Changing Sex Differentials in Leukemia

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THE CONTINUOUS increases in U.S. leukemia mortality rates for both sexes during this century have been well documented (*1–3*). The study reported here was designed to describe and evaluate the changes that have occurred in the sex differential of these rates.

Trends in U.S. Sex Ratio

Average, annual, age-specific mortality rates of leukemia for each sex and race in the United States were computed directly from published vital and census statistics (*4–7*) for eight 5-year periods and four 10-year periods from 1921 to 1960. These rates were used to calculate sex mortality ratios (SR=male-to-female death rates) for the various age groups in the white and nonwhite populations. A linear regression analysis determined whether the SR changed in relation to time; calculations were made of (*a*) slopes of lines generated by plotting each of the SR against calendar periods, thus showing the direction and magnitude of each trend, and (*b*) tests for independence, which provided a measure of the statistical significance and consistency of the trends.

The SR among whites, along with the age-sex-specific mortality rates of leukemia, are shown in table 1 for the eight 5-year periods. Two changes over time in SR are noteworthy: (*a*) a significant decrease for each of the childhood age groups (less than 1, 1–4, and 5–14 years); and (*b*) an increase for each age group over 24 years, which is significant between 35 and 74 years. These coincidental, contrasting trends are illustrated by plotting the average annual SR for the four 10-year calendar periods (fig. 1). Demonstrated also is a consistent bimodal curve for the SR: the first peak occurred with the group 5–14 years of age in 1921–40 and shifted to the 15–24 year group in 1941–60; a second peak has become increasingly evident over time with the age groups above 64 years. When the SR were arranged according to 10-year birth cohorts, there were no deviations from the patterns observed in figure 1.

Among nonwhites (table 2), the SR have not shown consistent or significant trends, with the exception of a decline in the group less than 1 year of age. Irregularities in the nonwhite rates and ratios may be attributed to the relatively small number of deaths from leukemia in that population.

Trends in Sex Ratio in England and Wales

To determine whether trends in the sex ratio similar to those among U.S. whites have occurred elsewhere, statistics were examined for England and Wales, where a rising leukemia mortality has also been observed. Table 3 shows the secular changes in SR which were calculated from age-sex-specific mortality rates for England and Wales, as recorded from 1931 through 1954 (*8*). Except for two age groups, 15–24 and 65–74 years, the trends (slopes) in SR are in the same direction, although not as consistent or significant (tests for independence) as those trends among U.S. whites. The comparatively minor shifts over time in SR for England and Wales are attributable, perhaps,

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to the smaller British population and the shorter span of time covered by these data, or to the same unknown factors which account for other geographic differences in mortality experience.

Sex-Specific Rates Among U.S. Whites

Each sex ratio observed in this study summarizes, for a particular calendar period and age group, a relative sex difference that has occurred within the general framework of rising leukemia mortality. The significance of secular trends in these ratios can be appreciated, and false inferences avoided, only when comparisons are made of the increases occurring in the leukemia death rates for each sex. For these comparisons it is important to consider the absolute increases (increments in actual death rates from one time period to the next) as well as the relative increases (rates of increase between periods).

Absolute increases. The absolute increments over time in sex-specific leukemia mortality among U.S. whites are shown in table 4. These were obtained in every age group by subtracting the death rate recorded for 1921–25 from the rates of each subsequent 5-year calen-

Table 1. Average annual U.S. leukemia death rates among white males and females and ratios of rates according to age group and 5-year calendar periods, 1921–60

Calendar periods	Age group									
	<1	1–4	5–14	15–24	25–34	35–44	45–54	55–64	65–74	≥75
	Average annual death rates per million									
Males:										
1921–25	21.57	23.02	10.79	10.18	11.41	13.96	23.83	46.56	52.43	44.58
1926–30	26.40	27.95	14.83	11.97	12.72	17.91	31.16	53.30	72.50	61.24
1931–35	33.39	35.86	17.67	15.02	14.85	24.10	36.95	72.43	100.72	85.39
1936–40	45.72	48.42	22.15	17.01	18.18	27.09	49.43	88.37	135.98	142.96
1941–45	54.01	57.15	26.84	25.55	23.82	29.86	57.30	113.61	184.62	198.08
1946–50	47.83	63.56	31.05	24.16	24.88	32.70	64.77	141.66	245.41	328.80
1951–55	31.46	64.96	34.73	27.24	25.55	36.34	71.28	155.17	320.46	472.51
1956–60	28.21	63.95	37.48	26.19	25.82	37.91	70.27	162.59	368.28	586.53
Females:										
1921–25	17.48	14.94	6.56	6.24	8.78	13.06	22.32	35.42	36.71	30.48
1926–30	19.47	22.02	8.95	8.53	10.87	16.79	27.35	43.53	51.43	35.61
1931–35	29.71	27.45	11.46	9.31	13.15	19.58	34.12	55.34	73.78	53.81
1936–40	39.24	38.72	14.61	12.16	14.35	23.38	41.08	65.04	92.06	84.01
1941–45	49.28	47.39	18.68	13.89	17.36	25.87	46.04	80.31	122.36	120.72
1946–50	41.45	52.84	24.27	15.07	18.41	27.63	51.92	97.73	154.63	190.63
1951–55	35.71	56.76	26.97	16.45	19.42	29.80	52.91	105.46	190.32	285.11
1956–60	26.41	54.26	29.41	16.96	19.01	28.76	51.56	104.46	212.48	347.75
	Sex mortality ratios									
Male/female:										
1921–25	1.23	1.54	1.64	1.63	1.30	1.07	1.07	1.31	1.43	1.46
1926–30	1.36	1.27	1.66	1.40	1.17	1.07	1.14	1.22	1.41	1.72
1931–35	1.12	1.31	1.54	1.61	1.13	1.23	1.08	1.31	1.37	1.59
1936–40	1.17	1.25	1.52	1.40	1.27	1.16	1.20	1.36	1.48	1.70
1941–45	1.10	1.21	1.44	1.84	1.37	1.15	1.24	1.41	1.51	1.64
1946–50	1.15	1.20	1.28	1.60	1.35	1.18	1.25	1.45	1.59	1.72
1951–55	.88	1.14	1.29	1.66	1.32	1.22	1.35	1.47	1.68	1.66
1956–60	1.07	1.18	1.27	1.54	1.36	1.32	1.36	1.56	1.73	1.69
Trends [1]	−.00833	−.00843	−.01262	.00257	.00460	.00557	.00864	.00826	.00986	.00390
Tests [2]	[3] −2.72	[3] −3.66	[4] −8.85	.55	1.98	[3] 3.45	[4] 7.84	[4] 6.52	[4] 6.04	1.60

[1] Slopes of lines generated by plotting each of the SR against calendar periods to show the direction and and magnitude of each trend.
[2] Tests for independence to provide a measure of the statistical significance and consistency of trends.
[3] Significant at the 5 percent level.
[4] Significant at the 1 percent level.

dar period (data from table 1). In childhood, the absolute increases in death rates have been approximately the same for males and females in the groups less than 1 and 1–4 years, while increases have been only slightly greater for males than females in the age group 5–14 years. In each of the older age groups, increases in the male rates have clearly exceeded those for female rates.

Relative increases. A somewhat different pattern emerges when the relative increases in sex-specific death rates are used for comparing males and females (table 4). Obtained by dividing the absolute increase in rate for each calendar period by the rate in 1921–25, the relative increase expresses the percentage change (or rate of change) in age-sex-specific leukemia mortality. In general, these increases have been (*a*) greater among females than males in each of the three childhood age groups, (*b*) similar for each sex between 15 and 34 years, and (*c*) greater among males than females in each of the older age groups. When the sex-specific death rates from table 1 are plotted on a semilogarithmic scale (which automatically shows the rate of change), the relative increases over time for each sex again demonstrate tendencies toward convergence in childhood, slight

Table 2. Average annual U.S. leukemia death rates among nonwhite males and females and ratios of rates according to age group and 5-year calendar periods, 1921–60

Calendar periods	Age group									
	<1	1–4	5–14	15–24	25–34	35–44	45–54	55–64	65–74	≥75
	Average annual death rates per million									
Males:										
1921–25	6. 64	5. 70	2. 95	5. 34	8. 15	10. 76	13. 75	18. 80	7. 68	9. 85
1926–30	19. 27	5. 90	5. 30	8. 61	8. 39	11. 52	12. 71	11. 04	25. 72	7. 78
1931–35	22. 45	9. 78	8. 51	9. 08	11. 02	16. 57	18. 64	27. 71	21. 09	28. 30
1936–40	18. 61	12. 29	9. 04	10. 42	14. 57	21. 59	34. 09	42. 32	35. 75	31. 75
1941–45	26. 76	15. 24	12. 59	14. 20	19. 41	25. 88	42. 25	54. 92	53. 57	36. 45
1946–50	47. 88	23. 51	14. 07	16. 76	19. 30	30. 71	48. 03	87. 71	88. 13	62. 72
1951–55	35. 59	27. 26	18. 24	22. 98	23. 22	35. 24	59. 41	116. 88	176. 12	156. 16
1956–60	20. 01	29. 60	19. 23	20. 66	29. 41	33. 39	62. 71	131. 55	236. 29	209. 44
Females:										
1921–25	2. 17	5. 74	3. 50	4. 04	4. 27	6. 56	12. 00	8. 18	14. 02	9. 05
1926–30	5. 62	8. 03	3. 86	3. 88	4. 35	10. 92	11. 83	13. 56	5. 61	--------
1931–35	15. 31	7. 66	3. 95	4. 44	10. 52	11. 20	17. 52	16. 87	6. 95	11. 27
1936–40	24. 79	10. 65	5. 28	8. 71	10. 27	19. 27	26. 11	25. 04	17. 47	11. 63
1941–45	28. 57	16. 48	8. 50	9. 00	11. 09	21. 64	31. 31	36. 18	29. 67	22. 59
1946–50	26. 26	16. 87	10. 91	12. 39	14. 53	23. 12	35. 67	45. 92	43. 96	29. 80
1951–55	28. 50	24. 02	12. 50	11. 79	16. 71	30. 06	57. 34	69. 07	79. 46	76. 22
1956–60	27. 18	22. 22	15. 81	14. 60	17. 65	33. 23	54. 79	98. 55	123. 46	96. 61
	Sex mortality ratios									
Male/ female:										
1921–25	3. 06	. 99	. 84	1. 32	1. 91	1. 64	1. 15	2. 30	. 55	1. 09
1926–30	3. 43	. 73	1. 37	2. 22	1. 93	1. 05	1. 07	. 81	4. 58	--------
1931–35	1. 47	1. 28	2. 15	2. 04	1. 05	1. 48	1. 06	1. 64	3. 03	2. 51
1936–40	. 75	1. 15	1. 71	1. 20	1. 42	1. 12	1. 31	1. 69	2. 05	2. 73
1941–45	. 94	. 92	1. 48	1. 58	1. 75	1. 20	1. 35	1. 52	1. 81	1. 61
1946–50	1. 82	1. 39	1. 29	1. 35	1. 33	1. 33	1. 35	1. 91	2. 00	2. 10
1951–55	1. 25	1. 13	1. 46	1. 95	1. 39	1. 17	1. 04	1. 69	2. 22	2. 05
1956–60	. 74	1. 33	1. 22	1. 42	1. 67	1. 00	1. 14	1. 33	1. 91	2. 17
Trends [1]	−. 06167	. 01067	. 00071	−. 00557	−. 00764	−. 01012	−. 00164	−. 00417	−. 01336	−. 05581
Tests [2]	[3] −2. 61	1. 75	. 06	−. 44	−. 78	−1. 67	−. 38	−. 29	−. 35	−. 85

[1] Slopes of lines generated by plotting each of the SR against calendar periods to show the direction and magnitude of each trend.
[2] Tests for independence to provide a measure of the statistical significance and consistency of trends.
[3] Significant at the 5 percent level.

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Table 3. Ratio of male to female average annual leukemia death rates according to age group and 3-year calendar periods, England and Wales, 1931–54

Calendar periods	Age group								
	<5	5–14	15–24	25–34	35–44	45–54	55–64	65–74	≥75
	Sex mortality ratios								
1931–33	1. 14	1. 36	1. 45	1. 24	1. 08	1. 14	1. 19	1. 53	1. 56
1934–36	1. 32	1. 31	1. 89	1. 27	1. 00	1. 00	1. 10	1. 53	1. 40
1937–39	1. 48	1. 38	1. 17	1. 15	1. 25	1. 07	1. 44	1. 51	. 81
1940–42	1. 19	1. 77	1. 31	1. 45	1. 11	1. 15	1. 21	1. 37	1. 37
1943–45	1. 45	1. 41	1. 21	1. 14	1. 05	1. 23	1. 32	1. 50	1. 58
1946–48	1. 35	1. 25	1. 36	1. 06	1. 14	1. 22	1. 45	1. 40	1. 49
1949–51	1. 07	1. 04	1. 59	1. 29	1. 17	1. 24	1. 35	1. 39	1. 59
1952–54	1. 31	1. 30	1. 41	1. 33	1. 14	1. 24	1. 41	1. 39	1. 53
Trends [1]	–. 00045	–. 00600	–. 00312	. 00036	. 00210	. 00579	. 00698	–. 00448	. 00712
Tests [2]	–. 09	–. 95	–. 41	. 01	. 87	[3] 3.21	2. 16	[3] –3. 01	. 88

[1] Slopes of lines generated by plotting each of the SR against calendar periods to show the direction and magnitude of each trend.
[2] Tests for independence to provide a measure of the statistical significance and consistency of the trends.
[3] Significant at the 5 percent level.

SOURCE: Reference 8.

Table 4. Increases in the average annual U.S. leukemia death rates since 1921–25 among white males and females, according to age group and 5-year calendar periods, 1926–60

Calendar periods	Age group									
	<1		1–4		5–14		15–24		25–34	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
	Absolute increase									
1926–30	4. 83	1. 99	4. 93	7. 08	4. 04	2. 39	1. 79	2. 29	1. 31	2. 09
1931–35	11. 82	12. 23	12. 84	12. 51	6. 88	4. 90	4. 84	3. 07	3. 44	4. 37
1936–40	24. 15	21. 76	25. 40	23. 78	11. 36	8. 05	6. 83	5. 92	6. 77	5. 57
1941–45	32. 44	31. 80	34. 13	32. 45	16. 05	12. 12	15. 37	7. 65	12. 41	8. 58
1946–50	26. 26	23. 97	40. 54	37. 90	20. 26	17. 71	13. 98	8. 83	13. 47	9. 63
1951–55	9. 89	18. 23	41. 94	41. 82	23. 94	20. 41	17. 06	10. 21	14. 14	10. 64
1956–60	6. 64	8. 93	40. 93	39. 32	26. 69	22. 85	16. 01	10. 72	14. 41	10. 23
	Percentage increase									
1926–30	22. 4	11. 4	21. 4	47. 4	37. 4	36. 4	17. 6	36. 7	11. 5	23. 8
1931–35	54. 8	70. 0	55. 8	83. 7	63. 8	74. 7	47. 5	49. 2	30. 1	49. 8
1936–40	112. 0	124. 5	110. 3	159. 2	105. 3	122. 7	67. 1	94. 9	59. 3	63. 4
1941–45	150. 4	181. 9	148. 3	217. 2	148. 7	184. 8	151. 0	122. 6	108. 8	97. 7
1946–50	121. 7	137. 1	176. 1	253. 7	187. 8	270. 0	137. 3	141. 5	118. 1	109. 7
1951–55	45. 9	104. 3	182. 2	279. 9	221. 9	311. 1	167. 6	163. 6	123. 9	121. 2
1956–60	30. 8	51. 1	177. 8	263. 2	247. 4	348. 3	157. 3	171. 8	126. 3	116. 5

Figure 1. Trends in sex ratios (M:F) of average annual age-specific leukemia death rates among white population; United States, 1921–60

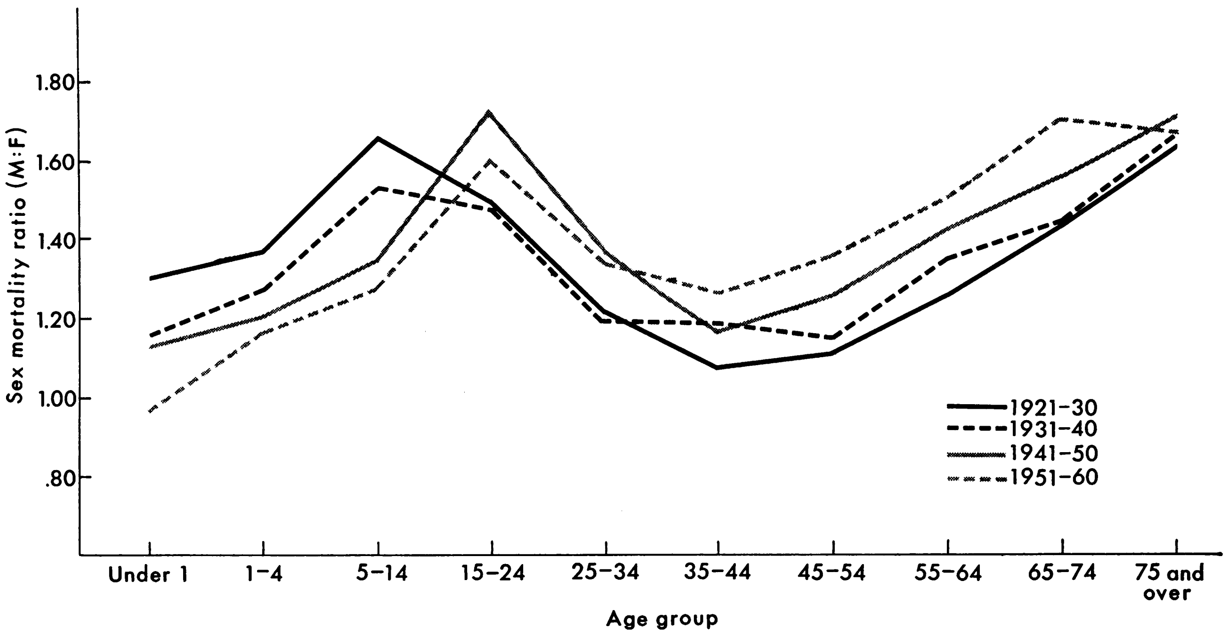


Table 4. Increases in the average annual U.S. leukemia death rates since 1921–25 among white males and females, according to age group and 5-year calendar periods, 1926–60—Continued

Calendar periods	Age group 35–44 Male	35–44 Female	45–54 Male	45–54 Female	55–64 Male	55–64 Female	65–74 Male	65–74 Female	≥ 75 Male	≥ 75 Female
	Absolute increase									
1926–30	3. 95	3. 73	7. 33	5. 03	6. 74	8. 11	20. 07	14. 72	16. 66	5. 13
1931–35	10. 14	6. 52	13. 12	11. 80	25. 87	19. 92	48. 29	37. 07	40. 81	23. 33
1936–40	13. 13	10. 32	25. 60	18. 76	41. 81	29. 62	87. 55	55. 35	98. 38	53. 53
1941–45	15. 90	12. 81	33. 47	23. 72	67. 05	44. 89	132. 19	85. 65	153. 50	90. 24
1946–50	18. 74	14. 57	40. 94	29. 60	95. 10	62. 31	192. 98	117. 92	284. 22	160. 15
1951–55	22. 38	16. 74	47. 45	30. 59	108. 61	70. 04	268. 03	153. 61	427. 93	254. 63
1956-60	23. 95	15. 70	46. 44	29. 24	116. 03	69. 04	315. 85	175. 77	541. 95	317. 27
	Percentage increase									
1926-30	28. 3	28. 6	30. 8	22. 5	14. 5	22. 9	38. 3	40. 1	37. 4	16. 8
1931–35	72. 6	49. 9	55. 1	52. 9	55. 6	56. 2	92. 1	101. 0	91. 5	76. 5
1936–40	94. 1	79. 0	107. 4	84. 1	89. 8	83. 6	167. 0	150. 8	220. 7	175. 6
1941–45	113. 9	98. 1	140. 5	106. 3	144. 0	126. 7	252. 1	233. 3	344. 3	296. 1
1946–50	134. 2	111. 6	171. 8	132. 6	204. 3	175. 9	368. 1	321. 2	637. 6	525. 4
1951–55	160. 3	128. 2	199. 1	137. 1	233. 3	197. 7	511. 2	418. 4	959. 9	835. 4
1956-60	171. 6	120. 2	194. 9	131. 0	249. 2	194. 9	602. 4	478. 8	1,215. 7	1, 040. 9

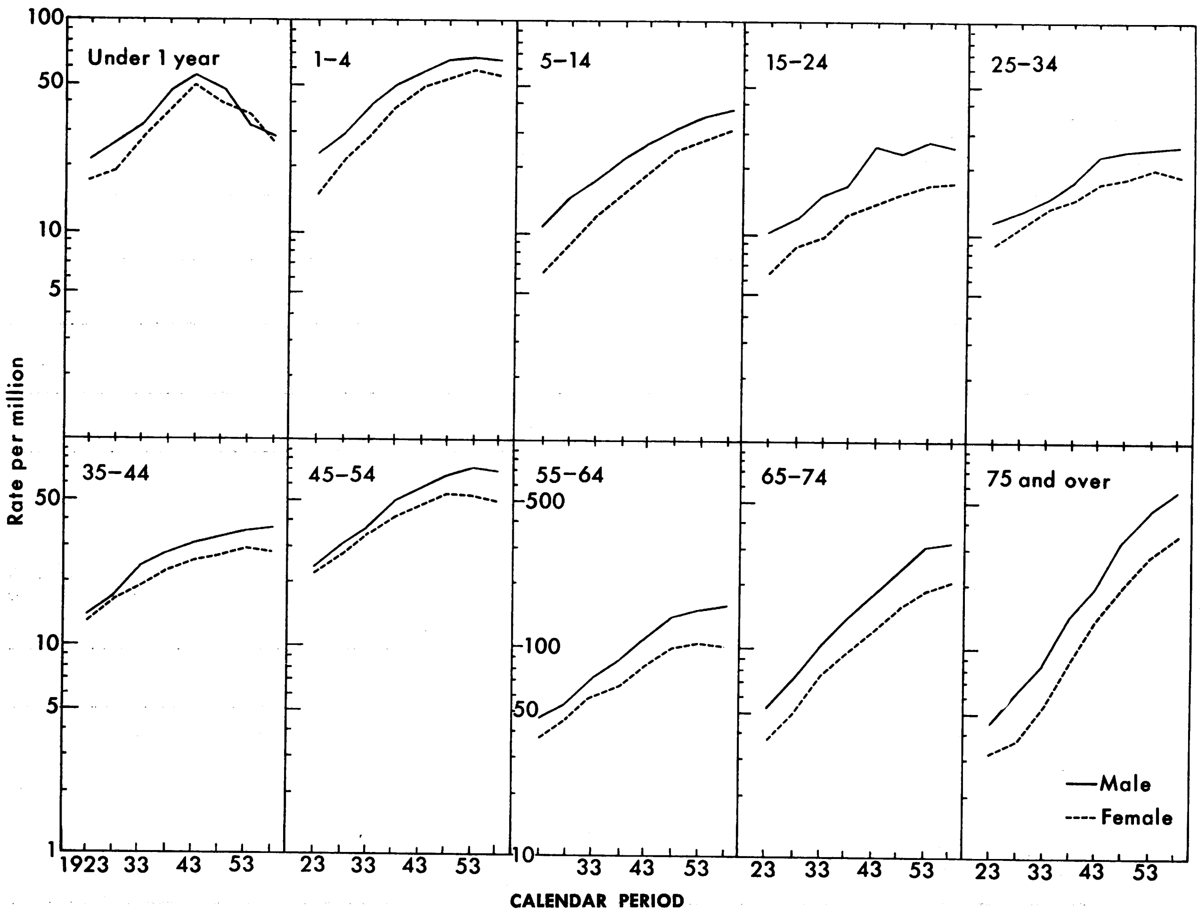
divergence but relative parallelism between 15 and 34 years, and divergence in the older age groups (fig. 2).

Discussion

The changes observed in the sex distribution of leukemia should be evaluated in context with basic trends of leukemia mortality reported for the United States. In a study covering the period 1921–55, Gilliam and Walter (*3*) demonstrated continuous increases in the age-adjusted leukemia rates for all ages, in each race and sex. Since 1940, however, a decline in the rate of increase has been observed among whites, but not among nonwhites (*3*). This tendency has been most dramatic in the younger age groups and progressively less evident with increasing age. Indeed, among children under 3 years of age, an actual diminution in leukemia mortality has occurred in recent years (*9*); for elderly persons, there has been no tendency for the rate of rising leukemia rates to diminish (*3*). Thus the early increases and gradual stabilization in leukemia death rates among whites in the younger age groups have coincided throughout with diminishing sex ratios, while the continuously rising mortality among older age groups has been accompanied by increasing sex differentials.

It is plausible that the contrasting sex trends observed in this study, like the multimodal age distribution of leukemia, are related to separate causal factors which place specific age groups at an increased risk of leukemia. Analysis of the age-sex-specific death rates reveals that the direction of changing sex differentials correlates with the excess of either females (in children) or males (in adults) contributing to the rate of

Figure 2. Trends in average annual age-specific leukemia death rates among white males and females, United States, 1921–60



increase in leukemia mortality. However, an appraisal of factors that might be responsible for these sex trends would appear to rely more on a comparison by sex of the absolute increases in age-specific rates. Secular changes in the recorded mortality for childhood leukemia, 1921–60, show that the rates of increase over time have been greater among females than among males. More importantly, however, the absolute increases in the age groups under 15 years have been quite similar for both sexes. Indeed, the reduction of relative sex differences since 1921–25, as manifested by the decline in sex ratios, can be ascribed a priori to the equal number of males and females contributing to the overall increase in mortality. To speculate, the mortality trends for childhood leukemia may be attributed to (*a*) the effect of leukemogenic factors which were newly introduced into the environment and affected both sexes equally, or (*b*) the result of improvements in the ascertainment of leukemia which would be expected to accrue equally to the sex-specific increases in mortality.

In adult leukemia, 1921–60, both the absolute and relative rises in mortality have been greater for males than females. Contrary to childhood leukemia, the decline in the rates of increase since 1940 has been particularly evident among females. Male preponderance in these rates of increase is apparent with the age groups 35–44 years and older; however, for the absolute increases a male excess can be observed as young as the group 15–24 years of age. While it is unclear what circumstances have accounted for the recorded increases in leukemia over time, the coincident widening of sex differentials among adults would not appear attributable to changes in disease ascertainment, as caused by improvements in diagnostic accuracy, disease certification, survival from infections in the preleukemic state, or survival following the development of leukemia. Instead, the mortality trends for adult leukemia suggest that since 1921–25 the males have been selectively affected by increasing leukemogenic factors in the environment.

Summary

The continuous increases in U.S. leukemia mortality since 1921 were found in this study to be associated with sex ratios (male-to-female death rates) which have declined among children and increased among adults. The shifts in sex ratio occurred only in the white population and were demonstrated in leukemia statistics for England and Wales. To evaluate these changes, a comparison was made of U.S. white males and females according to the "relative" and "absolute" increases which have occurred in age-specific leukemia death rates. In each age group the direction of the changing sex ratios reflected the excess contributed by either females (in children) or males (in adults) to the relative or percentage increases in mortality. Of greater significance were trends produced by the absolute increments, which contained an approximately equal number of males and females in the childhood age groups and an increasing preponderance of males in each adult category. These trends suggest that (*a*) the rise in mortality from childhood leukemia has been caused either by leukemogenic factors introduced into the environment since 1921 and affecting both sexes equally, or by improvements in ascertainment of the disease; and (*b*) the rise in leukemia among adults has been real and not primarily related to improved ascertainment, with males selectively affected by increasing leukemogens in the environment.

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Report on Oral Poliomyelitis Vaccine

The Surgeon General's Special Advisory Committee on Oral Poliomyelitis Vaccine is urging renewed drives by local communities during the fall and winter to vaccinate the younger age groups against poliomyelitis.

The committee's report states that the age groups to be immunized and the vaccine chosen for use should be determined locally. The committee says, however, that in its view the oral vaccination of persons over 18 should generally be recommended only in situations in which unusual exposure to poliomyelitis might be anticipated, such as epidemics, entry into military service, and travel to other countries. It further recommends alteration in the sequence of administering monovalent vaccine with type II the first to be given. The newly recommended order is types II, I, and III.

The committee strongly recommends immunization during the first year of life and the routine immunization of all children on entering school.

The recommendations were based on an exhaustive analysis of 87 reported cases of polio-like illness associated with the administration of oral vaccines which have occurred in nonepidemic areas since December 1961. The committee concluded that it is not possible to prove that any individual case was caused by the vaccine and that no laboratory tests available can provide a definitive answer. Nevertheless, the committee said, considering the epidemiologic evidence developed with respect to the total group of compatible cases, it is believed that at least some of these cases were caused by the vaccine.

The committee considered 57 of the 87 cases compatible; that is, possibly induced by the vaccine. These cases occurred largely among adults and were scattered throughout the country. Onset of illness fell between 4 and 28 days after vaccine administration.

Dr. Albert Sabin, developer of the oral vaccine and a member of the committee, filed a dissenting report calling for the continued immunization of all age groups.