A SURVEY OF LEUKAEMIA IN CORNWALL, 1948-1959

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Dameshek and Gunz (1958), discussing the incidence of leukaemia, remark that "statistical data available at present are fragmentary and too incomplete to permit definite conclusions about the prevalence of leukaemia. There is, moreover, no evidence so far that could show conclusively that the rate of leukaemia has actually risen."

They cite three sources of information available: (1) hospital series, (2) analysis of death certificates, and (3) special investigations to study the morbidity—and say it is not permissible to deduce the true incidence of leukaemia from hospital data, for many factors enter into admission to hospitals. At present the incidence of leukaemia is usually deduced from the mortality figures of the Registrar-General, and in general these figures lack the information necessary for accurate classification. The assumption is made that leukaemia is a lethal disease and therefore the death-rate must be an accurate reflection of its prevalence. That this is true of chronic leukaemia may be accepted, and reference to older textbooks gives a clear picture of the natural history of the disease. But in acute leukaemia the situation is different. Tidy (1954) refers to acute leukaemia as occurring under the age of 20 and most frequently in young children, and he makes no reference at all to the acute form as it arises in old people.

It is my experience that older practitioners brought up on similar teaching do not recognize acute leukaemia except among the young. Dameshek and Gunz say that it is "at least possible that the disproportionate rise in leukaemia mortality in the older age-groups represents the 'leeway' which has to be made up before there are comparable diagnostic facilities for all ages and with them comparable numbers of diagnoses of leukaemia."

The striking tendency of leukaemia to occur in old people was demonstrated over a large series of cases by Gunz and Hough (1956). In 553 cases of their own they found 57% over the age of 50. (Acute cases comprised 60% of these, and 46% of them were over the age of 50.) In Gunz and Hough's experience in New Zealand the assumption that manifestations of the disease remain the same at whatever age it occurs is not justified, and they believe that leukaemia presents a more insidious and less easily recognizable onset in old people.

It seems, therefore, that indisputable evidence is still required to show whether the rapid rise in the annual incidence which has been claimed by many workers during the last two decades is actual or only apparent. It is most important to know whether a steady annual rise can be observed and whether such an increase, if it occurs, does so in all age-groups or only in the elderly. It appears that the West Cornwall clinical area, in spite of its small size, provides an ideal locus for a study of leukaemia as it is arising to-day.

Only those who have worked in rural areas over the past 10 to 15 years know how greatly the scene has changed in respect of medical diagnostic facilities.

Before 1945 there were few laboratories serving practitioners in rural areas; and it may be of value to describe the situation as it existed in Cornwall, because this is probably representative of the situation in rural areas elsewhere. Previous to 1936 there was no laboratory service at all; after the war the service grew rapidly, but blood counts still had to be paid for. In elementary form they were available for the well-to-do patients, but it is most unlikely that any haematological investigations were carried out on old or impecunious people whose anaemia was not gross and who could be accounted for as dying of heart failure or pneumonia. Chronic leukaemia was generally recognized, but the acute form, as an elusive, difficult-to-diagnose disease of the aged, was unknown. After "the appointed day" laboratories were increasingly thrown open and facilities for diagnosis became available for general practitioners. The first marrow puncture to be performed in Cornwall took place in 1946, when a case of acute aleukaemic leukaemia was diagnosed.

It is therefore apparent that no figures for leukaemia in Cornwall are even worth considering before 1948. The incidence of the disease after this date has been closely watched, and if the numbers are small it is at least believed that they provide an accurate cross-section of the disease as it has occurred in a rural area over the past 12 years.

Background

During the years 1948-52 it was noticed that the incidence of acute leukaemia was unexpectedly high in the central part of Cornwall, though for the county as a whole the incidence was about the same as that of the rest of England (0.5 per 10,000), and this localized increase was thought worth investigating.

Only the West Cornwall clinical area, which comprises that two-thirds of the county west of Liskeard, has been included in the survey, because patients from the eastern part of the county are generally referred to Plymouth.

Cornwall, in both its geography and its geology, presents features which may be important in surveying a disease suspected of an unusual distribution; it is a peninsula, almost separated from the mainland by moorland and by the Tamar river; the population was almost completely isolated in the past, and even to-day tends to remain within the county. It should be possible to study leukaemia here in people who have lived their whole lives in the same district and among the same surroundings as their parents and grandparents before them and to consider the disease in relation to the land on which they live.

Hewitt (1955) has called attention to a gradient in leukaemia mortality from a low level in the north of England to a higher level in the south, but very few records of a topographical nature have appeared in the literature on leukaemia. Clemmesen *et al.* (1952) examined the topographical distribution of leukaemia and Hodgkin's disease in Denmark over the period 1942-6, and these cases were plotted on a map but showed no significant pattern. Gauld *et al.* (1953) reported on the disease in the east of Scotland and found a predominance of the lymphatic type compared with most other published reports, but he was reporting on a hospital population. MacMahon and Clark (1956) have reviewed the disease as it appears in the Borough of Brooklyn, but it seems that no field survey of individual cases such as this has been made.

There is little doubt that leukaemia can under certain circumstances follow irradiation (Medical Research Council, 1956). It is known that local levels of radioactivity are high in Cornwall, and through the kindness of Dr. E. J. B. Willey a radiometric survey of the county was made and the relationship of irradiation to the geographical site of the cases compared. Though isolated pockets of high radioactivity occur, particularly on the granite areas of moorland, no obvious relationship with leukaemia could be found. St. Ives, a town with the highest local level of radioactivity, has a particularly low incidence, and this when part of the town's water supply is derived from an old uranium mine.

Geographical Distribution

It is convenient to divide the West Cornwall clinical area into two halves, providing two areas of equal population (approximately 116,000) for comparison. In the extreme west there were 81 cases, in the centre 130.

TABLE I.—*Leukaemia Morbidity in West Cornwall Clinical Area (Population 254,700), 1948–1959. Morbidity Rate per 100,000 West Cornwall Clinical Area=8.2 per 100,000 (11 Cases Surviving)*

District	Population	Incidence	Incidence per Annum per 100,000 Population
Bodmin	6,300	5	6.6
Camborne-Redruth	35,410	26	6.1
Falmouth	16,490	22	11.1
Fowey	2,320	8	28.8
Helston	5,830	4	5.7
Lostwithiel	2,020	1	4.1
Newquay	10,020	17	13.9
Padstow	2,890	2	5.8
Penzance	19,980	21	8.7
St. Austell	23,490	16	5.7
St. Ives	8,550	3	2.8
St. Just	4,020	7	14.5
Truro City	13,420	11	6.8
Truro R.D.	26,760	26	8.1
Kerrier R.D.	22,000	7	2.7
St. Austell R.D.	21,800	14	5.4
Wadebridge R.D.	15,860	5	2.6
West Penwith R.D.	17,540	16	7.6

As this difference between the two halves was more remarkable at the outset of the survey but has persisted to a less extent with improved diagnostic facilities, it is worth reporting. Table I shows the distribution of cases in the local authority areas.

Leukaemia is particularly uncommon in children in the western half, only two cases being recorded in 12 years; it is unlikely that the disease would be missed in a child, and so this deficit in a population of 116,000 is of interest. Three towns in the whole area show an incidence notably above the average; in Fowey 8 cases among 2,300 people seems excessive (one only of these was a short-time resident). In no rural district of comparable population was there any increase. In the larger towns the cases have been plotted on street maps, and, while coincidence can certainly not be ruled out, it appears worth recording cases which have been found living in close proximity. In one bakery two occurred within a few months—one acute myeloid, the other chronic. In each of two isolated villages two cases occurred in the same street and within a few yards of each other. In the town of 10,000 inhabitants (17 cases) where chronic lymphatic leukaemia predominates and local levels of radioactivity are low, two cases have occurred in opposite houses in the same street and two cases of reticulosarcoma were

diagnosed near by. Here, within a radius of a quarter of a mile, seven leukaemias have been diagnosed within the last 12 years. In Fowey, owing to its small area, the cases were necessarily living in close relation to each other. E. J. B. Willey (1960, personal communication) has studied the radiometric aspects of these cases, visiting the patients' houses, and has found that the readings were uniformly low.

Clinical Study of Leukaemia in Cornwall

In 12 years 211 (115 acute) cases of leukaemia have been observed, and recorded according to age, type, and situation. Table II shows the number of cases diagnosed each year, with division into types. Table III shows that 25% of the patients are under the age of 40 and 75% over this age. The maximum numbers occurred in the 60–70 age-group, but in considering the numbers in extreme old age the population at risk has to be considered; the chance of acquiring the disease is gradually increased, and is obviously related to an increasingly aged population. It may be that people are surviving long enough to develop the disease. It is interesting that the rate per 100,000 of the population (Table IV) is almost identical in acute myeloid and chronic lymphatic leukaemia over the age of 70.

In 1948 eight cases of severe anaemia were referred for investigation and proved to be acute leukaemias. These, which would have been unrecognized before the day of marrow biopsy, raised the annual acute incidence considerably in that year, and it was not till 1952 that so high a level was reached again. There is therefore

TABLE II.—*Annual Incidence of Leukaemia According to Type*

Year	Myeloid, Acute		Lymphatic, Acute		Myeloid, Chronic		Lymphatic, Chronic		Total
	Male	Female	Male	Female	Male	Female	Male	Female	
1948	3	5	0	1	4	1	3	2	19
1949	3	4	0	0	2	3	0	1	13
1950	2	1	0	1	1	3	2	5	15
1951	2	2	3	0	1	4	1	0	13
1952	4	3	2	4	1	2	0	2	18
1953	9	2	3	0	0	0	5	1	20
1954	4	6	1	1	4	4	2	1	23
1955	4	2	0	2	0	1	4	0	13
1956	3	3	2	4	2	3	1	0	18
1957	3	1	1	1	3	0	2	3	14
1958	3	2	3	1	4	2	2	3	20
1959	7	5	1	1	1	3	3	4	25
Total	47	36	16	16	23	26	25	22	211

Acute Leukaemia—Mean Age of Onset in Four-year Groups:

1948–1951	1952–1955	1956–1959
27 years	46 years	60 years

TABLE III.—*Incidence of Leukaemia According to Age and Type*

Age-group	Myeloid, Acute		Lymphatic, Acute		Myeloid, Chronic		Lymphatic, Chronic		Total
	Male	Female	Male	Female	Male	Female	Male	Female	
0–5	2	1	6	4	0	0	0	1	14
6–10	4	0	2	0	0	0	0	0	6
11–20	3	3	0	1	0	0	0	0	7
21–30	4	4	1	1	0	0	0	0	10
31–40	2	4	2	2	2	2	0	1	15
41–50	6	3	0	0	2	6	1	1	19
51–60	5	11	1	3	1	5	4	4	34
61–70	10	4	1	3	11	6	7	9	51
71–80	9	5	2	2	6	5	10	5	44
Over 80	2	1	1	0	1	2	3	1	11
Total	47	36	16	16	23	26	25	22	211

TABLE IV.—Incidence of Leukaemia (Rate per 100,000) According to Age

Age-group	Myeloid, Acute		Lymphatic, Acute		Myeloid, Chronic		Lymphatic, Chronic	
	Male	Female	Male	Female	Male	Female	Male	Female
0-5	15	8	45	31	0	0	0	8
5-10	34	0	17	0	0	0	0	0
11-20	12	14	0	5	0	0	0	0
21-30	17	17	4	4	0	0	0	0
31-40	9	17	9	8	9	8	0	4
41-50	26	12	0	0	8	23	4	4
51-60	25	45	5	12	5	21	20	17
61-70	65	19	7	15	72	29	45	44
71-80	96	38	21	15	64	41	106	38
Over 80	77	21	38	0	38	42	64	21

no evidence whatever in these figures that the incidence of leukaemia has increased over the last 12 years. There is reason to suppose that there may have been a diagnostic deficit from 1949 to 1951; but 1955 and 1957 seem to have been years of genuinely low incidence. The average number of leukaemias in West Cornwall is between 17 and 18 per annum in a population of approximately 254,000, or about 0.6 per 10,000.

Leukaemias classed as acute have had a life-history of less than a year after the onset, but it is often difficult to be sure how long some sort of ill-health preceded the moment of recognition. Typing of leukaemias is often difficult, and no great stress has been laid on this; acute myeloid and monocytic cases, and acute cases with myelosclerosis, have all been grouped as myeloid in the tables. Three cases diagnosed as acute plasmablastic leukaemia from their unusual and primitive morphology and confirmed at necropsy have also been put in this group, together with one erythroleukaemia and two acute erythremias. Lymphatic leukaemias and lymphosarcomata with a leukaemic blood picture and generalized lymphoid infiltration of the tissues have been put together.

Among the chronic myeloid leukaemias, myelosclerosis and haemorrhagic thrombocythaemia have been included as being closely related. The Chart shows the distribution of all the types encountered.

Incidence

Mean Age at Onset.—In chronic leukaemia the mean annual age at onset has remained much the same. In 1948 it was 60, and in 1959 it was still 60 years. There was a fluctuation between 56 years in 1950 and 74 in 1958. In the acute leukaemias a very different picture

emerges (Table II). In 1948 the mean age at onset was only 19 years, but it has steadily risen since, remaining round about 30 until 1953, when it rose abruptly to 61, and in 1957 reached a peak at 69. The mean age was reduced in 1956 and in 1959 by the occurrence of two leukaemias in children. Taken over the whole period this is a startling rise, reflecting the absence of leukaemia in young people in Cornwall.

Leukaemia in Childhood.—Up to 1954 two or three cases occurred annually in young children. Since then only two—one in a baby, the other in a boy of 9—have been discovered.

In other surveys (Hewitt, 1955) the peak incidence has been found at 3 years of age and in boys; here this peak (four out of six under 5 years) appears in girls but not in boys. The numbers are, however, too small to be statistically significant. They do, however, show that there is no evidence of an increase of leukaemia among children in Cornwall, and it may be that there is an actual fall. This finding, for what it is worth, is encouraging and would account for the fact that there is no annual increase in cases in spite of the absolute increase in incidence among old people.

Incidence in Relation to Retirement Age and Short Residence.—It may be objected that there is an undue proportion of retired people in some of these Cornish towns and that they tend to overweigh the numbers at risk in the population. Thirteen patients over the age of 55 had retired here, though all except three had been living here for five years, and some for a considerable time. This gives a non-Cornish element of retired people of 6% to be taken into consideration—but it has little effect on distribution except in Fowey, where the number might be reduced by two. If retirement is a factor, the highest figures would be expected in such towns as St. Ives, Falmouth, Penzance, and Fowey. Seven other younger patients may have lived in the county for less than five years; among these was a child whose parents were temporary residents. The short-term total is therefore not more than 10%. Visitors have been excluded from the survey.

Sex Incidence.—In common with other surveys a predominance of males has been most pronounced up to the age of 10. It does seem that women are more prone to develop leukaemia during the fifties and men to develop it later in life. Acute myeloid leukaemia shows a predisposition towards males, but chronic lymphatic leukaemia, usually predominant in males, does not show this tendency to any great extent in Cornwall.

Method of Diagnosis

Diagnosis was made by marrow puncture in 88 acute and 27 chronic cases. It was confirmed by necropsy in 25, but it is often difficult to carry out post-mortem examinations on people dying in rural areas. In 21 cases confirmation by other haematologists was obtained, and in seven the diagnosis was made by biopsy. In 75 cases (39 acute and 36 chronic) the diagnosis was obvious from the clinical findings and the peripheral blood picture, and possibly this number (35% of the total) represents the hard core of incidence which would have been reported at any time in the last 25 years and in the absence of any special diagnostic facilities. It is interesting that rather more acute than chronic cases were diagnostically obvious, but the latter group includes 11 myeloscleroses requiring confirmatory investigation, three haemorrhagic thrombocythaemias,

and some chronic lymphatic leukaemias seen in the pre-leukaemic stage.

Onset of Leukaemia

To prove that the diagnosis of leukaemia, particularly in its acute forms, is often not immediately obvious, the first blood counts received from these patients were studied. In 52 (24%) a firm diagnosis would not have been possible from a blood count alone, at least when the patient was first seen, and it is surprising that 22 of these were chronic cases. A general practitioner suspecting anaemia may be reassured by the result of a single blood examination and fail to ask for a further investigation, and this is particularly true in the case of the very acute leukaemia where death may occur before the haemoglobin level has fallen significantly. The speed at which death can take place in an acute leukaemia must have rendered diagnosis in such a case virtually impossible in the past. On one occasion a general practitioner was called for the first time to see an old man *in extremis*. A blood film only was taken; this showed numerous blast cells, but the patient was already dead by the time the report was received. Five cases were recognized only at necropsy; two of them had defied definite diagnosis and two of the patients had died suddenly. Failure to examine the tissues histologically in three of these cases would have resulted in the diagnosis being missed.

The haemoglobin level at first appearance is remarkably high (Table V): 45 cases showed a haemoglobin over 10 g., and three were recorded at over 15 g.; 68 fell between 7.5 and 10 g., and none were seen with a haemoglobin level under 3 g.

TABLE V.—*Haematological Findings with Clinical Signs and Symptoms in 95 Cases of Acute Leukaemia*

Clinical Findings	% Incidence	Haemoglobin g./100 ml.	% Incidence	Leucocytes/c.mm.	% Incidence
Haemorrhages, including petechiae and bruising ..	45	15+	1	800,000+	2
Infections ..	36	12-15	8	400-800,000	3
Malaise and general ill-health ..	30	10-12	9	300-400,000	4.5
Splenomegaly ..	24	8-10	18	200-300,000	4.5
Lymphadenopathy ..	16	7-8	30	100-200,000	8.5
Skin lesions ..	12	5-7	14	50-100,000	13
Loss of weight ..	11	4-5	12	20-50,000	18.5
		3-4	8	10-20,000	13
				5-10,000	14
				1-5,000	17
				<1,000	2

In only 69 (50 acute) of these patients was the total white count over 20,000, and in 31 acute cases it was under 10,000.

Presenting Symptoms.—The history was known in 90 acute cases. A complaint of increasing fatigue was usual and indeed the only significant symptom in 24 cases, and it would seem that the appearance of a few petechiae, bleeding from a mucous membrane, or recent onset of bruising, combined with a moderate degree of anaemia, is the most common presentation of acute leukaemia. In 39 cases some form of sepsis occurred, such as boils or gum or tonsillar lesions, and three were referred direct from a dentist. A recent history of herpes labialis was found in seven cases personally investigated. Examples of atypical presentation were as follows: dermatoses, suspected ovarian cyst, agranulocytosis, thrombocytopenic purpura, pernicious anaemia, nutritional anaemia, and cases discovered on routine pre-surgical examination.

Past History.—In all cases seen after 1954 past illnesses, injuries, and x-ray status have been studied. Only 10 of the cases had been previously x-rayed; two of these had had intravenous pyelograms and two or three cholecystograms. Three had been to a mass x-ray unit. It seemed that a history of gall-stones was unduly common, but this may be discounted in that gall-stones are unduly common in Cornwall anyway. Thirteen patients had had pneumonia some time before the onset, and at least 20 dated the beginning of their illness at some febrile illness, usually called "flu." Skin lesions were associated with the onset in 10 cases. Once only was there a familial incidence, when a mother and son developed subacute lymphatic leukaemia within six months of each other. This compares with Guasch's (1954) incidence of 0.5%.

Prodromal Period in Acute Leukaemia.—In 57 cases it was possible to assess the time interval between the patient's first complaint and the diagnosis of the fully developed disease. In 11 cases it was 14 days or less, in 20 between two and six weeks, in 20 between two and six months, and in 6 there had been complaints of ill-health for two to three years. Six were seen in the pre-leukaemic stage, and a firm diagnosis was possible only after several months.

Radiology and Leukaemia

Following the work of Stewart *et al.* (1956) an inquiry into the x-ray status of the mothers of the leukaemic children was made. At the West Cornwall Hospital between 1942 and 1950, 391 pregnant women had abdominal radiographs; in addition there were 122 pelvimetries. These investigations have now been reduced to one or two annually.

At the obstetric centre at Redruth a survey has been made of all pregnant women undergoing x-ray examination between 1948 and 1959. Records of 1,175 women were scrutinized and 200 pelvimetry estimations were noted. No mother of a leukaemic child has been found in either investigation. The mother of one leukaemic child had had an abdominal x-ray examination, not in the pregnancy but in a previous one, and that child is healthy.

Investigations into the x-ray status of the mothers of the 20 leukaemic children showed that one only, an elderly primipara, had had a straight abdominal x-ray examination in the 35th week of the pregnancy.

Economic Background

Witts (1957) refers to leukaemia as more common in the rich than in the poor, in whites than in non-whites; this can be explained, at least in part, on the grounds that previously only the well-to-do could afford or even obtain the investigations necessary for making the diagnosis of an acute aleukaemic leukaemia. Study of the economic background of our series does not show any marked economic gradient. In all there were 20 cases in social group 1. Half of these were not Cornish, and some were comparatively recent residents. Thus an average of less than 2 per annum, or 10%, hardly justifies belief in a high economic gradient. On the other hand, most of the patients were comfortably housed and well fed in the Cornish manner; many were small farmers and agricultural workers, and if good nutrition predisposes to this disease there is nothing here to contradict that.

Notification to the Registrar-General

Death-certificate notifications were compared with clinical diagnoses in the western half of the area. There was a discrepancy of at least 11%, but this was largely cancelled out by five false-positive and four false-negative notifications. This investigation needs to be done on a larger scale, but it does not seem that any significant revision would have to be made.

Discussion

There is no evidence here to show that the incidence of leukaemia has increased during the past 12 years in Cornwall, but there may be some evidence that it is becoming less frequent in the very young. This is in accordance with the opinion of Gilliam and Walker (1958), who said that "presently evident trends in death rates from leukaemia offer no support for a theory that leukaemogenic factors in the American environment have increased sharply within the last 15 years." The disease is now more often diagnosed among the aged, and the mean age at onset shows a steady rise during the period 1948-59. It is argued that this is due to an increasing awareness of acute leukaemia as a disease of old people. Better facilities for diagnosis have resulted in the more frequent discovery of acute leukaemia at all ages over 50, and these facilities first became operative about 1948.

Poverty seemed to have no part in the aetiology of the disease. Saxton *et al.* (1944) showed that underfeeding of mice reduced the incidence of spontaneous leukaemia from 65% to 10%, and Engelbreth-Holm (1954) says that the restriction of calorie intake reduces the incidence of other spontaneous tumours besides leukaemia. The appearance of leukaemia in the well-nourished in Cornwall seems to support the experimental evidence.

There is no significant evidence here that x-ray films taken during pregnancy have been associated with leukaemias developing in children. Nor is there any evidence that high local levels of radioactivity associated with granite outcrops in Cornwall have any influence on the disease.

It may be that the type of leukaemia shows a variation in different parts of the country (cf. East Coast of Scotland), and further surveys of this kind might add to our information.

Summary

A survey has been made in Cornwall to determine the pattern of leukaemia as it is occurring in a localized area with a static population, and also to decide whether there is any evidence of an absolute increase in its incidence.

The influences which determine accuracy of diagnosis have been considered; past failure to recognize leukaemia as a disease of the aged probably accounts for the increasing notification of cases among the elderly. Improved laboratory diagnostic facilities play a part in the increasing accuracy of diagnosis.

The geographical distribution of the cases has been studied; there is a tendency to find tiny foci of victims living in close proximity but no significant predominance in any particular district.

In spite of improved facilities no evidence of an increasing incidence has been found in Cornwall since 1948. The possibility that the disease is becoming less common in children is suggested.

There is, on the other hand, clear evidence that the average age incidence of reported cases has increased steadily over the period.

The economic background of the patients is good.

Possible influence of leukaemogens on the incidence has been studied with particular reference to local radio-metric levels, which are high, and also to the irradiation of mothers during pregnancy. No significant relationship has been found.

The accuracy of notification of the disease to the Registrar-General has been investigated in a small population and has been found to be reasonably accurate, but there is no means of knowing how often the diagnosis of acute leukaemia has been missed in the past.

My thanks are due to Mr. J. W. Walker, chief technician at the West Cornwall Hospital, for tireless assistance in a laborious work; to Dr. E. J. B. Willey, who spent countless hours making a radiometric survey of Cornwall; to the staff of the x-ray department of the Camborne-Redruth and Penzance Hospitals for producing large numbers of records; to Dr. E. R. Hargreaves and his staff at County Hall, Truro, for much help; to Dr. W. R. S. Doll, of the Medical Research Council Statistical Unit, for criticism and advice; and to all the doctors, too numerous to mention, who kindly reported their cases of leukaemia to me. The expenses were defrayed by the Research Committee of the South-western Regional Hospital Board.

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World Health Day this year was devoted to malaria and to the world-wide campaign to eradicate the disease from which Great Britain herself only began to be free about 100 years ago. The Venerable Bede's *Historia* records a case in the Fens district as early as the seventh century, and a tertian ague was said to have killed James I in 1625 and Oliver Cromwell in 1658, and to have attacked Charles II. That there was malaria in Kent and Essex was common knowledge in Charles Dickens's day: Pip in *Great Expectations* says to the shivering convict: "You've been lying out on the meshes, and they're dreadful aguish." Other marshy areas in which agues were common were the Cambridgeshire and Lincolnshire Fens, the marshes of the Thames Estuary, of Romney and Pevensey, and of Bridgewater near the Bristol channel. In 1850 and 1860 between 12 and 60 per 1,000 admissions at St. Thomas's Hospital were for ague. In 1862 the building of the Thames Embankment meant draining and reclaiming land at the river margin, and by 1864 the disease was rapidly disappearing after at least twelve centuries. (From Dr. Harold Scott's *History of Tropical Medicine*.)