ADULT LEUKAEMIA

TRENDS IN MORTALITY IN RELATION TO AETIOLOGY

BY

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Variations in the mortality attributed to leukaemia throughout the world have been reviewed by the World Health Organization (1955) and by Clemmesen and Sørensen (1958). For all countries for which figures are available, the data agree in showing that: (1) the crude death rate has increased steadily over the past 30 to 40 years; (2) the male death rate has invariably been greater than the female rate, though never as much as twice as great; and (3) the death rate after being relatively high in the first five years of life falls to a minimum between the ages of 20 and 34 years and then rises again at age 35 years and above; in all countries but Japan the peak mortality in old age has been substantially higher than the peak in childhood.

There are, however, considerable differences between countries in the level of the death rate. Thus the crude rates have been highest in Denmark and the U.S.A. and lowest in Eire and Japan; in 1950–2, for example, the Danish rate for males was 73 per million, the rate in the U.S.A. was 71 per million, and those in Eire and Japan 35 and 20 per million respectively. The rate in England and Wales was intermediate at 49 per million. The differences are not due to variations in the age distributions of the populations, since the differences between death rates standardized for age are even greater (Registrar-General, 1958).

Since 1950 some countries have classified leukaemia deaths into several categories, according to the recommendations made in the *International List of Causes of Death* (Sixth Revision). The Registrar-General (1958) has reviewed the data for England and Wales and published separate data for the mortality by sex and age and for the trend in mortality with time for (*a*) lymphatic leukaemia, (*b*) myeloid leukaemia, (*c*) monocytic leukaemia, and (*d*) acute leukaemia of unspecified type. These data show substantial differences between the different types. The most striking is that the age distribution in both lymphatic and acute unspecified leukaemia is bimodal, with sharp maxima in early childhood and in old age, whereas the rates for myeloid and monocytic leukaemia increase slowly with age and at no period fall much below the level recorded for the first five years of life. In contrast the trend in mortality since 1950 is similar for all types. At the age of 15 years and above, the mortality of each type has increased, whereas below this age it has remained stationary.

The classification used in the *International List* failed, however, to distinguish between the acute and the chronic forms of the disease; this is unsatisfactory, as there is reason to suppose that some of the factors concerned in the causation of the two clinical types may be different.* There is, for example, no evidence to implicate ionizing radiations as a cause of chronic lymphatic leukaemia, although they may cause acute leukaemia and, perhaps to a less extent, chronic myeloid leukaemia. The distinction between chronic lymphatic, chronic myeloid, and acute leukaemia can, moreover, be made by cytological examination with some confidence, whereas the distinction between the various types of acute leukaemia is less certain and differences of opinion about the correct cytological classification of individual cases are common. Hospital data suggest that the proportion of acute cases diminishes steadily with age, that the mortality from both types of chronic leukaemia rises progressively from childhood, and that the bimodal form of the age distribution is confined to the acute cases (MacMahon and Clark, 1956).

It was thought, therefore, that information of interest might be obtained if the national data could be recast to show trends in mortality for (*a*) chronic lymphatic leukaemia, (*b*) chronic myeloid leukaemia, and (*c*) all forms of acute leukaemia grouped together. An opportunity to do this was provided by the Registrar-General of England and Wales when he extracted information from the records of all persons certified as dying from leukaemia between 1945 and 1957 and made it available to the Medical Research Council for the purposes of another investigation. It has been possible to use this information to reclassify the cases and to calculate separate mortality rates for the acute and chronic forms of the disease. The present paper relates to the data that have been obtained for adults aged 15 years and above. The trends in mortality in childhood have been discussed in detail elsewhere (Hewitt, 1955; Burnet, 1958).

Results

Full information about the clinical and cytological types of the disease is not provided with all death entries; the cases were therefore initially classified into the following nine groups: (1) acute lymphatic leukaemia; (2) chronic lymphatic leukaemia; (3) lymphatic leukaemia of unspecified clinical type; (4) acute myeloid leukaemia; (5) chronic myeloid leukaemia; (6) myeloid leukaemia of unspecified clinical type; (7) acute leukaemia of other and unspecified cytological types, including monocytic leukaemia and erythroleukaemia; (8) chronic leukaemia of unspecified cytological type; and (9) leukaemia not otherwise described.

Deaths attributed to plasma-cell leukaemia have been excluded, as it was thought that they ought to be classified with multiple myeloma.

Male death rates from each of these categories of leukaemia are shown in Tables I, II, and III for the three periods 1945–9, 1950–4, and 1955–7. In each period the rates are shown separately for five-year age groups from 15–19 years to 80 years and over. Since 1950 the Registrar-General has inquired about the cytological type whenever this has been omitted from the initial certificate, and it will be seen that the proportion of deaths attributed to "leukaemia," without further specification, has fallen substantially. The proportion of deaths attributed to lymphatic leukaemia or to myeloid leukaemia, in which the description of

*The classification has been modified in the seventh revision of the List and has been used by the Registrar-General of England and Wales for all leukaemic deaths occurring since the end of 1957.

TABLE I.—*Male Death Rate from Leukaemia per Million Living, England and Wales, 1945–9; Subdivided by Age and by Type of Leukaemia*

Age (Years)	Acute Lymphatic	Chronic Lymphatic	Unspecified Lymphatic	Acute Myeloid	Chronic Myeloid	Unspecified Myeloid	Other and Unspecified Acute Leukaemia	Unspecified Chronic Leukaemia	Unspecified Leukaemia	Total Leukaemia
15–	5·97	0·27	2·44	5·70	0·41	1·36	5·15	0·13	2·58	24·01
20–	2·65	0·25	1·39	2·65	0·88	2·39	5·03	0·25	1·26	16·75
25–	1·93	0·12	1·33	3·26	1·33	1·69	3·64	0·00	0·97	14·27
30–	1·74	0·37	2·24	5·97	1·99	3·98	3·97	0·13	1·61	22 00
35–	1·63	0·93	1·17	4·20	1·86	5·60	3·97	0·00	2·33	21·69
40–	1·59	1·22	2·44	4·88	2·56	5·49	6·96	0·12	1·22	26·48
45–	2·54	1·83	6·21	5·93	3·67	6·07	7·62	0·28	3·53	37·68
50–	3·98	4·15	7·47	4·65	3·65	8·30	8·31	0·17	5·48	46·16
55–	3·15	7·78	14·83	6·86	3·15	9·64	8·15	0·55	7·97	62·08
60–	5·34	12·59	21·56	6·62	5·34	14·30	8·32	1·07	12·38	87·52
65–	4·62	16·69	21·06	7·70	13·10	15·15	8·22	0·52	11·81	98·87
70–	6·56	15·88	29·71	4·49	8·98	14·85	8·98	1·38	12·78	103·61
75–	7·59	17·52	28·62	3·50	8·76	18·11	6·43	1·75	9·93	102·21
80+	4·73	13·24	11·35	2·84	1·89	8·51	4·73	0·00	8·51	55·80
All ages 15 yrs. +	3·22	3·94	7·25	4·98	3·18	6·43	6·06	0·31	4·29	39·66

TABLE II.—*Male Death Rate from Leukaemia per Million Living, England and Wales, 1950–4; Subdivided by Age and by Type of Leukaemia*

Age (Years)	Acute Lymphatic	Chronic Lymphatic	Unspecified Lymphatic	Acute Myeloid	Chronic Myeloid	Unspecified Myeloid	Other and Unspecified Acute Leukaemia	Unspecified Chronic Leukaemia	Unspecified Leukaemia	Total Leukaemia
15–	7·02	0·00	2·39	9·26	0·30	2·39	4·92	0·00	0·75	27·03
20–	4·72	0·29	2·57	5·86	1·00	2·43	4·29	0·00	0·00	21·16
25–	3·17	0·13	1·40	6·60	1·78	2·92	4·45	0·00	0·38	20·83
30–	2·62	0·50	1·12	5·49	2·49	2·74	3·86	0·00	0·37	19·19
35–	3·08	0·77	1·54	7·70	3·33	4·62	6·03	0·26	0·64	27·97
40–	3·00	1·08	2·04	8·75	3·83	5·88	6·84	0·00	0·84	32·26
45–	3·78	3·27	5·05	9·71	5·05	7·32	8·08	0·00	1·14	43·40
50–	4·39	6·29	8·05	9·66	5·56	8·78	6·28	0·00	1·90	50·91
55–	5·55	12·72	14·87	11·11	7·52	13·26	9·68	0·54	3·58	78·83
60–	7·75	20·33	21·37	14·04	11·11	18·86	14·04	0·21	4·19	111·90
65–	8·43	31·68	31·68	17·88	15·84	24·78	17·63	0·26	5·62	153·80
70–	7·78	33·15	35·52	15·56	19·96	27·74	12·18	0·68	5·41	157·98
75–	10·58	44·44	38·62	12·70	20·11	26·46	13·23	1·58	8·47	176·19
80+	3·30	36·30	34·65	18·15	9·90	23·93	10·73	2·47	2·48	141·91
All ages 15 yrs. +	4·74	7·54	8·75	9·48	5·51	8·70	7·47	0·19	1·63	54·01

TABLE III.—*Male Death Rate from Leukaemia per Million Living, England and Wales, 1955–7; Subdivided by Age and by Type of Leukaemia*

Age (Years)	Acute Lymphatic	Chronic Lymphatic	Unspecified Lymphatic	Acute Myeloid	Chronic Myeloid	Unspecified Myeloid	Other and Unspecified Acute Leukaemia	Unspecified Chronic Leukaemia	Unspecified Leukaemia	Total Leukaemia
15–	7·56	0·41	1·22	8·78	0·24	2·20	8·55	0·00	0·49	29·45
20–	6·10	0·00	0·99	7·80	1·46	1·95	5·87	0·00	0·73	24·90
25–	2·92	0·67	0·67	6·52	2·47	2·92	5·18	0·00	0·22	21·57
30–	3·32	0·21	1·24	7·26	2·28	2·69	5·80	0·00	0·42	23·22
35–	2·41	0·88	1·76	9·45	5·71	2·85	5·51	0·00	0·44	29·01
40–	3·33	3·12	1·67	10·81	3·74	6·86	7·28	0·00	0·21	37·02
45–	5·94	4·51	3·69	12·09	5·54	6·15	6·77	0·00	1·23	45·92
50–	4·21	6·21	4·88	13·75	8·20	7·76	8·65	0·22	1·11	54·99
55–	5·71	14·69	9·53	19·31	8·43	11·98	12·80	0·00	1·09	83·54
60–	9·57	25·64	16·61	19·14	17·09	19·49	18·47	0·34	2·74	129·09
65–	10·54	35·44	31·65	24·47	17·29	22·37	16·04	0·42	5·91	164·13
70–	11·74	48·65	40·27	36·91	26·84	33·00	25·73	0·57	7·27	230·98
75–	13·81	69·07	47·29	35·39	39 64	33·68	28·52	1·73	6·04	275·17
80+	10·95	83·04	54·95	21·94	40·29	25·64	25·72	2·46	8·53	273·52
All ages 15 yrs. +	5·72	10·69	8·25	13·44	7·89	8·72	9·83	0·16	1·53	66·23

TABLE IV.—*Estimated Male Death Rates from Chronic Lymphatic Leukaemia, Chronic Myeloid Leukaemia, and Acute Leukaemia, per Million Living, England and Wales, 1945–9, 1950–4, and 1955–7; Subdivided by Age*

Age (Years)	Chronic Lymphatic Leukaemia			Chronic Myeloid Leukaemia			Acute Leukaemia		
	1945–9	1950–4	1955–7	1945–9	1950–4	1955–7	1945–9	1950–4	1955–7
15–	0·5	0·0	0·5	0·6	0·4	0·7	22·9	26·6	28·2
20–	0·5	0·4	0·0	1·8	1·4	1·8	14·5	19·4	23·1
25–	0·2	0·2	0·8	2·0	2·4	3·3	12·1	18·2	17·5
30–	0·9	0·7	0·3	3·3	3·4	3·0	17·8	15·1	20·0
35–	1·5	1·2	1·4	4·0	5·1	6·9	16·2	21·8	20·8
40–	2·4	1·7	3·9	4·8	5·8	5·5	19·3	24·8	27·6
45–	5·0	5·8	6·3	6·8	7·8	7·7	25·9	29·9	32·0
50–	9·1	11·5	9·4	8·4	9·1	11·5	28·7	30·3	34·1
55–	22·5	24·5	21·8	7·3	13·7	12·2	33·3	40·6	49·5
60–	33·2	37·3	38·8	14·0	20·3	27·0	40·3	54·3	63·3
65–	38·0	59·0	62·4	26·0	28·6	27·7	34·9	66·2	74·1
70–	43·2	64·6	84·1	22·1	37·1	42·3	38·4	56·4	104·6
75–	42·8	80·6	112·1	24·7	38·7	59·3	34·7	56·9	103·8
80+	25·5	71·3	137·6	6·2	19·2	59·5	24·1	51·4	76·4
All ages 15 yrs. +	9·1	13·4	16·5	6·5	9·1	11·5	24·0	31·5	38·2

the clinical type is omitted, has also fallen, and it is necessary to take both these changes into account before the trend in mortality for the various types can be assessed. From the Tables it is seen that in each period the ratio of chronic to acute cases increases sharply with age, and it is reasonable to assume that at the younger ages the great majority of cases described as, say, lymphatic leukaemia were really of the acute type, whereas at ages 55 years and over the majority were probably chronic. The most reasonable assumption is that the proportions of acute and chronic cases among those in which the type was not described were, at each age, the same as the proportions among those in which the type was described.

For example, in 1945–9 at ages 15–19 years, the ratio of the death rates attributed to acute and chronic lymphatic leukaemia was 5.97 to 0.27. The death rate attributed to unspecified lympatic leukaemia was 2.44 per million, so that it is assumed that a further $\frac{5.97}{0.27+5.97}\times 2.44$ per million should have been described as acute leukaemia and $\frac{0.27}{0.27+5.97}\times 2.44$ per million as chronic leukaemia. The estimated rates for acute and chronic lymphatic leukaemia then become 5.97+2.33 (i.e., 8.30 per million) and 0.27+0.11 (i.e., 0.38 per million) respectively. Similarly, the estimated rates for acute and chronic myeloid leukaemia become 6.97 and 0.50 per million. Very few deaths were attributed to chronic leukaemia of unspecified cytological type (0.13 per million men in this age group during this period). If it is assumed that they were distributed between chronic lymphatic and chronic myeloid leukaemia in proportion to the estimated death rates for these two conditions, the rate for chronic lymphatic leukaemia becomes $0.38+\frac{0.38}{0.38+0.50}\times 0.13$ (i.e., 0.44) per million and the rate for chronic myeloid leukaemia becomes $0.50+\frac{0.50}{0.38+0.50}\times 0.13$ (i.e., 0.57) per million.

Finally, it is necessary to make some assumption about the true classification of those deaths certified as due to leukaemia without qualification. The rate attributed to this category of leukaemia was 2.58 per million. It has been estimated that, apart from these deaths, the rates attributable to chronic lymphatic, chronic myeloid, and acute leukaemia were 0.44 per million, 0.57 per million, and 20.42 per million (8.30 acute lymphatic, 6.97 acute myeloid, and 5.15 other and unspecified acute leukaemias). If the unspecified deaths were distributed in the same proportions the best estimates of the mortality attributed to the three selected types of leukaemia at ages 15–19 years become 0.50, 0.64, and 22.87 per million respectively. These may be compared with the uncorrected rates, derived from the deaths specifically attributed to these types of leukaemia on the death entries, of 0.27, 0.41, and 16.82 per million. The best estimates of the age-specific male rates for the three selected types of leukaemia in the three periods 1945–9, 1950–4, and 1955–7 are shown in Table IV and the trends in mortality are illustrated in Figs. 1 and 4.

From Fig. 1 it is seen that between 1945–9 and 1955–7 male mortality from leukaemia has increased at all ages. Below the age of 60 years the increase has been of the order of 25%, but at age 70 years and above the rate has more than doubled.

All three types of leukaemia have participated in the increase at the older ages (Table IV and Figs. 2, 3, and 4). At ages under 60 years the increase has been largely confined to acute leukaemia, although there has also been some slight increase in chronic myeloid leukaemia.

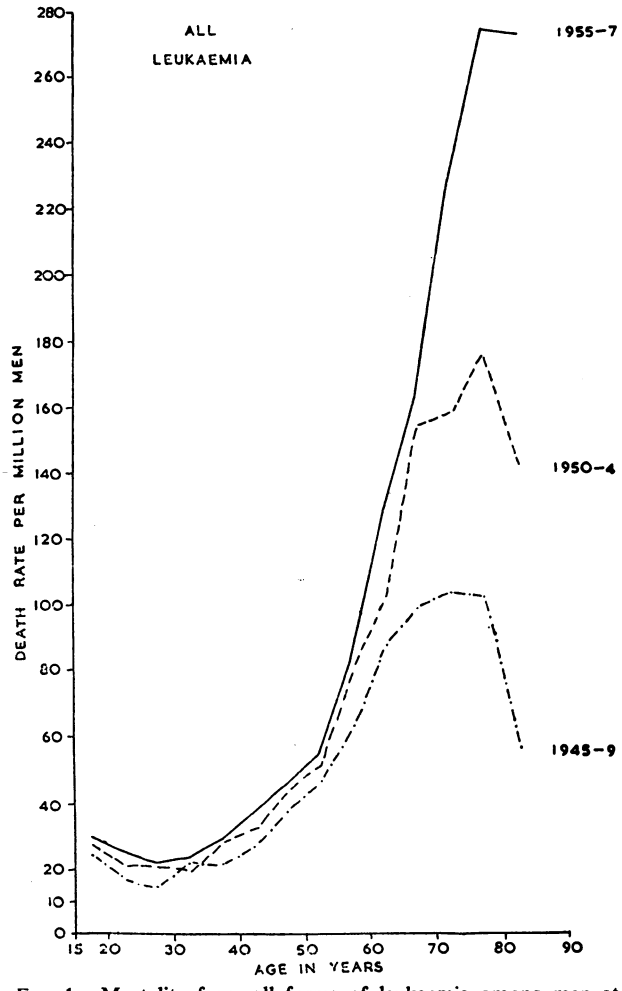

FIG. 1.—Mortality from all forms of leukaemia among men at different ages (from 15 years upwards) in England and Wales in 1945–9, 1950–4, and 1955–7.

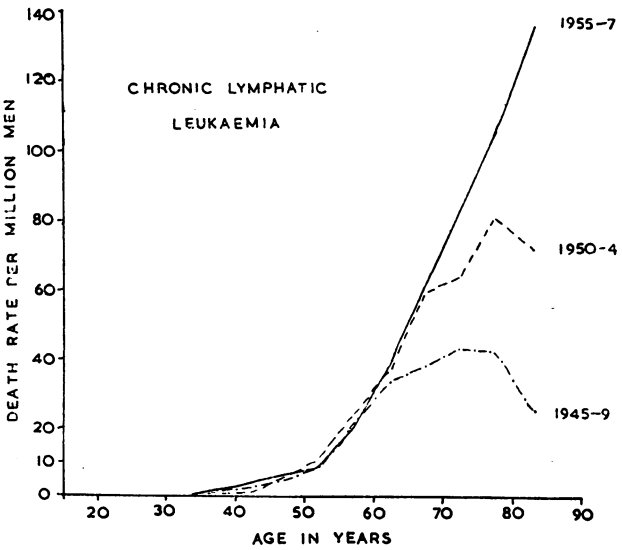

FIG. 2.—Estimated mortality from chronic lymphatic leukaemia among men at different ages (from 15 years upwards) in England and Wales in 1945–9, 1950–4, and 1955–7.

The estimated mortality from chronic lymphatic leukaemia at these ages has remained practically constant.

The change in mortality with age differs sharply between the various types of the disease. With chronic lymphatic leukaemia the estimated number of deaths below the age of 30 years is so small that it is not possible to recognize any particular relationship, but above this age the mortality increases rapidly, and in the latest period the increase continues into the oldest age group. In this period, it may be noted that between the ages of 30 and 80 years the estimated mortality increases approximately in proportion to the sixth power of the age. With chronic myeloid leukaemia the estimated mortality increases with age from 15 years upwards, and the mortality increases approximately in proportion to the third power of the age.

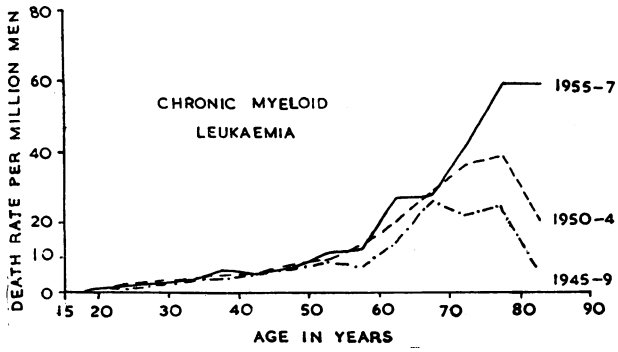

FIG. 3.—Estimated mortality from chronic myeloid leukaemia among men at different ages (from 15 years upwards) in England and Wales in 1945–9, 1950–4, and 1955–7.

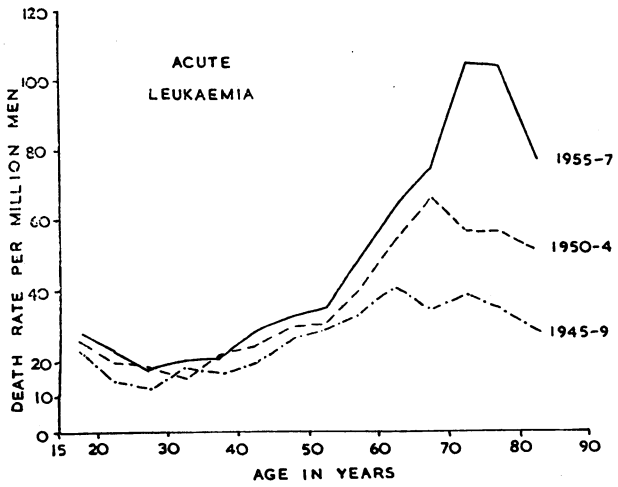

FIG. 4.—Estimated mortality from acute leukaemia among men at different ages (from 15 years upwards) in England and Wales in 1945–9, 1950–4, and 1955–7.

With acute leukaemia the general shape of the curve relating mortality to age is different. The mortality falls from age 15–19 years to a minimum at about 25–29 years and then increases slowly to a maximum at ages 70–74 years. Between the ages of 45 and 74 years, when the rate of increase is greatest, the estimated mortality increases approximately in proportion with the age to the power of 5/2. This rate of increase is slightly slower than that recorded for chronic myeloid leukaemia and is clearly distinguished from the rate of increase observed for chronic lymphatic leukaemia.

Death rates among women have been calculated in the same way as the rates shown for men in Tables I, II, and III. The total female mortality from leukaemia and estimates of the rates attributable to chronic lymphatic, chronic myeloid, and acute leukaemia are shown in Table V for the three periods 1945–9, 1950–4, and 1955–7. The increase in mortality among women has been slightly less than among men during the last few years, so that the sex ratio for all types at all ages has increased from 1.2 to 1 to 1.5 to 1. The trends in mortality with time and the relationships between mortality and age are, however, similar in both sexes. The only exception is that among women there is no evidence of an increase in the mortality attributed to chronic myeloid leukaemia below the age of 60 years.

It is striking that at most ages the sex ratio has a distinctive value for each of the three types of leukaemia studied. In the latest period the crude ratio for chronic lymphatic leukaemia was 2.0 to 1, for chronic myeloid leukaemia it was 1.2 to 1, and for acute leukaemia it was 1.4 to 1. All the ratios have increased since 1945–9, but they have maintained the same hierarchical order.

Sources of Error

It has been possible to calculate separate mortality rates for chronic lymphatic, chronic myeloid, and acute leukaemia only by making the assumption that, at each age and at each of the periods studied, the cases of leukaemia which were incompletely specified were, in fact, distributed among the three types in the same proportions as the cases in which the type was given. If this is not so, the data in Tables IV and V will be inaccurate and the conclusions based on them correspondingly weakened. The proportion of cases

TABLE V.—*Estimated Female Death Rates from Chronic Lymphatic Leukaemia, Chronic Myeloid Leukaemia, and Acute Leukaemia per Million Living, England and Wales,* 1945–9, 1950–4, *and* 1955–7 *; Subdivided by Age*

Age (Years)	Chronic Lymphatic Leukaemia			Chronic Myeloid Leukaemia			Acute Leukaemia			Total Leukaemia		
	1945–9	1950–4	1955–7	1945–9	1950–4	1955–7	1945–9	1950–4	1955–7	1945–9	1950–4	1955–7
15–	0·0	0·0	0·0	0·4	0·4	1·3	16·3	16·7	15·8	16·7	17·1	17·0
20–	0·9	0·2	0·0	1·0	2·1	0·0	10·8	12·3	14·9	12·7	14·6	14·9
25–	0·4	0·4	0·3	2·4	1·7	2·9	10·1	13·5	17·3	12·9	15·6	20·5
30–	0·5	0·5	0·0	3·7	2·5	1·5	13·0	13·2	17·0	17·1	16·3	18·5
35–	0·8	1·3	0·3	3·5	3·9	3·2	16·7	16·5	17·6	20·9	21·7	21·1
40–	2·3	1·7	1·4	6·0	4·6	6·9	16·0	24·6	21·5	24·3	30·9	29·8
45–	3·8	2·2	2·6	8·1	7·4	10·6	20·6	22·6	24·4	32·6	32·2	37·5
50–	3·5	6·4	4·6	9·4	12·2	8·8	22·6	24·8	29·9	35·5	43·3	43·3
55–	8·4	10·5	9·2	13·9	17·0	12·2	22·1	34·0	38·1	44·3	61·5	59·4
60–	12·9	18·4	16·6	15·4	21·9	21·0	32·7	36·6	46·2	61·0	77·0	83·8
65–	18·1	25·3	19·4	20·3	28·6	26·3	32·8	51·0	57·3	71·2	104·8	103·0
70–	24·3	39·0	42·9	19·2	30·9	34·8	28·4	46·8	56·5	71·9	116·6	134·2
75–	21·3	40·9	57·6	18·5	39·3	32·7	21·2	41·6	68·7	60·9	121·8	159·2
80+	22·0	36·9	50·3	14·5	23·3	35·6	6·2	27·7	42·2	42·7	87·9	128·1
All ages	5·3	8·3	8·3	7·7	10·3	9·7	19·1	25·6	27·0	32·1	44·2	45·1

which were described simply as leukaemia was, however, small—of the order of 10% in each age group in 1945–9, 3% in 1950–4, and 2% in 1955–7—and any error due to the wrong allocation of cases in this group cannot have been large. The main possibility of error lies in the classification of the fairly large proportion of cases which were described as lymphatic or myeloid leukaemia, without reference to the clinical type. The age distribution of these cases was, however, intermediate between the age distributions of the acute and chronic cases, and they cannot have consisted wholly of cases of one type. Apart from the oldest age groups, the rates attributed to these types of leukaemia were fairly constant in the three periods studied and the allocation of the unspecified cases to acute and chronic leukaemia in other proportions would have little effect on the apparent trends in the mortality, so long as the proportion remained the same at each period. The estimated mortalities for the three types of leukaemia may not be exact, but the patterns of mortality are similar to those reported for morbidity by MacMahon and Clark (1956), and it is reasonable to believe that they will not require serious modification.

General Aetiological Considerations

It is uncertain whether the increase in the mortality from leukaemia shown in Figs. 1–4 reflects a real increase in the incidence of the disease. The greater increase at older ages could be a cohort effect; that is, it may have resulted from the introduction of a new leukaemogenic agent at some time in the past, such that it is only recently that men and women can have reached the old age groups and yet have been exposed to the new agent at a susceptible period of their lives. There has, however, been no equivalent increase at younger ages previously, and it seems more likely that much of the increase at age 65 years and over is due to improvements in diagnosis and in death certification. A large increase in mortality at these ages has been recorded for several other causes of death (for example, cancer of the lung and gastric ulcer) and a large decrease has been observed in the deaths attributed to senility. Between 1947 and 1956 (the mid-years of the first and the last of the periods studied) the death rate attributed to senility fell from 97 to 8 per million at ages 65–69 years, from 872 to 252 per million at ages 70–74 years, from 3,885 to 1,420 per million at ages 75–79 years, and from 18,689 to 8,586 per million at age 80 years and over. There has therefore been ample opportunity for an increase to be recorded in the mortality from more specific causes of death at these ages, solely as a result of more detailed and more accurate death certification.

If the changes in mortality at the older ages are ignored, it must be concluded that the data obtained in this study show no evidence of any real change in the incidence of chronic lymphatic leukaemia over the past 13 years. In contrast, the data for acute leukaemia suggest that there has been an increase in the mortality of approximately one-third at all ages under 65 years and in both sexes, and it is reasonable to regard this increase as being largely due to a real increase in the incidence of the disease. It may, however, be considered that the diagnosis of acute leukaemia is more sophisticated than that of chronic lymphatic leukaemia, and that consequently the diagnosis of acute leukaemia has not been made as often as it should until the last few years. The data for chronic myeloid leukaemia are difficult to assess. The estimated rates show an increase at most ages for men which is comparable with the increase for acute leukaemia. There is, however, no similar trend in the female rates, and, in view of the small number of cases on which the rates at the younger ages are based in the last period, it seems preferable to suspend judgment on the trend for this type of leukaemia until more data are available.

The sharp differences revealed in the sex ratio of the mortality rates and in the rate of change in mortality with age provide evidence that the causes of the three types of leukaemia are distinct. The relationship between age and the death rate from chronic lymphatic leukaemia is identical with that recorded for most epithelial tumours: for the purposes of comparison the relationship between age and death rate for cancer of the stomach and for chronic lymphatic leukaemia is shown in Fig. 5. This type of relationship is consistent

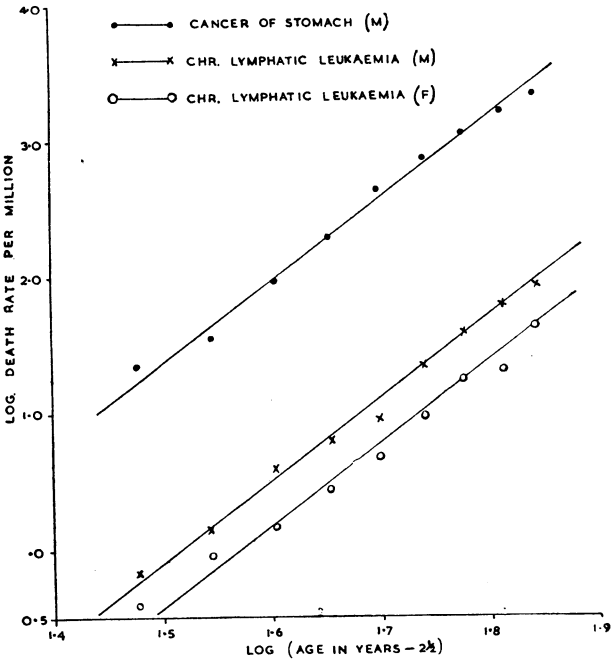

FIG. 5.—Relationship between age and estimated mortality from chronic lymphatic leukaemia in men and in women in 1955–7 compared with the relationship observed for cancer of the stomach in men in 1956. The logarithm of the death rate per million persons is plotted against the logarithm of the age less 2½ years, for ages 30 years to 74 years. The straight line through the points has been drawn arbitrarily to give the best fit, subject to the gradient being 6 to 1 (Armitage and Doll, 1954, 1957).

with a mechanism of cancer induction which takes place in two or more stages and which results in a long latent period (Armitage and Doll, 1954, 1957). The relationships for chronic myeloid leukaemia and for acute leukaemia are in sharp contrast. In none of the epithelial cancers which have so far been examined is the rate of increase in mortality in middle age so slow. This difference may perhaps be related to the finding that the average latent period for radiation-induced leukaemia (characteristically acute leukaemia, and, to a less extent, chronic myeloid leukaemia) is shorter than for other types of cancer, being of the order of four to eight years.

The rate of increase with age which is estimated for acute leukaemia is only slightly less than that for chronic

myeloid leukaemia, but the real difference may be appreciably greater. Some cases of chronic myeloid and chronic lymphatic leukaemia terminate in an acute phase, and it is possible that cases which are first diagnosed in this phase may be recorded as acute when they are really chronic. Since the mortality from chronic lymphatic leukaemia increases rapidly with age, any error of this sort would tend to inflate the mortality attributed to acute leukaemia disproportionately at the older ages, and it is possible that the true incidence of acute leukaemia increases with age after the age of 30 years even more slowly than has been estimated.

In none of the three types of leukaemia is the relationship between age and mortality similar to that recorded for the hormone-dependent tumours (Armitage and Doll, 1954), and this is evidence that the difference in the sex ratios is not dependent upon hormonal factors. The differences may therefore be regarded as depending on differences in the degree to which men and women are exposed to external leukaemogenic agents. It follows that the principal causes of chronic lymphatic leukaemia are likely to be such that in England and Wales men are exposed to them two to three times more heavily than women. In contrast, men and women must be equally or nearly equally exposed to the principal causes of chronic myeloid and acute leukaemia.

The one major difference between chronic myeloid and acute leukaemia is that the mortality from acute leukaemia is relatively high in adolescence, and is even higher in childhood—for nearly all leukaemia deaths in childhood are due to acute leukaemia—and that the mortality falls until the age of about 30 years, before it begins to rise. In contrast the mortality from chronic myeloid leukaemia is low in childhood and rises continuously with age from adolescence. This difference might be explained if the two diseases had a common cause which acted through two different mechanisms, or if the principal causes of the two diseases were distinct.

Ionizing Radiations: A Specific Aetiological Factor

Ionizing radiations are the only leukaemogenic agents for which there is convincing epidemiological evidence that they affect man. It is also certain that there has been an appreciable increase in the exposure to the general population, particularly from *x* rays in medical diagnosis, and that men and women have probably been equally affected. The extent to which this exposure may be responsible for at least some of the recorded increase in leukaemia mortality has been the subject of controversy.

On the one hand, on the basis of a hypothesis that even the smallest doses of radiation can be leukaemogenic, it has been supposed that some cases result from the use of *x* rays in diagnosis (Stewart, Webb, Giles, and Hewitt, 1956; Court Brown and Doll, 1957). The hypothesis was put forward from studies of (1) histories given by the mothers of children who died of malignant disease, and (2) the relationship between the dose and leukaemia incidence in patients treated with *x* rays for ankylosing spondylitis. In the latter study one interpretation of the data was that over the lower ranges of dose the relationship might be linear, and that there might be no level of dose below which cases did not occur. If this was so, it would seem likely that some cases of leukaemia develop on the basis of a gene mutation. On the other hand, an alternative view has been summarized by Loutit (1958), who says of the above hypothesis that it is based on "a theory of carcinogenesis that has been discussed for many years and found wanting, certainly as a sole cause." Loutit adds that "the theory would also require that leukaemia be increased in incidence with increasing age and accumulation of radiation dose from natural radiation. In fact, certain statistics show that only chronic lymphatic leukaemia increases in this way, and this is the only type of leukaemia which historically has not been linked with radiation."

It has not previously been possible to study the age-specific death rates for the different types of leukaemia sumultaneously with the trends in these death rates with time. The results of this present study are of interest in that they have a bearing on the above controversy and they may go some way towards resolving it.

It has been shown, for each of the three periods studied and for each of the three different classes of leukaemia, that there is an appreciable increase in mortality with age during a large part of adult life. There is, however, an important difference in the trends of the mortality rates with time. Thus in each age group the mortality of acute leukaemia has increased between 1945 and 1957, whereas the mortality from the chronic leukaemias, with the exception of chronic myeloid leukaemia in men, has increased during the period of observation only in the older age-groups. At these ages the mortality has increased for all types of leukaemia in both sexes, but the increase in chronic lymphatic leukaemia in men has been outstanding. It is suggested that the observed increase in the age-specific death rates of acute leukaemia at ages under 60 years is largely real and due to increasing exposure of the population to leukaemogenic factors in the environment, but that most of the increase in the death rate from the chronic leukaemias is due to their better recognition consequent upon improved medical care for the elderly.

In this context it is important to note the evidence that radiation exposure has been associated with an increase in acute leukaemias more often than with chronic myeloid leukaemia, and not at all with an increase in chronic lymphatic leukaemia. Thus of the 50 cases which have occurred to date in the spondylitis series, inclusive of the 41 cases originally reported (Court Brown and Doll, 1957), no fewer than 38 have been examples of the acute disease and only 8 chronic forms have been found, the data in the remainder being insufficient to determine the clinical type. Only one of the eight chronic leukaemias was lymphatic in type. Similar results have been observed among the survivors of the atomic explosion at Nagasaki, but cases of chronic myeloid leukaemia have been reported with about the same frequency as cases of the acute disease among the survivors at Hiroshima (Wald, 1957).

The extent to which the increases in the national mortality rate from acute leukaemia may be related to increases in our artificial radiation background can be adequately assessed only with greater knowledge of the basic mechanisms of cancer induction and of the relationship between radiation dose and incidence. If, however, a leukaemic process can be initiated not only by a gene mutation but also, and possibly more frequently, by a complex genetical disturbance depending on gross chromosome damage, then the more important physical factor may be the rate at which a

radiation dose is given rather than the total dose. In this case it could be important that radiation for medical purposes is given at high dose rates in the approximate range of 40 to 100 r a minute, while the average dose rate from natural background radiation is 2×10^{-6} r a minute.

Summary and Conclusions

The deaths from leukaemia in England and Wales for the period 1945 to 1957 have been classified under three headings—acute leukaemias of all types, chronic myeloid leukaemia, and chronic lymphatic leukaemia. The age-specific mortality rates have been calculated for each type of leukaemia, for each sex, and for three periods of time—1945 to 1949, 1950 to 1954, and 1955 to 1957.

A study of these data suggests that the principal feature in the real increase in leukaemia is a change in the incidence of acute leukaemia. This is compatible with the concept that an increased exposure to ionizing radiations plays some part in the changed incidence of the disease.

We are indebted to the Registrar-General of England and Wales for the extraction of the data and for permission to publish the results, and to Miss F. Callaby, Mrs. A. Frackiewicz, Mrs. E. A. O. Gray, and Mrs. V. Peetz for their assistance in the analysis.

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On April 27 England and Wales will have new standards for ice-cream. The main changes made by the new regulations are that standards are to be fixed for dairy ice-cream and for milk ice which are required to contain milk fat and must not contain any other fat; that saccharin and other artificial sweeteners are not to be used in any ice-cream or in milk ice, and no mimimum sugar content is laid down; that ice-cream made with non-milk fat is not to be labelled or advertised in a way which is suggestive of butter, cream, or milk; but such ice-cream may continue to be sold as "ice-cream" and it may bear a statement that it contains skimmed milk solids; that, after November 30 of this year, all pre-packed ice-cream which is made with non-milk fat must be labelled as containing vegetable or non-milk fat if it is sold as "ice-cream." The present requirements that ice-cream must contain not less than 5% fat and not less than 7½% milk-solids-not-fat are included in the new regulations and so continue in force. The new regulations will revoke and replace the existing Food Standards (Ice-Cream) Order, 1953. The Secretary of State for Scotland proposes to make corresponding regulations which will apply in Scotland.

P.T.C. TASTE RESPONSE AND THYROID DISEASE

BY

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For over a hundred years a familial disposition in thyroid disease has been known. Since Romberg (1851) recorded Graves's disease in twins there have been many genetic studies using the classical method of pedigree analysis, but the results have been conflicting. Bartels (1953), on the basis of his own work (Bartels, 1941) and a review of the literature, concluded "that sporadic thyroid affections such as simple goitre, hypothyroid, and hyperthyroid states are probably genetically determined."

Fox (1932) discovered that some people taste phenylthiocarbamide (P.T.C.) and others do not. Further investigation established that this bimodal taste response was an example of human genetic polymorphism; about 30% of Europeans and white Americans were non-tasters and 70% were tasters (Barnicot, 1950; Harris and Kalmus, 1950a).

In 1942 Richter and Clisby noticed marked thyroid hyperplasia in rats which had been fed with P.T.C., and subsequent work has established that the thiocarbamides in general are active goitrogenic substances. Among them are to be found the thiouracils as well as some naturally occurring goitrogens which have been isolated from turnips, brussels sprouts, rape, and kale, and found to belong to the same chemical family—all having the $-N-C-$ grouping.
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This relationship between P.T.C. and thyroid gland activity led Harris, Kalmus, and Trotter (1949) to test the taste response to P.T.C. of groups of patients with thyroid disease. Their data suggested that non-tasters of P.T.C. were slightly more susceptible to the development of adenomatous goitre than controls, but they found a normal taste distribution in patients with toxic diffuse goitre ("primary thyrotoxicosis"). As no subsequent study of this kind has been reported we have carried out a survey at the Thyroid Clinic, David Lewis Northern Hospital, Liverpool, and describe here the results of testing the P.T.C. taste response of 447 patients with thyroid disease and compare the results with those in 265 control individuals.

Material

The 447 patients who had undergone thyroidectomy were taken at random from attendances at the thyroid clinic between May, 1956, and May, 1958, and were taste-tested with P.T.C. by the method described below. In addition, we selected eight patients with toxic