations in total cancer mortality. Nevertheless, it seemed that some association might exist between total cancer mortality and the organic content of the soil on which much of the vegetable food supply is grown. Thus the heavy rainfall of North Wales and Cumberland, together with their glaciated topography, is likely to give rise to water-logging and the accumulation of peat; and the high organic content of the original soil may well have been maintained by the dung of the large flocks of hill sheep kept in these areas. In Cheshire, a fairly heavy rainfall and a subdued relief have led to the formation of "mosses," considerable areas of which are now under cultivation; and large numbers of dairy cattle are kept in proportion to the arable acreage of the county. The four Fenland counties contain relatively large areas of peaty soils which have long been under cultivation, and which produce for the London market.

The low-mortality areas of the east are for the most part well drained, and their agriculture is largely arable, so that excessive dunging of cultivated land is improbable. The areas of peat that occur in Kesteven and Norfolk are small in proportion to the total arable area in either county. The low-mortality area of the south-west has conditions of good soil drainage in its populous cultivated parts, and it is probable that the "hungry" nature of the soil over much of the area may offset manuring from the strongly developed pastoral side of its agriculture.

Ignition-loss Test

Unfortunately, quantitative data on the organic contents of British soils are rare. I therefore obtained soil samples from as many of the areas as possible, and subjected them to an ignition-loss test similar to that described by Marbut (1935). The samples consisted of approximately 5 c.cm. of top soil from at least two arable fields, and were taken by local residents unaware of the ultimate objective of the survey.

The ignition-loss figure (Table I) includes loss of water not removed by the initial drying of the sample and the loss of carbon dioxide from calcium carbonate, in addition to the loss from the combustion of organic matter. Since none of the samples came from a clay area, variations in the

TABLE I.—Cultivated Soil Ignition-loss in the Areas of Abnormal Total Cancer Mortality

Area	County	Sample	Ignition-loss % Dry Weight	Remarks
H1a	Anglesey	1, 2	12.2, 10.6	Mixed samples from separate rural districts
	Caernarvon	3, 4	13.2, 12.1	No. 3 very slightly effervescent with HCl
	Denbigh	8, 7, 5	13.6, 12.7, 12.6	Mixed samples from separate rural districts
	Flint	6, 6A	7.3, 4.8	Rural districts of abnormally low gastric cancer mortality
	Merioneth	9	14.3	Mixed sample from one rural district
H2	Montgomery	10	10.8	
	Lincoln (Holland)	20	18.6	Highly effervescent with HCl. Peaty
	" "	21	10.6, 7.3	Non-peaty
L1	Radnor	11, 12	8.6, 8.7	Mixed samples from separate rural districts
	Hereford	13, 14	9.0, 7.1	Some effervescence with HCl
	Worcester	15	11.8, 4.2, 9.5, 7.9	
	Devon	16	11.8, 9.1	Highly effervescent with HCl
	I. of Wight	17, 18	7.1, 7.3	Mixed sample
L2a	N. Riding	19	10.2, 7.3, 5.9	
L2c	E. Suffolk	22	6.9	Mixed sample. Some effervescence with HCl

loss of water are probably not serious; and the cases in which loss occurred through the decomposition of calcium carbonate are indicated by the qualitative acid test. It would therefore seem that soils in the high-mortality area of North Wales are indeed rich in organic matter, and that soils of considerably lower organic contents are common in the low-mortality areas of the south-west, the North Riding, and East Suffolk.

Gastric Cancer Mortality and Soil Ignition-loss in North Wales Rural Districts

Fig. 2 shows the standardized gastric cancer mortality ratios (Legon, 1951) of the North Wales rural districts for which soil samples have been obtained. There seems to be a close association of mortality from gastric cancer with the ignition-loss of the soil except in the case of Aled Rural District.

TABLE II.—Gastric Cancer and Cultivated Soil Ignition-loss in North Wales Rural Districts

Mortality Ratio	Rural District	Ignition-loss % Dry Weight
Over 175	{ a. Hiraethog b. Penllyn	13.6 14.3
145-175	{ c. Gwrfai d. Ogwen e. Ruthin f. Twrcelyn	12.1 13.2 12.7 12.2
115-145	{ g. Aethwy h. Llanfyllin	10.6 10.8
85-115	{ i. Aled j. New Radnor	12.6 8.7
55-85	{ k. Knighton l. St. Asaph	8.6 7.3
Under 55	m. Overton	4.8

This association lends strong support to the view that the high gastric cancer mortality which exists in North Wales may be due to the high organic content of the soil over most of the area, and is fundamentally similar to the high mortalities from cancers of most sites that exist in the Fenlands; and that the difference in site-distribution between the two areas is a result of secondary factors—namely, specific gastric irritants that several writers have suggested exist in North Wales.

Discussion

The association of total cancer mortality with soil organic matter suggests that a carcinogen may exist in food plants grown on soils of high organic content, or, alternatively,

FIG. 2.—The rural districts are: a, Hiraethog; b, Penllyn; c, Gwrfai; d, Ogwen; e, Ruthin; f, Twrcelyn; g, Aethwy; h, Llanfyllin; i, Aled; j, New Radnor; k, Knighton; l, St. Asaph; m, Overton.

that a protective substance may be lacking in such plants. In view of the fact that copper deficiency sometimes occurs in crops grown on peat (although obvious copper-deficiency lesions have not been reported in England and Wales), brief reference may be made to copper metabolism.

Dawson and Nair (1950) have confirmed the power of soil organic matter to fix copper in a form that is unavailable to plants. It is probable, therefore, that plants and soil organic matter may compete for the copper present in the soil, and that the appearance of copper-deficiency diseases in crops is merely an extreme case.

Summary

It is suggested that the major geographical variations in cancer mortality in England and Wales are associated with variations in the organic content of cultivated soils,

and may be conditioned by micronutrient deficiencies in food plants grown on soils of high organic content; and that populations whose diets include vegetable foods grown on such soils may be subjected to the action of carcinogens, or may be deprived of protective substances.

I thank Mr. G. C. Worters for the original suggestion that total cancer mortality might be at a maximum on soils of high reducing power and at a minimum on well-oxygenated soils; and the General Register Office for granting access to unpublished statistical data. Most of the work on which the paper is based has been done during the tenure of a research studentship of the London School of Economics.

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BILATERAL GIANT RENAL CALCULI

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Giant renal calculi have not infrequently been described in the literature, but only four weighing over 1 kg. have been reported, Pohl's (quoted by Legueu, 1921) being 2,005 g. Although such calculi have been reported in one kidney, accompanied by a small calculus in the other, bilateral giant renal calculi are rare. Morrison (1921) described the case of a man aged 50 who had a left renal calculus weighing 1,130 g., together with a smaller one on the right side. Everett (1934) described an example in a woman aged 59, in whom the right kidney contained a calculus weighing 622 g., while the left contained one weighing 329 g. Gutierrez (1939) described three cases. A further case is reported below. It demonstrates the extraordinary adaptation of which the kidneys are capable, and seems to be the largest example of bilateral renal calculi yet recorded.

Case History

The subject was one of a family of eight children, of whom one died in infancy, another of pulmonary tuberculosis at 25 years, while the other five are alive and well. His father was a small farmer who died of old age at 88. His mother died at 83 from a fractured femur. He was apparently well and free from illness until 15, when he began to experience recurrent attacks of pain in the abdomen and back, occurring at intervals of three to five weeks and lasting sometimes up to 24 hours. He developed an aversion to sitting down, as this tended to bring on the pain. His preference for spending his time engaged in some such pursuit as carpentry, instead of performing his milking duties with the other sons, for a time earned him the disapproval of his family and the reputation of a malingerer. Eventually a doctor was consulted. He was admitted to hospital for a month, during which time he was symptom-free. On returning home his symptoms recurred. He learnt to ease his pain during attacks by riding on a bicycle over rough ground as hard as he could. He became a butcher and also kept a smallholding.

At the age of 27 a large stone and some smaller ones were removed from one kidney at Guy's Hospital. To his great disappointment, however, the symptoms recurred as soon as he returned home. Thereafter he eschewed medical advice as much as possible. As time went by the attacks of pain became less frequent, but he experienced bouts of haematuria, and episodes when his urine became foul-smelling and offensive, presumably being heavily infected. A constant dull aching pain in the back developed. From the age of 45 onwards he attended his doctor infrequently for episodes of haematuria and urinary infection. Further operative treatment was advised but refused. At the age of 61 his doctor attended him for a severe bout of haematuria and found him to have easily palpable and very hard kidneys. His blood pressure was 210/100; he was obviously anaemic, yet managed to do his work. X-ray examination revealed enormous bilateral renal calculi. He would consent to no

FIG. 1.—Radiograph showing large bilateral renal calculi.

further investigations, yet offered his kidneys for examination after his death. He experienced periods of sickness and headache, and usually had a brown furred tongue. He continued his work, smoking heavily and consuming a pint of beer daily until May, 1949, when, during a local influenza epidemic, he became ill with headache and a cough. After initial improvement he became drowsy and began to vomit; his urinary output fell, and he died 10 days after going off sick.

Specimens

The right kidney weighed 1,680 g. (see Fig. 2). It consisted of a thin shell of renal tissue covering an enormous coralliform calculus measuring approximately 19 by 10 cm. On hemisection, septa of renal tissue only 2 to 4 mm. in thickness were seen to extend down in between the stout processes of the stone. The renal tissue covering the stone varied from 1 to 3 mm. in thickness, except at those places from which the septa arose, where triangular areas of renal tissue were present, each having a base of approximately 1 cm. One ureter appeared to be a little thickened. The calculus was mostly white, was very hard, and resembled marble in appearance. In the lower part of what had once been the renal pelvis a central yellow and brown stone was present which appeared older than the rest. When freshly cut, laminations running parallel to the convex surfaces were visible throughout the calculus and fine radial markings were also apparent. Until cut the calculus was in one piece. The kidney (unfrozen) was clamped in a vice for cutting, a process which took about one hour with a hacksaw.