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NORMAL LEUKOPOIETIC STRESS AND LEUKEMIA

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Summary

Leukopoietic stress is defined here as increasing proliferative pressure on the leukopoietic system. This paper calculates the heightened leukopoietic stress due to normal growth and to pregnancy, and epidemiologically associates it with increased leukemia mortality. In particular, for each sex, changes in the rate of leukemia mortality from birth to maturity duplicate and follow by about 3 years changes in stress. Comparison of birth rates and sex ratios for leukemia mortality shows that the leukopoietic stress of pregnancy among older women is followed after 6 years by their increased relative mortality from leukemia, mostly of chronic form. The discussion of these results contains etiological conjectures about the induction of chronic or acute leukemia and about the relative female advantage.

INTRODUCTION

The various suspected or recognized causes of human leukemia, such as the strain of embryonic development (1), myelo-suppressive drugs, pyogenic and viral infection, somatic and germ-cell mutation, and ionizing radiation, have in common the exertion of stress on the leukopoietic system. By such stress I mean the force due to an increasing demand for competent white cells or to a numerically depleted leukopoietic population that accelerates the proliferative process. Stress, then, is simply mounting proliferative pressure. As I show here, periods of heightened stress occur during normal growth and pregnancy. The total stress on the leukopoietic system is the combination of normal and pathological stresses. If leukopoietic stress can actually induce or promote leukemia, as some authors think (1, 2), then periods of increased normal stress should be reflected in periods of increased leukemia incidence or mortality. This paper documents that reflection for the stresses of growth and pregnancy by establishing an epidemiological association between them and leukemia mortality. This paper does not consider the precedence of stress or disease.

In the next section I calculate leukopoietic stress from birth through adolescence and compare it with mortality to conclude that changes in the rate of death from leukemia during that period duplicate and follow by about 3 years changes in stress. The difference in stress between the sexes is preserved in their death rates.

The section, Pregnancy, uses mainly birth rates and sex ratios for leukemia mortality (those are the ratios of male to female rates of death from leukemia). Data from Japan, the United States, and Latin

America allow the conclusion that the period of reduced advantage of females over males with respect to leukemia is prolonged where birth rates are high for women more than 30 years old. This suggests that a high birth rate for those women is associated with their later increased mortality from leukemia. Japanese data from 1948 to 1961 show that the effect of substantial change in birth rates is evidenced in the sex ratio for mortality 6 years later, and that the stress of pregnancy has greatest influence in women more than 40 years old. Evidence is presented from Japan and from England and Wales that implicates chronic leukemia especially. Thus the paper displays the following association between the leukopoietic stress of pregnancy and leukemia: the stress among older women is followed after 6 years by their increased relative mortality from leukemia, mostly of chronic form. It is notable that, although the stress of normal growth seems inevitable, the stress of middle-aged pregnancy may be avoided.

Finally, the Discussion criticizes the foregoing results, sketches a theory that complements them, and introduces a mechanism that can explain the relative female advantage with respect to leukemia.

NORMAL GROWTH

If the average sojourn of leukocytes in a normal person's circulation is known as a function of his age, then the normal daily production of leukocytes at each age can be calculated from his blood volume and his differential cell count at that age. Increasing the production of white cells entails leukopoietic stress, and the rate of increase measures that stress. Figure 1a shows this rate of increase as a function of age for each sex, using the data of Wintrobe (3) and Altman (4). In con-

structing figure 1a I assumed that the sojourn of leukocytes other than lymphocytes is 1 day, that the average sojourn of lymphocytes starts at 1 day in the infant and increases to 2 weeks in the adult, and that the child's decrease in lymphocyte count is due to a decrease in the proportion of large, short-lived lymphocytes in the circulation. These assumptions are in accord with reported lymphocyte behavior (5, 6). Introducing different reasonable sojourns for the various kinds of white cell alters insignificantly the qualitative appearance of figure 1a.

Figure 1b shows the average annual age-specific rates of death from leukemia, by sex, in England and Wales, 1945-1959 (7). These rates are representative for many nations. Comparison of the leukopoietic stress of figure 1a with the death rates of figure 1b reveals that mortality duplicates the general features of stress with a delay of about 3 years. Naturally, one expects a distribution of delays, even if stress and death are causally related, and the comparison suggests that this distribution is confined to 0-6 years with mean at about 3 years. The female sustains less stress than the male except during the first 3 years of life, according to figure 1a, and this is reflected in her lower mortality rates. However, the lower relative rates for girls less than 3 years old are not explained by the pictured stress. This point is discussed later.

PREGNANCY

Near term the average pregnant woman has 5.1 liters of blood (3) containing 10,800 white cells, including 1,900 lymphocytes, per cubic millimeter (4). The number of lymphocytes in the circulation remains relatively unchanged by pregnancy. With a constant, 1-day sojourn by white cells other than lymphocytes, that cellular concentration results

in a required production of 453×10^8 cells per day, which is to be compared with the datum of 190×10^8 cells per day in the mature nonpregnant female. Therefore the minimal leukopoietic stress due to pregnancy is 351×10^8 leucocytes per day per year, or about five times the maximal stress of normal growth shown in figure 1a. This great stress seems to influence leukemia mortality.

Age-specific birth rates are shown in figure 2a for Japan, 1948 and 1954; for the United States, 1957; and for Latin America, 1960 (8). The rates for Latin America are approximate, having been calculated from incomplete birth and population data for Chile, Colombia, Mexico, and Venezuela from 1951 to 1961. The four birth rates shown divide naturally into two pairs: Latin America and Japan, 1948, with high rates after the age of 30 years, and the United States and Japan, 1954, with low rates then.

Figure 2b shows the age-specific sex ratios, M/F, of male to female average annual death rates from leukemia for Japan, 1953-1955 and 1959-1961 (9), for the United States, 1960-1964, and for Latin America, 1959-1965 (10). Again the rates for Latin America were assembled from incomplete data for Chile, Colombia, Mexico, and Venezuela. The four sex ratios divide naturally into two pairs according to where their terminal rise begins: Latin America and early Japan begin their final increase at the age group 55-64; the United States and late Japan begin theirs at 35-44. By the criteria stated, recent birth rates and later sex ratios for Canada (8, 11) and for England and Wales (8, 12, 13) would be classed with those for the United States and Japan. Thus for the situations examined the period of reduced relative female

advantage with respect to leukemia is prolonged by about 20 years where women over 30 years old have high birth rates. Although direct, quantitative comparison of the four sex ratios is not meaningful, the foregoing conclusion suggests that high birth rates after the age of 30 years are associated with increased relative mortality of females between the ages of 45 and 64 years.

A similar connection can be made for the United States with the birth rates in 1920-1954 (8, 14) and the sex ratios in 1921-1960 (15). Moreover, these data from the United States suggest that disproportionately high birth rates among young women are associated with the early reduction of the female advantage.

The possible effect of parity on the association between pregnancy and leukemia is interesting, but its epidemiological analysis is difficult because in all available data high parity accompanies elevated birth rates for older women.

Japan demonstrates a temporal relation in the association of leukemia and the leukopoietic stress of pregnancy because of the recent steep decline in her birth rates. This decline is pictured in figure 3a, which shows the age-specific birth rates for Japan in 1948, 1951, and 1954 (8). Intervening years follow the same pattern. Although data are not available on Japanese births during relevant years before 1947, in which year the rates were similar to those in 1948, it is reasonable to assume that birth rates were moderate during World War II and rose swiftly in 1946 and 1947 to the levels shown.

The age-specific sex ratios, M/F, for Japan are displayed in figure 3b for four periods in 1950-1961 (9). Comparison of the sex ratios

for 1950-1952 and 1953-1955 shows that the beginning point of final rise shifts from age group 45-54 to age group 55-64, reflecting the (assumed) increase in birth rates 6 years earlier. Comparison of the sex ratios for 1953-1955 and 1956-1958 shows that the beginning point of final rise shifts from age group 55-64 to age group 35-44, reflecting the steep decline in birth rates between 1948 and 1951. The smaller decrease in birth rates between 1951 and 1954 induces no evident change in the corresponding sex ratios. Thus a decrease in birth rate is associated with a change in sex ratio 6 years later, and, although not so clearly shown, an increase in birth rate is also associated with a change in sex ratio 6 years later.

The evident changes in sex ratio refer to the age group 45-54, and the delay of 6 years directs their reference to the birth rate for women at least 40 years old. Therefore in Japan in the period considered, a change in the rate of birth to women at least 40 years old was associated with an inverse change in their relative mortality from leukemia 6 years later.

My later discussion includes a reason for the particular susceptibility of older women, but it is notable that the greatest proportional decreases in the birth rates shown in figure 3a occurred among those women. For that reason the effect on older women can be expected to dominate any change in the sex ratios shown. Moreover, secular changes in the sex ratio that are not directly related to natality trends may hide the smaller influence of those trends on the mortality of younger women.

Examination of type-specific mortality rates furnishes a hint about the morphological type of leukemia mainly involved in the association

between the disease and pregnancy. The average annual reciprocal sex ratios, F/M, for acute, chronic myeloid and chronic lymphatic leukemia are shown in figure 4a for Japan, 1958-1964 (9). Those for England and Wales, 1961-1964 (13), are shown in figure 4b. The critical, initial point of the terminal rise of the sex ratio, M/F, occurring recently both in Japan and in England and Wales at age-group 35-44 is signalled by the initial point of final decrease of F/M at that age-group. It is evident from figure 4a that chronic myeloid leukemia is relevant in Japan and from figure 4b that chronic lymphatic leukemia is relevant in England and Wales.

This conclusion suggests that the leukopoietic stress of pregnancy is associated with the later appearance of leukemia, mostly chronic myeloid in Japan and mostly chronic lymphatic in England and Wales. Since diagnostic confusion between these forms is unlikely, the difference is probably real and may be related to the known comparative rarity of chronic lymphatic leukemia in Japan.

DISCUSSION

The leukopoietic stress caused by demand for circulating white cells may be exacerbated in two ways. The demand may be applied to a numerically depleted population of leukopoietic cells, or it may be applied to a population of leukopoietic cells whose replicative cycle is relatively prolonged. If leukopoietic stress promotes or induces leukemia and if depletion and prolongation are associated respectively with the acute and chronic forms, then explanations are at hand for several features of the disease. The replicative cycle of human cells is generally and gradually prolonged with advancing age (16); hence the observed

increasing frequency of leukemia, especially chronic leukemia, with increasing age. Ionizing radiation both depletes cellular populations and prolongs their reproductive cycle (17); hence the induction by ionizing radiation of both chronic and acute leukemia even in childhood, as recorded for Hiroshima and Nagasaki (18). With respect to the pregnancy-leukemia relations displayed in this paper, the stress of pregnancy is superimposed on the stress of ageing, so that pregnancy in older women would be more effective than in younger women as a promoter of leukemia, especially chronic leukemia.

The advantage of females over males with respect to leukemia is obvious (figures 1b, 2b, 3b, 4a, and 4b). This advantage is least during the childbearing period, and, in view of the great leukopoietic stress of pregnancy, makes plausible the existence of a female mechanism for absorbing leukopoietic stress. Such a mechanism could be a short reproductive cycle for leukopoietic cells, but this would tend to heighten the female advantage with respect to chronic leukemia, contrary to the association that this paper makes between pregnancy and chronic leukemia. If the protective mechanism consists mainly of a relatively larger population of leukopoietic cells, then the female advantage is explained for the period after the attainment of the larger population, but the female must suffer at some time the additional stress caused by this expansion of the leukopoietic system. Such stress might promote a kind of leukemia that is particularly virulent in course as well as acute in classification.

Female rates exceed male rates of death from leukemia during infancy in several countries (19), and in others the sex ratios for infancy show a secularly decreasing trend (7, 20). This circumstance suggests

that females indeed suffer additional stress in infancy (perhaps even in utero) and that this stress promotes a leukemia particularly difficult to diagnose but becoming better recognized. Detailed morphological information about recent infant leukemia may validate this suggestion, and, in fact, Stewart's data (1) tend to do so. Returning to the difficulty raised in Normal Growth of explaining sex differences in infant leukemia mortality on the basis of stress, I conjecture that the completely endogenous female stress just discussed must be included in the stress of normal growth, that both figures 1a and 1b are incorrect for female infants, and that both the leukopoietic stress (perhaps before age zero) and the death rate are greater for female than for male infants.

The relations between leukopoietic stress and leukemia demonstrated in the foregoing have been shown valid at most in the few situations examined, and the relations provide only etiological suggestions. It is remarkable, however, that the associations made with stress were predicted from the idea of promotion by stress rather than from epidemiological observation. An association between leukemia and pregnancy is here better established than an assocation between leukemia and the stress of pregnancy, and the former association might be mediated by sex hormones, for instance, rather than by stress. The area of validity of the relations may be broadened by more epidemiological studies of the sort sketched in this paper, but such studies are difficult because wherever birth rates are high (and therefore interesting in this context) diagnostic facilities and reporting methods are generally inadequate. A decisive test of the association made with pregnancy lies in information about prior pregnancies in leukemic women. An inclusive 2-year study of women in the United States

would be conclusive, although a longer study would be necessary to answer questions about morphological type and the effect of parity. Relations involving stress may be elaborated and elucidated by the study of other situations of normal or pathological leukopoietic stress.

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Titles for Figures

Fig. 1a. Leukopoietic stress or rate of increase of normal daily production of leukocytes, by sex, from birth to maturity.

Fig. 1b. Average annual mortality rates from birth to maturity, by sex, for leukemia in England and Wales during 1945-1959.

Fig. 2a. Average annual age-specific birth rates for Japan, 1948 and 1954, United States, 1957, and Latin America (Chile, Colombia, Mexico, and Venezuela), 1951-1960 (approximate).

Fig. 2b. Age-specific sex ratio, M/F, of male to female average annual age-specific rate of leukemia mortality for Japan, 1953-1955 and 1959-1961, United States, 1960-1964, and Latin America (Chile, Colombia, Mexico, and Venezuela), 1959-1965 (approximate).

Fig. 3a. Age-specific birth rates for Japan, 1948, 1951, and 1954.

Fig. 3b. Age-specific sex ratio, M/F, of male to female average annual age-specific rate of leukemia mortality for Japan, 1950-1952, 1953-1955, 1956-1958, and 1959-1961.

Fig. 4a. Age-specific inverse sex ratio, F/M, of female to male average annual age-specific rate of leukemia mortality for Japan, 1958-1964, by morphological type.

Fig. 4b. Age-specific inverse sex ratio, F/M, of female to male average annual age-specific rate of leukemia mortality for England and Wales, 1961-1964, by morphological type.

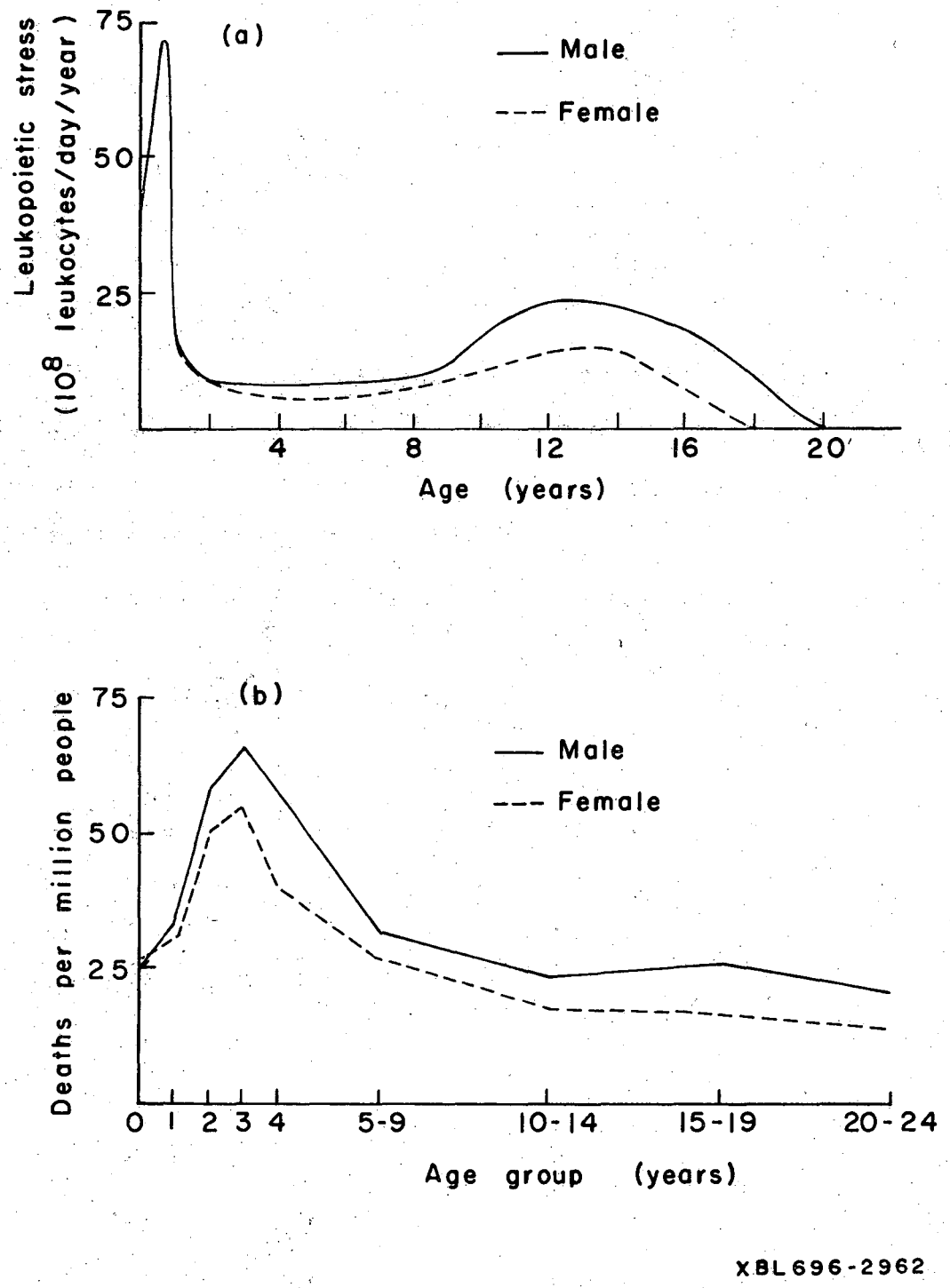
(a)
Male
Female
Leukopoietic stress
(10^8 leukocytes/day/year)
75
50
25
4
8
12
16
20
Age (years)
(b)
Male
Female
Deaths per million people
75
50
25
0
1
2
3
4
5-9
10-14
15-19
20-24
Age group (years)
XBL696-2962

Fig. 1

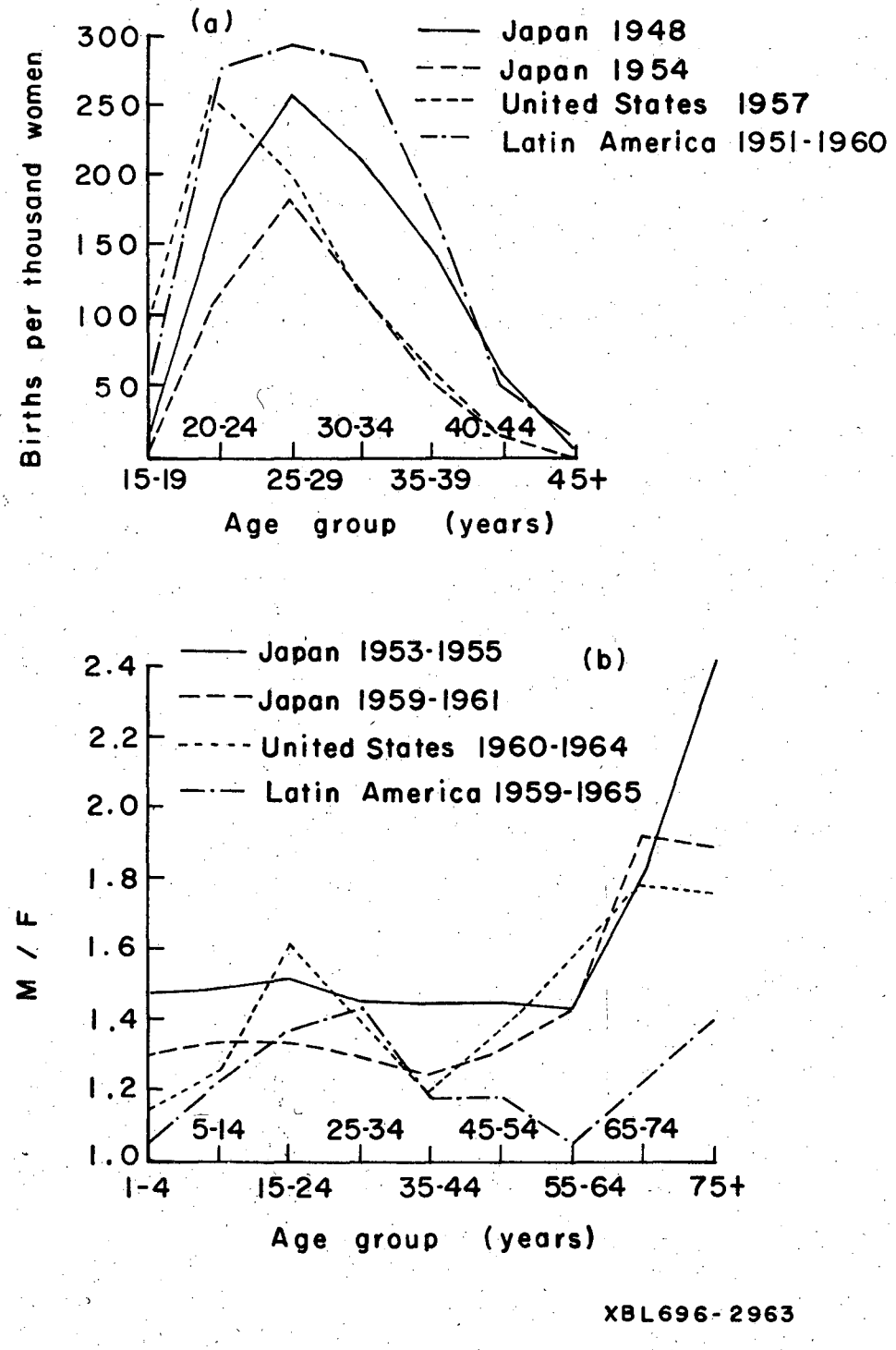
(a)
Japan 1948
Japan 1954
United States 1957
Latin America 1951-1960
Births per thousand women
300
250
200
150
100
50
20-24
30-34
40-44
15-19
25-29
35-39
45+
Age group (years)
(b)
Japan 1953-1955
Japan 1959-1961
United States 1960-1964
Latin America 1959-1965
M / F
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
5-14
25-34
45-54
65-74
1-4
15-24
35-44
55-64
75+
Age group (years)
XBL696-2963

Fig. 2

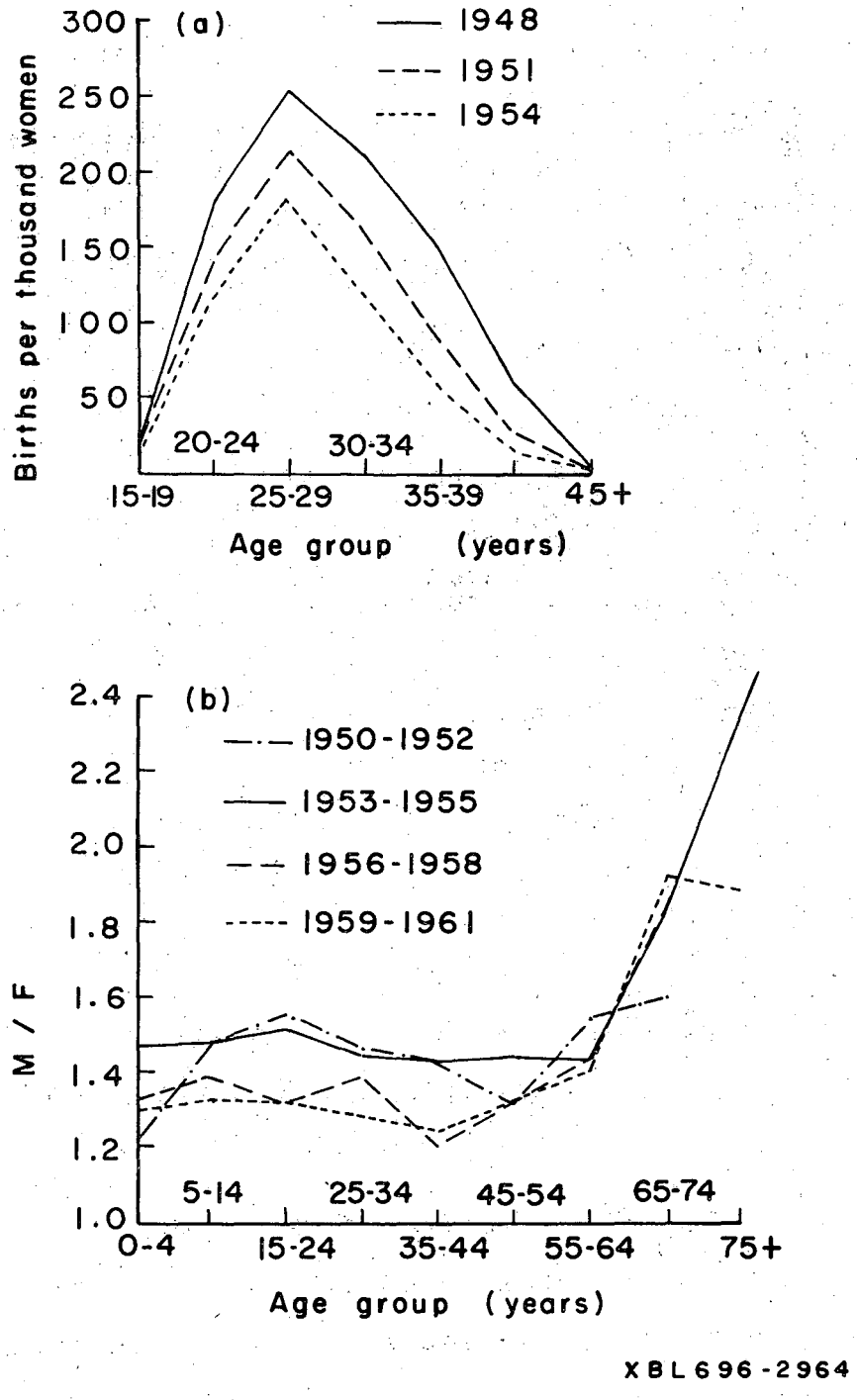
(a)
1948
1951
1954
Births per thousand women
300
250
200
150
100
50
20-24
30-34
15-19
25-29
35-39
45+
Age group (years)
(b)
1950-1952
1953-1955
1956-1958
1959-1961
M / F
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
5-14
25-34
45-54
65-74
0-4
15-24
35-44
55-64
75+
Age group (years)
XBL696-2964

Fig. 3

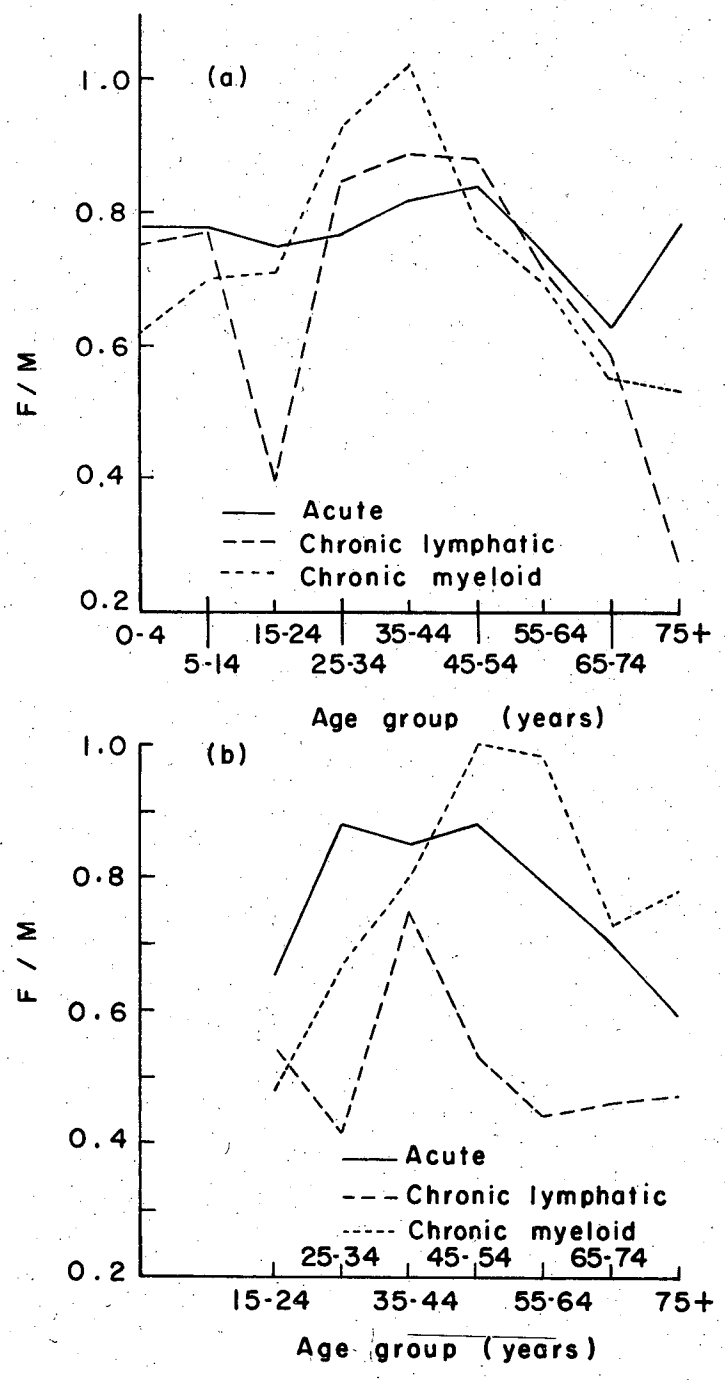
(a)
1.0
0.8
0.6
0.4
0.2
F / M
Acute
Chronic lymphatic
Chronic myeloid
0-4
5-14
15-24
25-34
35-44
45-54
55-64
65-74
75+
Age group (years)
(b)
1.0
0.8
0.6
0.4
0.2
F / M
Acute
Chronic lymphatic
Chronic myeloid
15-24
25-34
35-44
45-54
55-64
65-74
75+
Age group (years)
XBL696-2965

Fig. 4

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