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TIME SERIES ANALYSIS OF AGE-SEX SPECIFIC DEATH RATES FROM APLASTIC ANEMIA AND THE TREND IN PRODUCTION AMOUNT OF CHLORAMPHENICOL

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ABSTRACT

To explore the epidemiological features of aplastic anemia, the mortality statistics (1958-1978) in Japan were examined by age and sex. Mortality trends by age were fitted by the regression curves derived from Akaike Information Criteria Method and correlated to the trend in annual per capita production amounts of chloramphenicol (CP), taking into consideration the time-lag between the production of CP and the aplastic anemia deaths. A gradual decrease in age-specific death rates was apparent from 1960 onwards in males aged less than 45 years. In males aged 45 years and over, the year in which the mortality started to decrease apparently shifted to much more recent years with advancing age groups. Quite similar mortality trends by age were observed in females, though the year in which the mortality began to decrease shifted more quickly to recent years in females than in males. Annual per capital production amount of CP had a negative correlation in the younger age groups, particularly in males, but a significantly positive correlation in the advanced aged population, though the largest correlation coefficients were obtained with different time-lags in different age groups. The time-series analysis suggested that CP appeared to be hazardous to the aged population, but this was not fully evidenced by the present analysis.

Keywords: Aplastic anemia, age specific mortality, polynomial fitting, chloramphenicol, causality.

INTRODUCTION

In Japan, the age-adjusted mortality rate from aplastic anemia apparently increased after World War II with a subsequent stable trend; the mortality began to decrease from 1974/75 onwards in both sexes. In this paper, in order to clarify the epidemiological features of aplastic anemia, the mortality trends were examined by age and sex, and time series analysis was attempted between age-sex specific mortality and production amount of chloramphenicol (CP) since this compound has long been incriminated as one of the possible causal agents in aplastic anemia.

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MATERIALS AND METHODS

Information on deaths from aplastic anemia was provided from the mortality statistics in Japan (1958-1978) (1). Age-adjusted mortality rates were calculated by the direct method, using Segi-Doll's world population (2) as a standard. Age-sex specific death rates were calculated for the quinquennial age groups for the period of 1958-1978. The trends in the mortality rates for each quinquennial age group were analysed by fitting the regression curves of 0th to 7th degree polynomials by the minimum AIC (Akaike Information Criteria) method (3).

Annual production amounts of CP were obtained from either the Annual Statistics of the Drug Industry Products (4) or the Japanese Journal of Antibiotics (5-7). Annual production amount per capita was later calculated. Correlation between the age-specific death rate from aplastic anemia and per capita production amount of CP was evaluated, taking into consideration the time-lag between the production of CP and the aplastic anemia deaths.

RESULTS

I. *Trend in Age-adjusted mortality rate*

The age-adjusted mortality rate from aplastic anemia increased remarkably for the period of 1947-1958 in both sexes. The mortality trends for 1960-1978 are illustrated in Figure 1.

In males, the mortality was quite stable; the rate being 0.94-0.99 per 100,000 with a slight decrease from 1974 onwards. In females, the mortality was also stable with the rates of 0.9 per 100,000 in 1960-1964, followed by a gradual increase in 1965-1974. After attaining the peak of 1.10 per 100,000 in 1974, the mortality tended to decrease in females. Recent decline in the mortality is more prominent in females than in males.

Of epidemiological interest is the fact that male to female ratios of the mortality rates have been approximately the same over the years (1947-1976).

II. *Mortality by age and sex*

Figure 2 illustrates age-specific death rates from aplastic anemia in 1958-62 and 1977-78. Age-specific death rates in 1977-1978, as compared to the rates in 1958-62, markedly decreased in those males aged less than 60 years and in those females aged less than 65 years, with the substantially increased rates in the advanced ages. The rate of decrease, however, differed in the age groups of less than 60 years, being relatively small in the age groups of 10-24 in males and in that of 0-4 years in females.

III. *Trends in age-specific death rates*

Figure 3 presents the trends in age-specific death rates from aplastic anemia in males aged 0-44 years by quinquennial age group. Dotted lines represent the regression curve of the minimum AIC among curves of polynomial regressions from 0th to 7th order, which were obtained by the minimum AIC method. The transverse straight lines indicate the mean value of the age-specific death rates for these 21 years. Age-specific death rates for the age groups of 0-44 years tended to decrease gradually over the years, though minor random fluctuations seemed to be observed in different years in different age groups.

Figure 4 shows the mortality trends for quinquennial age groups of 45-69 years in males. The mortality trend for the age groups of 45-49 years was quite similar to that observed in Figure 3. The mortality for the age group of 50-54 years tended to increase gradually for the

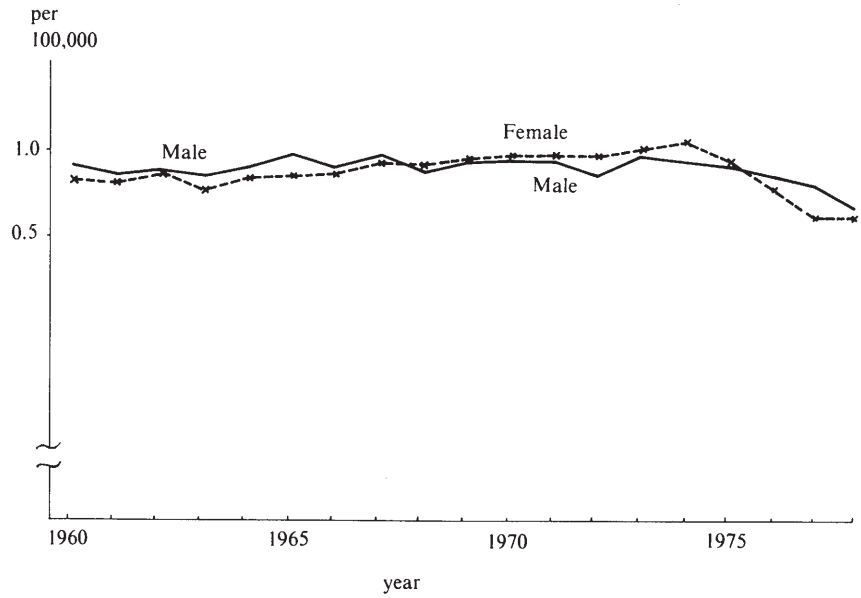

Fig. 1. Trend in age-adjusted mortality rate from aplastic anemia for the period of 1960-1978 in both sexes in Japan.

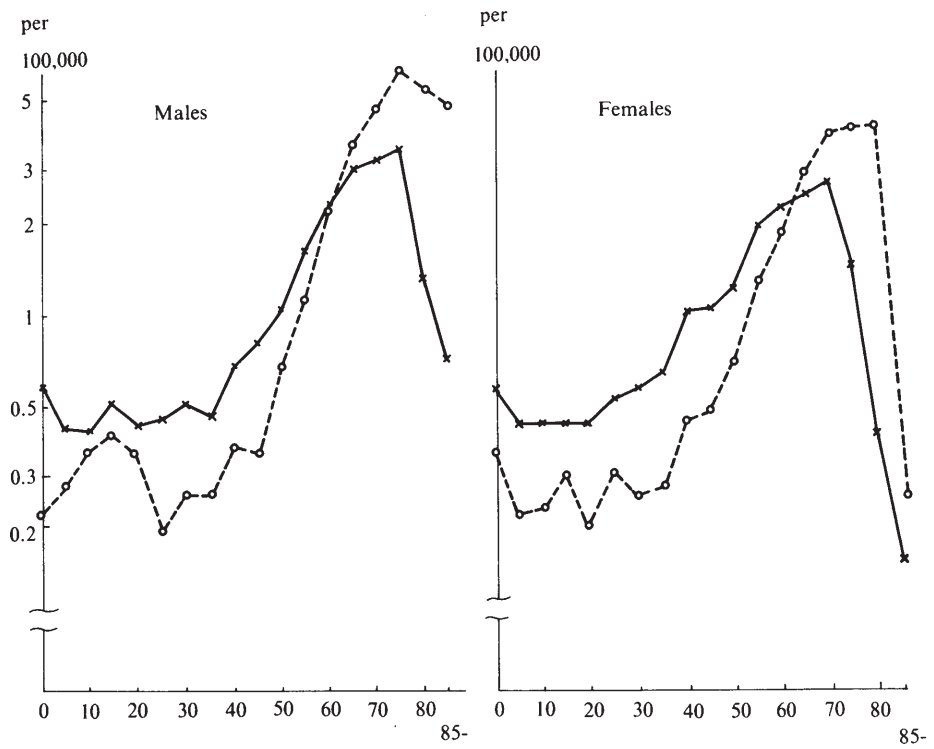

Fig. 2. Age-specific death rates from aplastic anemia in 1958-62 and 1977-78 by sex

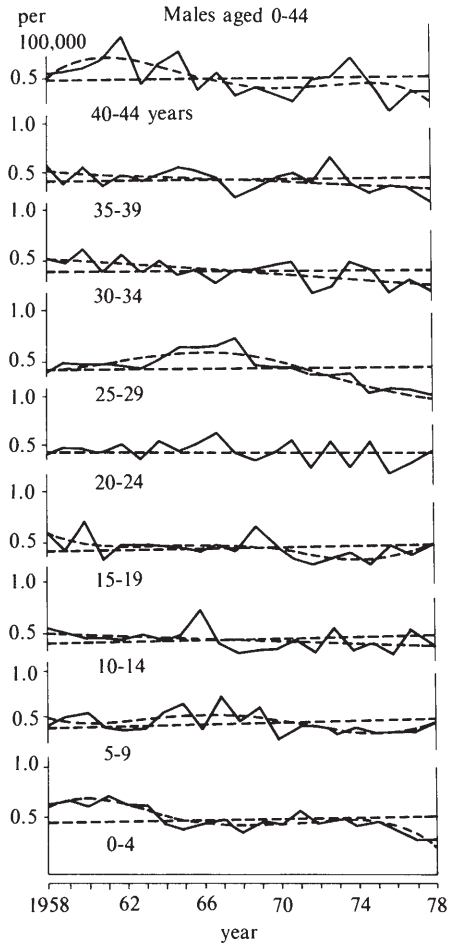

Fig. 3. Trends in age-specific mortality rates from aplastic anemia in 1958-1978.

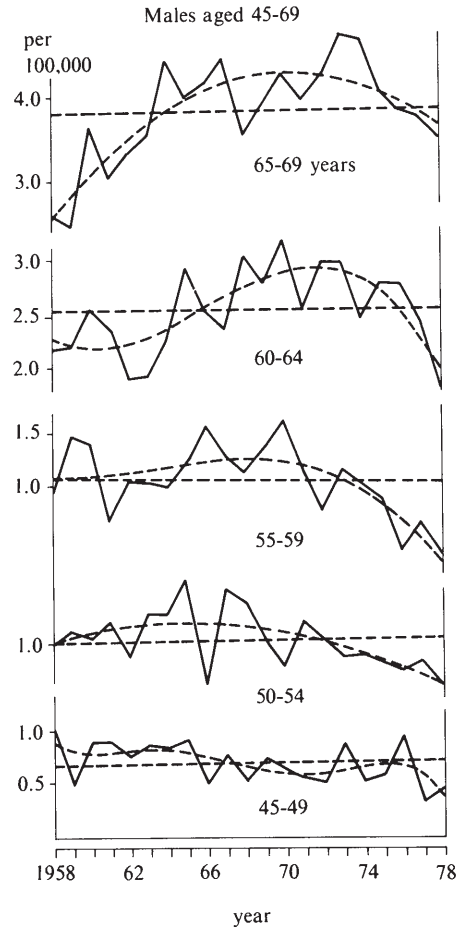

Fig. 4. Trends in age-specific mortality rates from aplastic anemia in 1958-1978

first 10 years with a peak in the years of 1964-67 and to decrease thereafter. The mortality for the age group of 50-59 years showed three peaks; 1959-60, 1966, and 1970, decreasing mortality being apparent from 1970 onwards. The mortality for the age group of 60-64 years increased from 1958 to 1970 with considerable random fluctuations, then decreased from 1971 onwards. The upward mortality trend was observed in the age group of 65-69 years for the period of 1958-72 with four peaks in 1960, 1964, 1970 and with a subsequent decline.

Figure 5 illustrates the trends in age-specific death rates for the group of males aged 70 years and over. The increase in mortality was obvious in all age groups of 70 years and over. The mortality decreased from 1975 in the age group of 70-74 years and from 1976 in that of 75-79 years, after attaining peaks in 1974 and 1975, correspondingly. The age curve of the mortality for the age groups of 80-84 years was somewhat similar to that for the age group of 75-79 years, but the latest peak was observed in 1976. The mortality for the age group of 80 years and over fluctuated markedly, showing high peaks in 1966 and 1970. The mortality seemed to increase even after 1976 in this extreme age group.

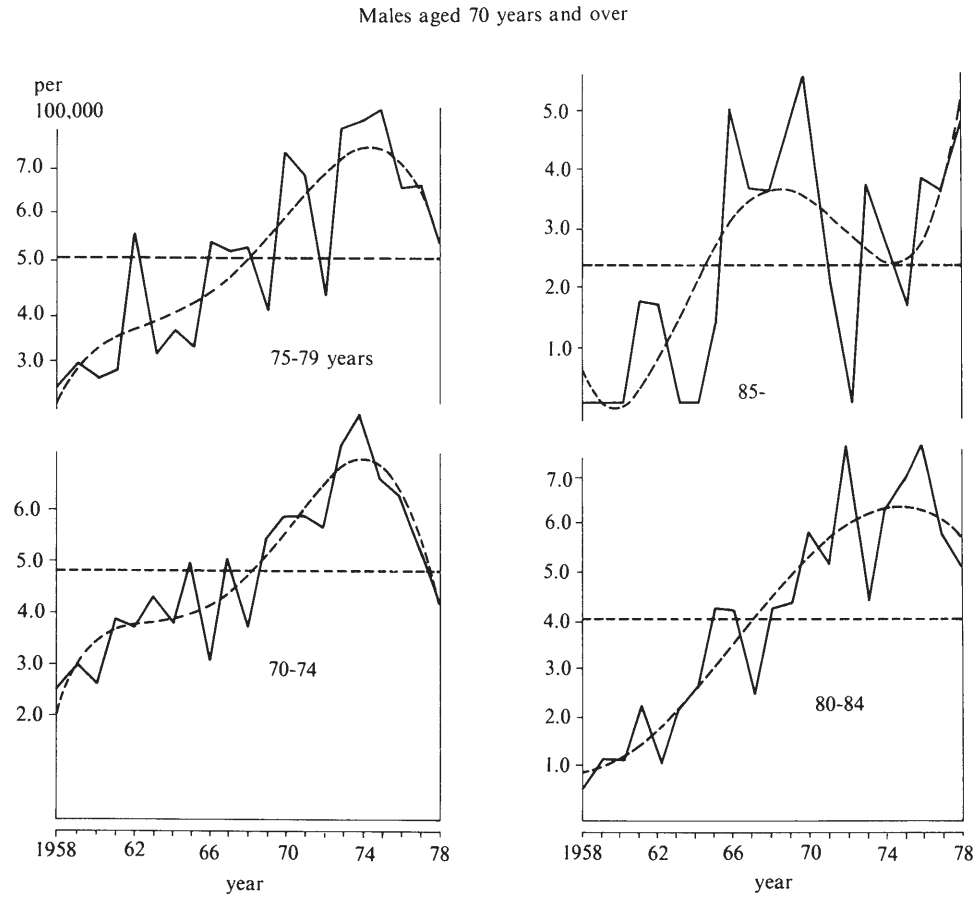

Fig. 5. Trends in age-specific mortality rates from aplastic anemia in 1958-1978

In females, much the same trends as those in males were observed, although there were some variations in each age group.

In short, taking the fitted regression curves into consideration, the mortality rates from aplastic anemia seemed to decrease gradually in the age groups of less than 45 years in both sexes from 1960 onwards. In males aged 45 years and over, the mortality appeared to decrease from 1965, but the year in which the mortality began to decrease apparently shifted to more recent years with advancing quinquennial age groups. The years in which the mortality began to decrease seemed to be later for in females than for males, though the peak years of the mortality appeared to shift more quickly to more recent years in females than in males with advancing age groups.

IV. *Prolongation of mean age at death from aplastic anemia*

The mean age at death from aplastic anemia increased by 12.2 years in males and 4.4 years in females between 1960 and 1970, and 3.2 and 6.0 years between 1970 to 1975 and −0.4 and 4.3 years between 1975 to 1978 respectively. The increase in the mean age at death from 1960 to 1978 was 14.1 years in males and 15.7 years in females. There is no difference of mean age at death between both sexes for these 18 years, although there were some differences in the trends.

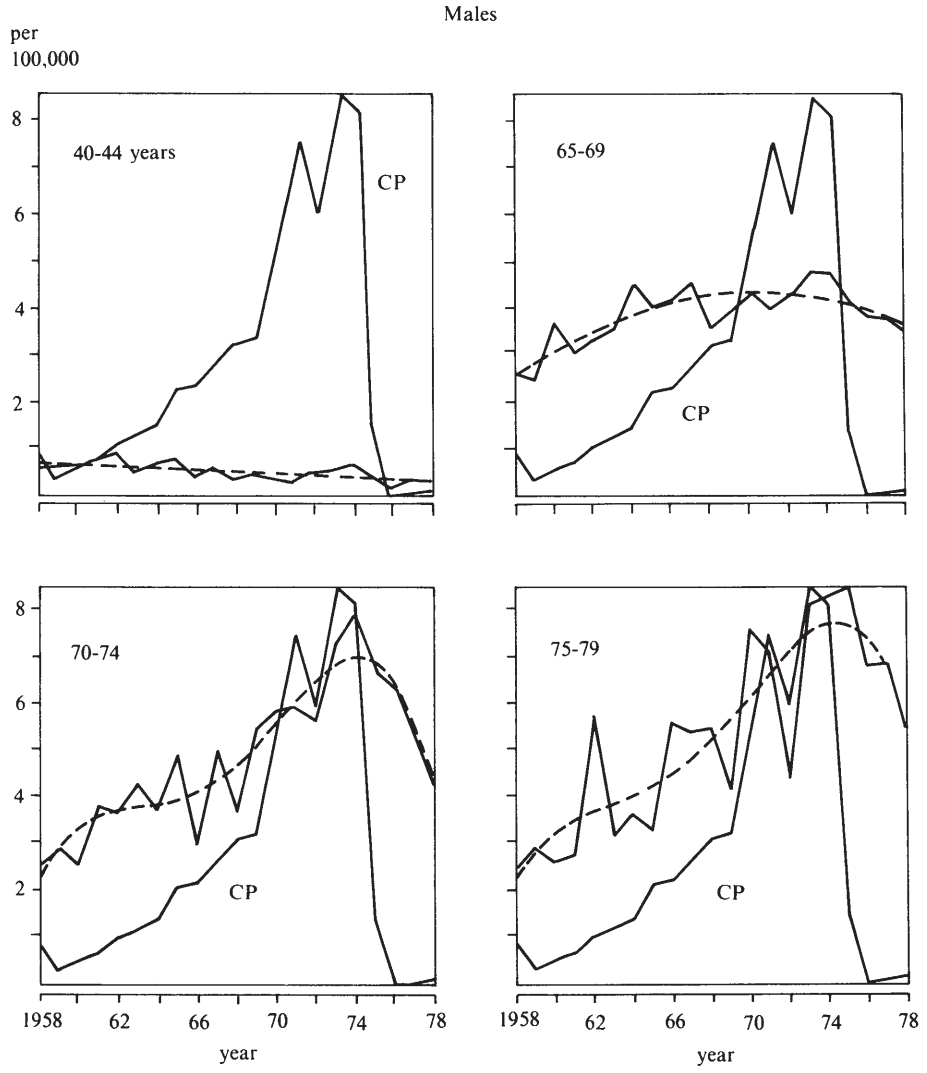

Fig. 6. Trends in per capita production amounts of CP and age-specific death rates for the age groups of 40-44, 65-69, 70-74 and 75-79 years old in 1958-1978

The prolongation of mean age at death from all causes was less marked during these 18 years: 9.2 years in males and 10.2 years in females.

V. *Correlation between per capita production amount of chloramphenicol and age specific death rates from aplastic anemia*

Figures 6 and 7 graphically present the trends in per capita production amounts of CP and age-specific death rates for the age groups of 40-44, 65-69, 70-74, and 75-79 years. The age group of 40-44 years was presented as a representative of the age groups of less than 45 years, since the trends in age-specific death rates for these age groups were mutually quite similar, as shown in Figures 3.

In the age group of 40-44 years, the trend curves were apparently unrelated for both sexes; this was also true in the age groups of 45-64 years, though not shown. However in the age groups of 70-74 and 75-79 years, the trend curves seemed to parallel each other well for both sexes.

Table 1. Correlation coefficients between per capita production amount of CP and age-specific death rates from aplastic anemia

	Time lag between production of CP and onset of aplastic anemia death							
	Males				Females			
age-group (year)	+the same year	+1 year later	+2 years later	+3 years later	+the same year	+1 year later	+2 years later	+3 years later
0- 4	−0.089	−0.119	−0.221	−0.478*	0.607**	0.790**	0.637**	0.307
5- 9	−0.206	−0.272	−0.410	−0.535*	0.230	−0.013	−0.115	−0.372
10-14	−0.212	−0.342	−0.408	−0.348	0.163	0.212	−0.093	−0.501*
15-19	−0.363	−0.553*	−0.486*	−0.446	0.049	−0.158	−0.360	−0.540*
20-24	0.060	−0.043	−0.213	−0.490*	0.556**	0.623**	0.518*	0.172
25-29	0.100	−0.185	−0.430	−0.611**	0.224	0.020	−0.153	−0.399
30-34	−0.058	−0.093	−0.337	−0.318	0.033	−0.005	−0.133	−0.229
35-39	0.271	0.024	−0.002	−0.177	0.255	0.216	0.039	−0.351
40-44	−0.063	−0.084	−0.309	−0.399	−0.050	−0.048	−0.147	−0.256
45-49	−0.177	−0.256	−0.039	−0.289	−0.296	−0.185	−0.033	−0.339
50-54	0.029	−0.114	−0.300	−0.439	0.663**	0.572**	0.375	−0.114
55-59	0.324	0.087	−0.126	−0.338	0.657**	0.620**	0.414**	−0.065
60-64	0.501*	0.488*	0.562*	0.357	0.742**	0.804**	0.445	−0.052
65-69	0.632**	0.592**	0.550*	0.341	0.686**	0.679**	0.553*	−0.443
70-74	0.640**	0.739**	0.810*	0.774**	0.545*	0.623**	0.661**	0.654**
75-79	0.509*	0.591**	0.679**	0.722**	0.494*	0.675**	0.766**	0.713**
80-84	0.382	0.588**	0.705**	0.745**	0.206	0.413	0.571*	0.777**
85-	0.208	0.001	0.099	0.210	0.223	0.156	0.451	0.489*

* $p < 0.05$ ** $p < 0.01$

+ Correlation of the production amount per capita with age-specific death rates in the same year, 1 year later, 2 years later and 3 years later, respectively.

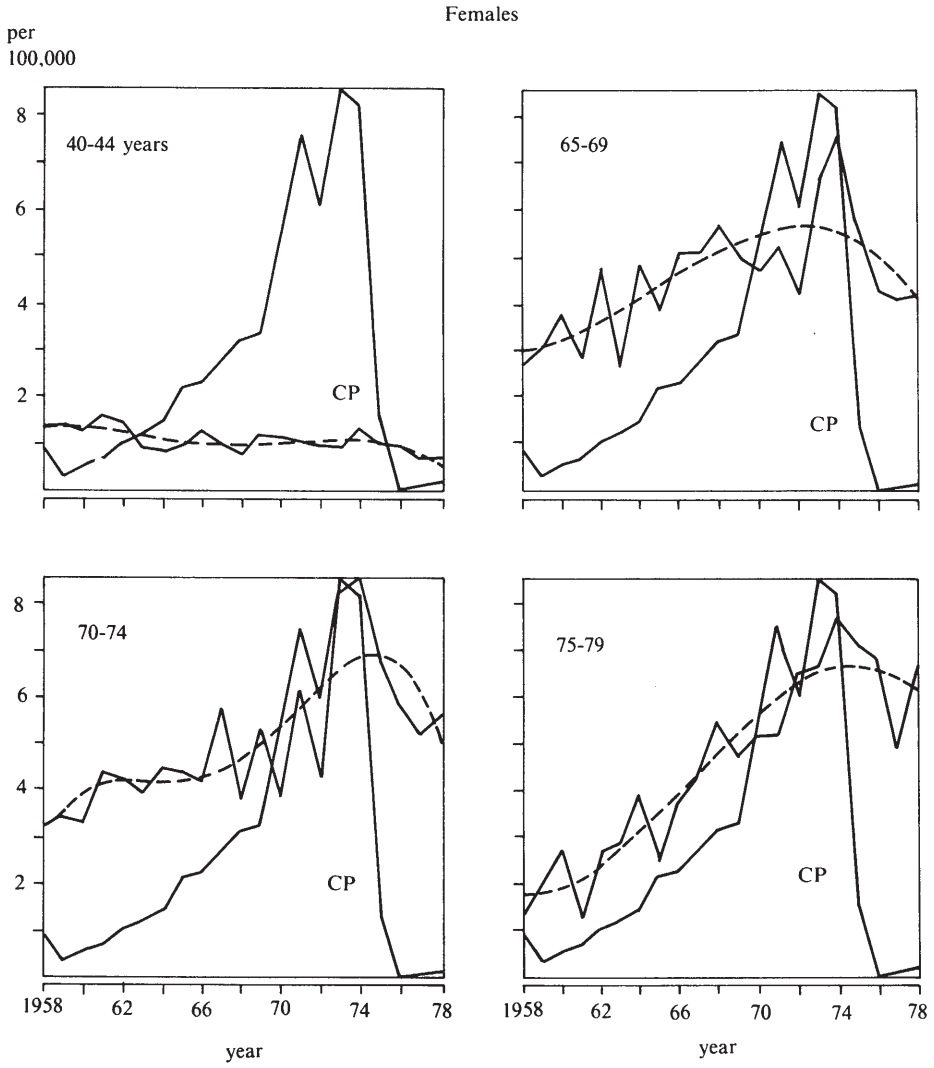

Fig. 7. Trends in per capita production amounts of CP and age-specific death rates for the age groups of 40-44, 65-69, 70-74 and 75-79 years old in 1958-1978

To examine the magnitude of correlation between these trends, correlation coefficients with their significance levels were calculated for each quinquenneal age group, taking into consideration the time-lag between the production of CP and the aplastic anemia deaths. To resolve the issue of a lag period, correlations between the annual per capita production amount of CP and the age-specific death rates were examined for the same year, 1 year later (e.g. 1970 production amount and 1971 age-specific death rate), 2 years later (e.g. 1970 production amount and 1972 age-specific death rate) and 3 years later.

Table 2 details the correlation coefficients thus obtained.

In males, the correlation coefficients were mostly negative for those aged less than 60 years. Significantly negative coefficients were observed in the age groups with lag periods as follows: 0-4 years with a 3-years lag period, 5-9 years with a 3-year lag period, 15-19 years with a 1 and 2-year lag period, 20-24 years with a 3-year lag period, and 25-29 years with a 3-year lag period. In males aged 60-84 years, the correlation coefficients were positive and mostly significant, the largest coefficient being 0.562 in the age group of 60-64 years with a 2-year lag period, 0.632 in that of 65-69 years with no lag period, 0.810 in that of 70-74 years with a 2-year lag period 0.722 in that of 75-79 year with a 3-year lag period and 0.745 in that of 80-84 years with a 3-year lag period. The coefficients for males aged 85 years and over were positive, but not significant.

In females, significant negative coefficients were observed in the age groups of 10-14 and 15-19 years with a 3-year lag period. The coefficients were positive and mostly significant in the age groups of 65 years and over, the seme as in males. The largest positive coefficients in no time lag series were 0.633, 0.657 and 0.686 for the age groups of 50-54, 55-59, and 65-69 years, respectively. In a 1-year lag period, 0.790, 0.623, and 0.804, were the largest positive coefficients for the age groups of 0-4, 20-24, and 60-64 years, respectively. In a 2-year lag period, the largest positive coefficients were 0.661 and 0.766 for the age groups of 70-74 and 75-79 years, respectively; 0.777 for that of 80-84 years in a 3-year lag period.

In short, the anuual per capita production amount of CP had a negative correlation in the younger age groups, particularly in males, but a significantly positive correlation in the advanced age groups of both sexes.

DISCUSSION

In Japan, the mortality trend of aplastic anemia could be divided into three phases; the first phase being 1947-1959, the second phase 1960-1970, and the third phase 1971 and thereafter.

In the first phase, 1950-1959, the age-adjusted mortality rate from aplastic anemia apparently increased with increasing age-specific death rates throughout the quinquennial age groups. Interestingly, the upward mortality trend in this period coincided with the remarkable reduction in deaths from infectious diseases and concomitant increase in deaths from malignant neoplasms and stroke (1). It is reported in England and Wales that the trend in the deaths from haematopoietic disorders is inversely correlated with the trend in the deaths from infectious diseases (8). This phenomenon may possibly suggest that those who would likely succumb to infectious diseases because of their impaired haematopoietic system might supposedly die not from infectious disease, but from the haematopoietic disorders themselves when the remarkable reduction of deaths from infectious disease is attained by modern medicine (9). This is not fully evidenced, but may in part explain this particular phenomenon of counter-balancing between infectious disease and haematopoietic disorders.

In the second phase, 1960-1970, the mortality from aplastic anemia was virtually unaltered in both sexes, as shown in Figure 1. Examination of the mortality by age demonstrated the gradually decreasing mortality in the age groups of less than 50 years and the increasing mortality in those of 60 years and over, the rate of increase being much more apparent in those aged 70 years and over. The mortality trend in the advanced ages had the peaks in 1968-1974; the peak year shifted to much more recent years with advancing age groups.

In the third phase, the mortality trend was characterized by a small peak in 1973-1975 and subsequent decline. Age-specific death rates noticeably decreased from 1975/76 onwards in every quinquennial age group except that of 80 years and over. The increase in the deaths from apalstic anemia for the period of 1971-1975/76, particularly in the advanced age groups, may partly be attributed to the increased rate of clinic visitation by those of advanced age (10) and also to the enhanced attention to this particular disease following nationwide epidemiological surveys conducted in 1972 and 1973 (11). The temporal drop in the rate of clinic visitation in Japan during 1971-1972 was partly due to the walkout of medical practitioners in protest against the health insurance system in Japan. In 1973, a substantial increase in the rate of clinic visitation was observed in all age groups. Since then the rate has leveled off (10). The decrease in mortality, on the other hand, began from approximately 1965, 1970 and 1974/75 in the age groups of 50-59, 60-64, and 70 years and over, respectively. Since the decrease in mortality after 1974/75 was much more remarkable in those over 65, some strongly influencing factors are supposedly involved.

The prolongation of the mean age at death from aplastic anemia during 1960 to 1975 suggests the increased risk-reducing factors of this disease, including the improvement of treatment.

The time-series analysis of age-sex specific death rates from aplastic anemia was carried out using the minimum AIC method.

Taking the fitted regression curves into consideration, the mortality rates seemed to decrease gradually in the age groups of less than 45 years in both sexes from 1960 onwards. In both sexes aged 45 years and over, the mortality appeared to decrease from around 1965, but the year in which mortality began to decrease apparently shifted to more recent years with advancing quinquennial age groups.

Various factors might affect the mortality rate from aplastic anemia. Therefore, it may not be so easy to elucidate the secular trends in age-specific death rates from aplastic anemia.

Of interest is the coincidence between the downward mortality trend after 1974/75 and the regulation concerning chloramphenicols issued in 1975 as a result of an ad hoc committee on drug effect reevaluation of the Ministry of Health and Welfare of Japan. As already stated, CP has long been incriminated as one of the possible causal agents in aplastic anemia.

Production amount of chloramphenicols was 6.3 tons in 1955 and remarkably increased to 160 tons in 1974; then it decreased to 30 tons in 1975 and to 1-3 tons in 1976-1978 (4-7). The decline in mortality from aplastic anemia after 1975 was suggested to be closely related to this reduced amount of CP production (12).

According to the results obtained by the three studies conducted by the Research Committee of Aplastic Anemia for the period of 1973-1978 (13-14), those with exposure to potentially hazardous agents such as drugs, radiation or chemical compounds accounted for 43.5%, 38.2% and 40.9% among 237, 89 and 66 reported cases in the first, second and third studies, respectively. Chloramphenicols were prescribed in 14.8% (35 out of 237 cases), 10.1% (9 out of 89 cases) and 3.0% (2 out of 66 cases) in the first, second and third studies, respectively. The prescription rate of chloramphenicols was comparatively low in the third

study. Following the regulation of indication for chloramphenicols which was issued in December, 1975, the numbers of CP prescriptions as well as the dose prescribed were apparently reduced.

Seven out of 9 cases with CP prescriptions in the second study (study period: July, 1975-September, 1976) were diagnosed before February, 1976. One of two cases reported in the third study was known to have ingested only a total amount of 0.75g of CP (0.35×3 times), and the other case ingested 2g of CP for 2 days in total. These two cases were not diagnosed as secondary aplastic anemia. Dose-response relationship between CP and the incidence of the disease was not observed. It was not suggested by the Research Committee that the causal relationship between chloramphenicol ingestion and aplastic anemia could readily be established from these clinical observations.

According to the pharmaco-epidemiological surveys of the prescription rates and doses of the drugs suspected to induce the subsequent haematologic disorders in a defined population in Nagoya (15), chloramphenicols were prescribed in 13.3%, 7.9% and 0.08% in the first, second, and third surveys, respectively (survey periods; April-September 1972, October 1975-March 1976 and October 1977-March 1978). The average duration of prescription for chloramphenicols tended to decrease in the third survey.

Prescription of chloramphenicols in combination with other drugs also suspected to induce the subsequent haematologic disorders decreased over the periods in this population in Nagoya. Marked reduction of doses and prescription rate of CP in Nagoya coincided well with the remarkably reduced amount of CP produced in Japan after 1975.

The present time-series analysis demonstrated that the amout of CP produced per capita was unrelated in the younger age groups, but the trend curves were seemingly well parallel to each other in the advanced age groups. This finding may possibly indicate that chloramphenicols are especially hazardous to the aged population. If CP were to have some effect on the death rates, it is considered that the effect would influence all age groups. The present analysis, however, indicated the downward mortality to start in different years in different age groups. Further analysis, taking into consideration the time-lag between production of CP and deaths, revealed that the annual amount of CP produced per capita siginificantly correlated with the age-specific death rates in the advanced aged population, although the correlations were shown in different age groups with different time lags. The correlation between amounts of CP produced and the regression curves of minimum AIC showed much the same results as the observed age-specific death rates. It is reported that the time interval from CP intake to onset of so called CP suspected aplastic anemia ranged from several days to 4 years. Smick reported that the correlation coefficiency with significant level was calcualted, taking into consideration year unit time-lag between amount of CP produced and aplastic anemia deaths (16).

To resolve the issue of a lag period, correlations between the annual amount of CP produced per capita and the age-specific death rates for the same year, 1 year later, 2 years later and 3 years later were examined.

The results obtained did not show sufficient evidence concerning the relationship between the two indicators, even in the aged population.

These findings can not be interpreted straightforwardly, however, since only fatal cases of aplastic anemia are included in the analysis and since the amount of CP produced does not mean the amount ingested in a population in a defined period. CP has long been incriminated as one of the causal agents in aplastic anemia, and many case reports have been documented throughout the world (17, 18). The incidence rate of aplastic anemia is very low in each country; the rate being 0.5 to 1.0 per 100,000 population (19). The proportion of so called CP-

induced cases were less than 5% of all aplastic anemia cases in our nation-wide survey in Japan (20). The low frequency may preclude clarification of the statistical association between CP and the disease.

The prescription rates of drugs other than CP, which are suspected to induce subsequent haematologic disorders, decreased simultaneously in the same periods; therefore, the pharmaco-epidemiological effects of these drugs should also be evaluated.

The decrease in mortality from aplastic anemia since 1974 might be related, to some extent, to the possibility of much more attention being paid to preleukemic conditions and other allied diseases as well as aplastic anemia from the viewpoint of differential diagnosis (21-23). The improved treatment, including systematic anabolic hormone therapy for aplastic anemia might also affect the reduced mortality (24).

Continuous observation and further analysis are required accordingly in order to clarify the picture further, using the data of incident cases occurring in a defined area. Since the fatality rate of aplastic anemia has grown lower during the last decade (25).

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