Epidemiology of Exogenous Estrogens

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EPIDEMIOLOGY, because of its concern with populations rather than individuals, is able to give unique insights into the etiology and prevention of disease and the influence of man's environment upon his health. The increasingly widespread use in recent years of exogenous estrogenic hormones by relatively healthy women has added a powerful new environmental agent to the influences on the health of large proportions of our population. Much of the needed information on the long-term effects of oral contraceptives and of estrogens used for replacement will be obtained only by epidemiologic studies (*1–2*). We shall review existing epidemiologic data and present some new data based on U.S. mortality statistics through the year 1967.

Definition of Problem

Extent of estrogen use. Available information on the extent of estrogen use in the United States is totally inadequate for most epidemiologic purposes. We have, however, used U.S. Department of Commerce figures on the value of shipments of pharmaceutical preparations for domestic consumption (*3*) to arrive at a rough approximation of the number of women using estrogens for replacement and oral contraception. We estimated that the annual cost for estrogen replacement or oral contraceptives would be about the same for each woman—$15. From this annual cost, we arrived at the number of users (table 1). Although the procedure is crude and is based on the assumption that no price change occurred over the 6-year period, the results suggest that the proportion of women 45 through 64 years using estrogen for replacement may not be grossly different from the proportion 15 through 44 years using oral contraceptives. It is likely, in fact, that estrogen replacement is more common among women in certain 5-year age groups over 45 than oral contraception is in some of the age groups 15 through 44. Both uses were at fairly low levels in 1962, but by 1967 the use of estrogens for replacement had more than doubled and the use of oral contraceptives had increased more than four times.

The estimates of oral contraceptive users in table 1 are of the same magnitude as those published in 1966 by the Food and Drug Administration (*4*). They are also fairly consistent with the results of Ryder and Westoff's 1965 survey (*5*). Our estimates on the extent of use of estrogens for replacement are considerably less than those made by Shelton in 1954 (*6*) or by Wilson in 1964 (*7*). It is not clear, however, to what age groups or to what usage of estrogens the estimates of Shelton and Wilson referred.

From discussions and informal statements in the literature, we infer that physicians began to pre-

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scribe estrogens some time after 1930. Shelton mentions that crystallin estrin was discovered and used in 1929 (*6*); Wilson stated estrogens were not yet in use in 1930 (*7*); Wallach and Henneman said in 1957 that estrogens had been in use for more than 25 years (*8*). Pharmaceutical company representatives have told us that not until the 1940's was there an appreciable market for these drugs among women of menopausal ages. While these representatives were unable to supply information on the trend in sales of estrogens before 1962, their impressions of the trends since 1962 conform with the upsurge in use indicated in table 1. Our information on the trends in the use of estrogens for oral contraception is more secure since estrogens for this purpose are known to have been first marketed in the United States in 1961.

Table 1.—Estimated number of U.S. women 15–44 years of age using oral contraceptives and 45–64 years of age using estrogens for replacement, 1962–67

Year	Estrogens—women 45–64		Oral contraceptives—women 15–44	
	Number	Percent	Number	Percent
1962	1,103,600	5.8	1,560,600	4.2
1963	1,228,467	6.3	2,482,800	6.6
1964	1,400,600	7.1	3,530,866	9.2
1965	1,705,533	8.5	4,861,733	12.5
1966	2,478,571	12.1	5,659,733	14.3
1967	2,681,733	12.9	6,844,800	17.0

NOTE: Estimates are based on assumptions that the drugs cost $15 per year per woman and that use was confined to the age groups indicated.

Effect of estrogens. The need for epidemiologic study of a number of undesirable events associated with estrogen replacement and oral contraception was first suggested by case reports. In 1939 cancer of the breast was observed coincidentally with estrogen treatment (*9*), and in 1946 cancer of the endometrium was noted in association with prolonged estrogen therapy (*10*). Additional reports which followed were reviewed by Hertz and Bailar in 1966 (*2*). Probably because of the relatively short period oral contraceptives have been used, case reports concerning them have dealt with nonneoplastic conditions. These conditions have included pulmonary embolism (*11*), cerebrovascular disease (*12*), coronary disease (*13*), depression (*14*), infertility upon drug withdrawal (*15*), hypertension (*16*), psychosis (*17*), retinal edema (*18*), and mesenteric thrombosis (*19*). Additional case reports of undesirable events that have occurred while women were using oral contraceptives are included in a review by Tietze in 1968 (*20*).

Other case reports have indicated physiological changes related to use of oral contraceptives which are difficult to classify as to their desirability, such as electroencephalographic changes (*21*), changes in excretion of urinary steroid and gonadotrophin (*22*), and melasma (*23*). A variety of changes in mood and behavior, some desirable and some not, have been reported in association with both the use of oral contraceptives and their withdrawal (*24–27*).

Our review of the epidemiology of exogenous estrogens began with epidemiologic studies in which we measured the extent of the association between estrogen use and certain effects without regard to the sequence of events. Since causes and effects are always associated, but association does not necessarily indicate a cause and effect relationship, such studies tend to be more easily interpreted when they are negative rather than positive.

We do not discuss clinical trials of these drugs because our concern has been to evaluate the effects of the drugs upon populations rather than upon individuals. Thus, although clinical trials provide unique information on the effects of drugs, they would concern us only if the study groups were representative of defined subgroups of the general population. Such representation is rarely possible in clinical trials, which generally involve volunteers.

Two studies have dealt with the association between oral contraceptives and trends in annual mortality rates for selected causes. Vessey and Weatherall (*28*) found that the mortality rates for venous thromboembolism for women 20 through 34 in England and Wales were increasing relative to the mortality rates for women before 1962 and relative to the rates for men. For deaths from this cause, these authors used categories 463–466 of the seventh revision of the International Classification of Diseases (ICD). For the age groups 35 through 44, however, the increase in mortality for women from venous thromboembolism was accompanied by similar increases for men.

In a comparable analysis of mortality trends in the United States (*29*), it was found that women's mortality rates for venous and pulmonary thromboembolism (categories 460–468 of the seventh revision of the ICD) had increased for the age groups 20 through 44 years relative to women's rates before 1962 and relative to men's rates. There were no

clear-cut indications of increases in women's mortality from coronary disease (ICD 420) or from cerebral thrombosis (ICD 332).

Moos, in a survey of wives of graduate students at a large university in the United States (*30*), has measured the association of oral contraceptive use with psychological changes. Although hampered by a large nonresponse rate (50 percent), he concluded that women using oral contraceptives tended to have fewer menstrual symptoms than women not using them.

Shelton, in 1954, compared the death rates for cancer of the breast and of the uterus for the years 1940 and 1950 with the rates for these diseases in 1930, "the year of Doisy's discovery of Estrogen" (*6*). Since the rates had not changed, he concluded that estrogen replacement was not carcinogenic. Eleven years later, Shimkin (*31*) again suggested that the stability of age-adjusted death rates for breast cancer in white women between 1930 and 1956 and the less complete, but equally stable, data on the incidence of breast cancer provided evidence against the belief that exogenous estrogens were significant in the etiology of this disease. Neither Shelton nor Shimkin, however, attempted to estimate the proportion of women in the United States using estrogens. Unless this proportion is sufficiently large, even sizable increases in relative risk would have little effect on mortality trends.

Among epidemiologic studies of oral contraceptives whose designs permit evaluation of the sequence of associated events, the retrospective approach has been applied in at least four and is being applied in at least one more. Results of three of these studies—by a subcommittee of the British Medical Research Council in 1967 (*32*), by Vessey and Doll in 1969 (*33*), and by Inman and Vessey in 1968 (*34*)—suggested that oral contraceptives were associated with significantly increased risk from pulmonary and venous thromboembolism, possibly with increased risk from coronary thrombosis, but not from cerebral thrombosis. A case-control study of venous thromboembolism in several eastern U.S. hospitals (*35*) confirmed the association noted by the British between venous thromboembolism and the use of oral contraceptives. An additional U.S. case-control study, currently in progress, is concerned with oral contraceptives and cerebral thrombosis.

We know of no case-control studies of women receiving estrogen replacement. Such studies would

Table 2.—Mean annual percentage changes in mortality of U.S. women from underlying causes involving thromboembolism, 1962–66 and 1962–67

Color and age group (years)	Cerebral embolism and thrombosis ICD 332		Arteriosclerotic heart disease ICD 420		Diseases of veins ICD 460–468	
	1962–66	1962–67	1962–66	1962–67	1962–66	1962–67
Whites:						
15–19	(—7.5)	(+20.2*)	(+40.3)	(+35.7*)	(—17.3*)	(—18.6*)
20–24	(—14.2)	(+0.7)	+8.0*	+3.2	(+4.8*)	(+4.5*)
25–29	(+6.1*)	(+15.8*)	+0.6	—2.5	+3.5	+4.3
30–34	(—2.2)	(+1.8)	+1.1	+4.9*	+9.0*	+4.9*
35–39	—15.6*	—7.4	+3.6*	+3.7*	+13.5*	+12.1*
40–44	—0.1	—2.7*	—3.0	—0.6	+12.6*	+11.7*
45–49	+2.0*	+1.4*	—0.5	—0.3	+1.3	+2.1
50–54	—6.3*	—5.4*	+0.1	—0.4	+5.5	+2.4
55–59	—3.5	—2.6	+0.3	+0.4	—0.2	—0.8
60–64	—3.2*	—2.4*	—1.4*	—1.6*	—2.0*	—3.0*
Nonwhites:						
15–19	(—39.4*)	(—20.4)	(—19.8)	(—5.5)	(—1.8)	(+5.0)
20–24	(—6.9)	(—10.2)	(+5.8)	(+5.3)	(+4.1)	(+2.2)
25–29	(+16.0*)	(+31.6)	+0.4	+5.2	(+0.8)	(—2.3)
30–34	(+25.4*)	(+22.4*)	+10.1*	+11.5*	+14.6*	+20.6*
35–39	(—23.8*)	(—19.6*)	+4.5	+5.0	+13.1*	+10.1*
40–44	—0.7	+3.5	+0.4	+0.8	+2.0*	+1.5
45–49	—8.0	—5.9*	+7.2*	+6.6	+16.5*	+12.2*
50–54	—1.6	—2.1	—0.6	—0.3	—0.8	—3.4
55–59	—1.7	—2.4	+1.6	+0.8	+2.6	+4.0
60–64	—6.0*	—5.4*	—6.1	—6.3*	—9.6*	—12.5*

* Sign is consistent on four parameters (see text).
( ) Based on less than 20 deaths in any 1 year.

NOTE: The classification of diseases used in all the tables and throughout this paper is based on the International Classification of Diseases (ICD), seventh revision, World Health Organization, Geneva, 1957.

Figure 1. U.S. mortality rates for diseases of veins and other diseases of circulatory system (ICD 460–468) for whites 25–44 years, 1951–67, by sex and 5-year age groups

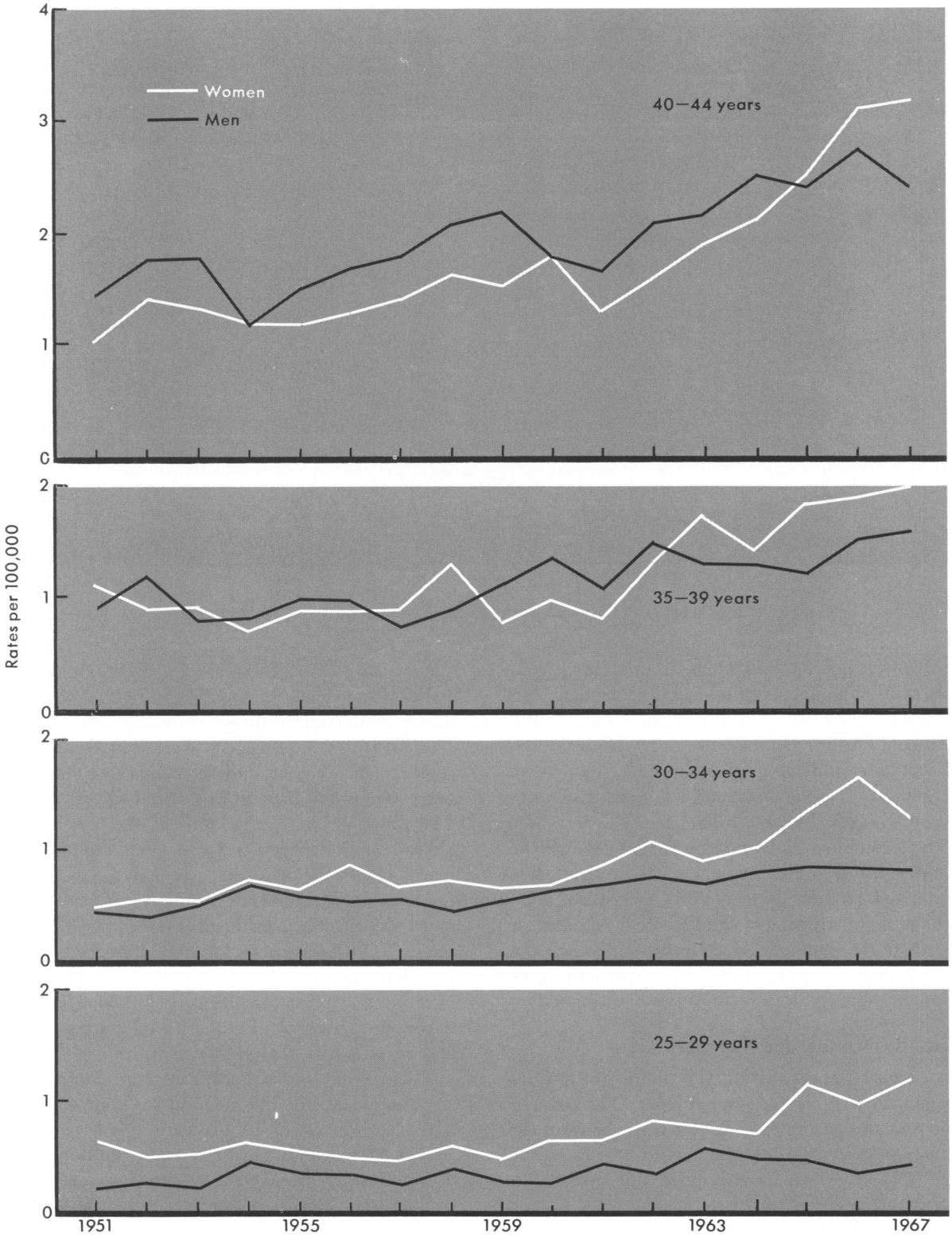
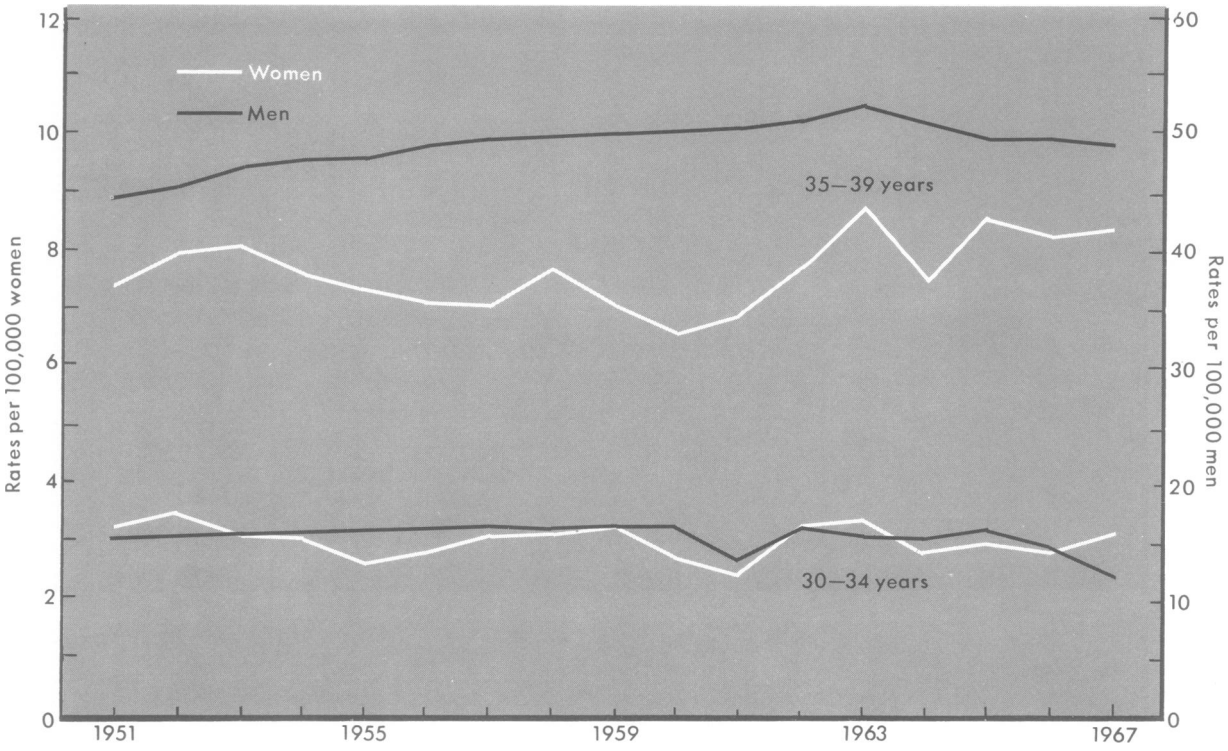


Figure 2. U.S. mortality rates for arteriosclerotic heart disease including coronary disease (ICD 420) for whites 30–39 years, 1951–67, by sex and 5-year age groups



NOTE: Use scale on left for women's rates; scale on right for men's rates.

involve formidable difficulties in matching controls and obtaining, retrospectively, medical histories and histories of use of the drug. They would be susceptible also to a tendency of physicians, when diagnosing conditions in women using estrogens, to favor those diagnoses currently suspected of association with estrogen use (*36*).

The possibility that oral contraceptives may be carcinogenic is under evaluation in at least two prospective studies (*20*). We are not aware, however, of any prospective epidemiologic studies of women in the menopausal age groups in which the relation of estrogen treatment to carcinogenesis or to other undesirable effects is being evaluated.

Mortality Trends and Estrogen Use

A previous report presented a method of analyzing mortality trends for women from 1962 through 1966 and comparing these trends with the rates for women in previous years and with the rates for men (*29*). We have now applied this method to additional causes of death.

In this method, mortality trends for women since 1962 are compared with four different sets of "expected" values. The first set consists of mortality trends for women in the 5-year period 1957–61, before oral contraceptives were marketed in the United States or estrogens were widely used for replacement. The second set consists of the mortality trends for men during the 1962–67 period. The third set is a "correction" of the first for any change in the mortality for women that had already begun before 1962, as measured by the difference between trends during the years 1951–55 and 1956–61. The fourth set is a comparable "correction" of the second set for any difference between trends in men's and women's mortality that may have already existed in the period 1956–61, before the rapid increase in the use of oral contraceptives and of estrogens for replacement.

These four comparisons are then summarized in a single statistic, the mean of the four comparisons. The mean is an estimate of the annual change in women's mortality rates in the United States since 1962 and is presented in terms of the annual percentage change in mortality since that year.

The first year of widespread use of oral contra-

ceptives, 1962, was considered the beginning of the study period. Since the major increase in the use of estrogens for replacement also seems to have begun in 1962, the same analytic technique, based on the same study period, was used for evaluating the possible effects of this use.

Thromboembolism. In table 2, the mortality trends for U.S. women from 1962 through 1966 are compared with the trends from 1962 through 1967 for three causes of death involving thromboembolism. The 1966 data have been published in a different form (*29*). The last two columns of the table show that trends in mortality for diseases of the veins (ICD 460–468), which appeared to be upward based on the 1966 data, continue to rise when data for 1967 are added to the analysis. Figure 1 shows these trends for diseases of the veins for the four 5-year age groups of white women 25 through 44 years. The widening gap between the rates for men and those for women in the three 5-year age groups 30 through 44 reflects the large and consistently positive percentage changes in women's rates seen in table 2.

In the earlier report (*29*), Markush and Seigel judged the results for arteriosclerotic heart disease (ICD 420) as "equivocal." Although most age-color groups 20 through 44 years showed some relative increase, these increases were either small or based on relatively small numbers of deaths. The 1967 data suggest no change in this conclusion. Figure 2, showing trends for the two age groups 30–34 years and 35–39 years, presents more clearly the results shown in table 2.

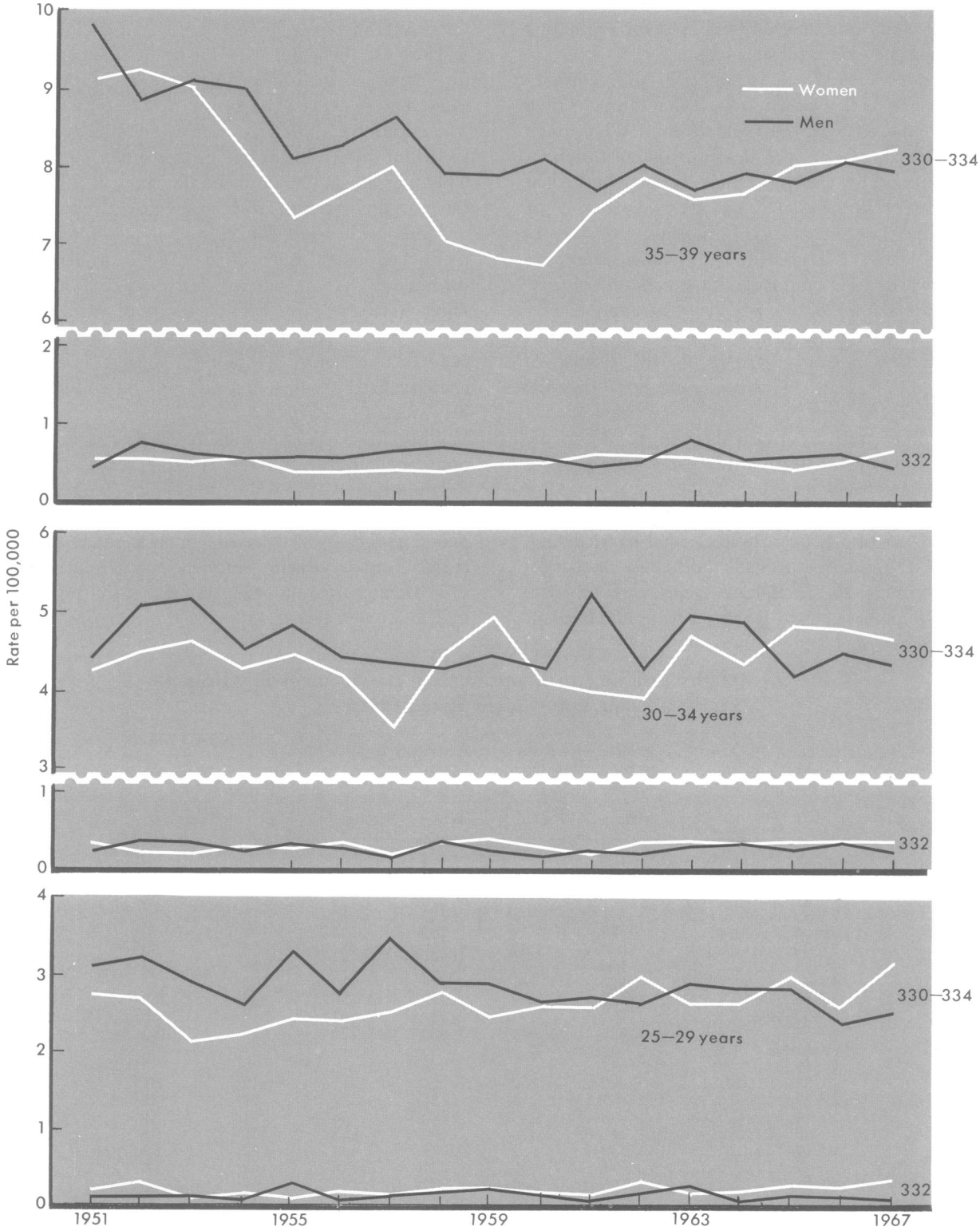
Through 1966, the data on trends in mortality for cerebral embolism and thrombosis (ICD 332) showed no evidence of a relative increase for women. The addition of 1967 data increases the mean rates for white women in the age groups under 30 years. This increase is the result of increases in 1967 in the mortality rates for white women relative to their previous rates and relative to the rates for white men. The mean rates of mortality for cerebral thrombosis that include 1967 data therefore give somewhat more cause for concern than mean rates based only on data through 1966. The trends for ICD 332 in figure 3, however, suggest that any changes in this category must still be considered equivocal.

While Markush and Seigel included data for the postmenopausal years in their 1969 report (*29*), they did not attempt at that time to associate the relative changes in mortality among women in the menopausal age groups with possible increases in estrogen replacement treatment. Since the relative increases in ICD categories 460–468 were rather sharply limited to women below 45 years, the relationship of

Table 3.—Deaths assigned to 3 underlying causes involving thromboembolism, United States, 1966

Color and age group (years)	Cerebral embolism and thrombosis—ICD 332		Arteriosclerotic heart disease—ICD 420		Diseases of veins—ICD 460–468	
	Men	Women	Men	Women	Men	Women
Whites:						
15–19	9	2	27	10	14	16
20–24	9	4	75	39	22	53
25–29	7	11	198	59	17	51
30–34	17	19	709	135	39	78
35–39	30	27	2,529	431	75	95
40–44	106	63	6,475	1,143	151	176
45–49	195	141	12,716	2,319	235	215
50–54	477	252	21,252	4,556	345	265
55–59	961	491	30,752	7,961	513	355
60–64	1,626	1,042	37,989	13,170	612	469
Nonwhites:						
15–19	2	1	8	3	2	5
20–24	0	2	26	11	12	21
25–29	2	4	54	37	13	31
30–34	8	8	179	98	21	31
35–39	19	19	406	228	32	64
40–44	39	32	876	434	42	69
45–49	71	55	1,327	718	62	71
50–54	166	125	1,982	1,127	69	62
55–59	255	218	2,658	1,634	135	98
60–64	355	353	3,330	2,153	126	128

Figure 3. U.S. mortality rates for vascular lesions of the central nervous system (ICD 330–334) and cerebral embolism and thrombosis (ICD 332) for whites 25–39 years, 1951–67, by sex and 5-year age groups



mortality to the use of oral contraception among women under 45 and of estrogen replacement among women over 45 may be totally different. The data for the three thromboembolic diagnoses in table 2 for the eight age-color groups within the age range 45 through 64 years do not suggest any major relative increase or decrease in the mortality for women that might be related to increasing use of estrogen replacement.

The relative importance of the three diagnoses as underlying causes of death varies considerably. Table 3 shows the frequency with which, in 1966, physicians listed each of these three diagnoses (ICD 332, 420, and 460–468) as the underlying cause of death of white and nonwhite men and women 15–64 years of age.

Trends for selected other causes. Only a small portion of deaths from stroke in the 15- through 44-year age group are coded to cerebral thrombosis (ICD 332). Arbitrary statistical coding practices, together with the recognized difficulties in the differential diagnosis of strokes, suggest that an appreciable proportion of deaths in the categories 331 and 333 to 334 may also involve cerebral thrombosis (*37, 38*). The possible involvement of other statistical categories has prompted us to analyze all ICD categories of vascular lesions of the central nervous system. The results are summarized in table 4 and figure 3 for selected age-color groups.

The results of surveying ICD categories 330–334 through 1967 can be summarized as showing a somewhat more suspicious picture among women in the reproductive ages than the negative one previously reported for category 332 by itself (*29*). The suspicion arises because of the fairly large proportion of positive results in the three categories in which thrombotic cerebral disease may be coded (331, 332, and 333–334). Figure 3 indicates how these changes have affected the mortality trends among white women 25–39 years in the broad 330–334 group. Not all age groups of women using oral contraceptives were affected. Nor were there significant changes in the trends for the menopausal or postmenopausal age groups that might be related to estrogen replacement.

We include the frequencies of diagnoses in the categories 330–334 in 1966 to indicate their relative importance as causes of death (table 5). Category 331 is the largest of the three suspect categories; the majority of deaths of women under

Table 4.—Mean annual percentage changes in mortality of U.S. women from 3 underlying causes involving vascular lesions of the centra nervous system, 1962–67

Color and age group (years)	Total vascular diseases of the central nervous system—ICD 330–334	Subarachnoid hemorrhage—ICD 330	Cerebral hemorrhage—ICD 331	Other vascular diseases of the central nervous system—ICD 333–334
Whites:				
15–19	0.0	+0.4	−4.0	(+3.9*)
24–25	−1.8	+0.5	−5.8	(−6.6)
25–29	+0.3	+1.2	−0.9	(−1.7)
30–34	+2.7	−0.5	+8.6*	(+8.1*)
35–39	+1.5*	−0.6	+7.1*	(+4.9)
40–44	+0.9*	−2.0	+4.2	+5.8*
45–49	+0.2	−2.4	+1.6	−0.7
50–54	+1.1	+0.7	+2.1	+1.1
55–59	+1.0	0.0	+2.1	+3.8
60–64	−0.3	+0.7	+0.5	−2.7
Nonwhites:				
15–19	−3.7	(−10.9*)	(−7.2)	(+29.2*)
20–24	+2.6*	(−2.1)	(+6.1)	(+24.1*)
25–29	+0.9	−4.6	+3.5	(+3.6)
30–34	+3.0	−1.0	+2.9	(+18.3*)
35–39	−0.4	+3.1*	−0.3	(+9.6)
40–44	+3.3	+9.4*	+3.3	−0.7
45–49	+2.2	+9.8*	+1.8	+13.9*
50–54	−0.1	+6.9*	+0.8	−5.0
55–59	−1.2	−3.2	0.0	−3.5
60–64	−6.6*	−6.6	−5.9*	−11.1*

*Sign is consistent on four parameters (see text).
( ) Entries based on less than 20 deaths in any 1 year.

Table 5.—Deaths assigned to 3 underlying causes involving vascular lesions of the central nervous system, United States, 1966

Color and age group (years)	Total vascular diseases of the central nervous system—ICD 330–334		Cerebral hemorrhage—ICD 331		Other vascular diseases of the central nervous system—ICD 333–334	
	Men	Women	Men	Women	Men	Women
Whites:						
15–19	100	67	21	18	25	13
20–24	104	93	28	32	15	9
25–29	118	128	41	41	10	9
30–34	211	231	59	58	12	9
35–39	411	419	134	129	18	12
40–44	777	752	342	289	30	28
45–49	1,248	1,232	668	568	39	33
50–54	2,354	1,835	1,361	990	103	66
55–59	3,722	2,676	2,218	1,622	156	94
60–64	5,702	4,114	3,402	2,453	323	217
Nonwhites:						
15–19	28	21	11	11	4	2
20–24	29	50	10	18	5	4
25–29	63	63	27	25	6	3
30–34	100	154	40	61	9	9
35–39	214	276	135	147	8	8
40–44	432	466	278	306	26	14
45–49	614	630	415	429	33	30
50–54	900	855	588	574	64	46
55–59	1,166	1,069	783	718	69	64
60–64	1,500	1,468	959	950	132	108

Table 6.—Mean annual percentage changes in mortality of U.S. women from 4 broad causes, 1962–67

Color and age group (years)	All causes—ICD 000–E999	All causes excluding violence—ICD 000–795	All causes excluding neoplasm and violence—ICD 000–139, 240–795	All neoplasms ICD 140–239
Whites:				
15–19	+2.0	+1.0	+2.3*	−2.5*
20–24	−0.6	−0.6	−1.5	+2.3
25–29	−1.8	−1.7	−2.0	−0.6
30–34	−0.1	+0.6	+0.2	+1.4
35–39	−1.0	−0.7	−0.4	−1.2*
40–44	0.0	0.0	−0.6	+0.5
45–49	−0.1	−0.1	−0.1	−0.1
50–54	+0.3	+0.3	0.0	+0.4
55–59	+1.3	+1.2	+0.8	+1.7
60–64	−0.8	−0.8	−1.2*	+0.1
Nonwhites:				
15–19	−1.0	−2.4	−3.3	+4.3
20–24	−0.8	−2.2	−2.7	+2.8
25–29	−2.1	−3.0	−3.5	+0.8
30–34	−0 4	+0.1	+0.1	+0.5
35–39	0.0	0.0	+0.7	−2.0
40–44	−2.2	−1.9	−1.2	−4.2*
45–49	+3.0	+2.6	+3.4	+0.1
50–54	−1.2	−1.2	−1.2	−1.1
55–59	+1.0	+1.0	+0.8	+1.8
60–64	−5.6*	−5.6*	−5.6*	−5.3

*Sign is consistent on four parameters (see text).

age 45 which were ascribed to one of the categories 330–334 were in category 330.

Trends in broad cause-of-death categories. In the previous trend study in which these analytical methods were used, an alternative interpretation for the increasing trends in ICD categories 460–468 was offered (*29*). Instead of a true increase, physicians certifying death certificates may have merely been showing a greater preference for these diagnostic categories.

ICD categories 460–468 represented only about 1 percent of all deaths in 1967 of women in the United States in the age groups 15 through 64 years. Yet, since thromboembolism is involved indirectly in many diseases and, in fact, appears on more than seven times as many death certificates as those on which it is coded as the underlying cause of death (*29*), it is possible that broad cause-of-death groups may also reflect the increases observed in ICD 460–468.

Table 6 indicates that the mortality for women in most age-color groups has remained relatively unchanged since 1962 with respect to overall death rates. That there are no consistent increases or decreases in any of the broad diagnostic subgroups suggests that any apparently harmful effects of oral contraceptives since 1962 have been (*a*) confined fairly completely to infrequent causes of death, (*b*) counteracted by benefits, or (*c*) caused merely by a change in diagnostic practices. Furthermore, estrogen replacement is not associated with any appreciable changes in the broad categories in table 6, including neoplasms.

If any of the apparent increases in ICD categories 420 and 460–468 indicated in table 2 are in fact true increases in mortality, one would expect an increase in the death rate from all causes, assuming that rates for other causes remain unchanged. If, however, the observed increases in 420 and 460–468 merely reflect changes in diagnosis from other categories, then there should be no changes in mortality from all causes. In table 7 we estimate the effect that observed changes in categories 420 and 460–468 should have on all causes of death and on all causes excluding violence and neoplasms if no diagnostic bias has occurred, that is, if the excess deaths in categories 420 and 460–468 represent an increase in all deaths. It can be seen that the percentage increases in all deaths that these observed changes would cause are all small; almost all, in fact, are smaller than the variations in either direction that actually occurred (table 6).

Table 7.—Calculated effect of observed relative changes in mortality of U.S. women from venous thromboembolism and coronary thrombosis on their mortality from all causes, 1962–67

Color and age group (years)	Effect of percentage change on—	
	All causes [1]	All causes excluding violence and neoplasms [1]
Whites:		
15–19	0.0	+0.1
20–24	+0.1	+0.1
25–29	0.0	0.0
30–34	+0.2	+0.3
35–39	+0.2	+0.5
40–44	0.0	+0.1
45–49	0.0	−0.1
50–54	0.0	−0.1
55–59	+0.1	+0.1
60–64	−0.5	−0.7
Nonwhites:		
15–19	0.0	0.0
20–24	+0.1	+0.2
25–29	+0.1	+0.2
30–34	+0.7	+1.0
35–39	+0.4	+0.6
40–44	+0.1	+0.1
45–49	+1.0	+1.3
50–54	−0.1	−0.1
55–59	+0.2	+0.2
60–64	−1.4	−1.7

[1] Assuming that the rates for all causes except venous thromboembolism (ICD 406–468) and coronary thromboembolism (ICD 420) remained constant.

We have also analyzed mortality trends for violent deaths, including the three major subcategories of accidents, homicides, and suicides. This analysis gave no indication that estrogen use was associated with any of these causes of death.

Discussion

The unfavorable mortality pattern for women in the United States, which was noted for diseases of the veins through 1966, continued through 1967. The equivocal results observed through 1966 for coronary thrombosis remained equivocal in 1967. The formerly negative pattern for cerebral thrombosis, however, appeared less negative when the data for 1967 were added. Yet the overall mortality pattern for U.S. women is relatively favorable. Since trends for broad cause-of-death groups have not changed, any unfavorable trends in proportionally small diagnostic categories are being eclipsed by more profound and favorable changes in other categories. There is always a possibility that diagnostic biases and other well-recognized difficulties

characteristic of retrospective studies may be responsible for some of the positive results in such studies. The extent of the association of oral contraceptives with specific diseases may thus be less than retrospective and trend studies have indicated.

Results from clinical trials and case reports cannot be generalized and applied to the population as a whole. Yet existing epidemiologic data are clearly inadequate, a deficiency which has even broader implications than the potential influence of estrogens on health. Our present epidemiologic methods are apparently inadequate for the surveillance of the widespread transformations that man is increasingly able to inflict upon his internal and external environment. Even additional retrospective and prospective studies may not resolve the issue of whether thromboembolism is related to oral contraception, since unique problems arise in the application of standard epidemiologic techniques to studies of estrogen use. Should drug usage change in the near future, definitive answers may never be found. After about 35 years of estrogen use, we have not yet resolved the issue of carcinogenesis and estrogen replacement.

The techniques used in our report entail comparisons of rates for women with rates for men so that we have not included data on cancer of the breast or uterus. A preliminary review of trends for these diseases, however, suggests that a rise in cancer of the breast in selected age groups may have reversed the downward mortality trend for women reported by Lilienfeld (*39*). Additional retrospective and prospective studies of the effects of estrogenic agents are in progress, but the current level of uncertainty is disturbing in view of the millions who have been using estrogens for so many years.

Improved epidemiologic surveillance, however, may offer at least a partial solution. Surveillance cannot replace the need for refined retrospective and prospective studies, but it might provide prompt clues to major changes in the health of our populations and provide valuable guidance for more definitive research. The most urgent need is improved information on the population's exposure to new agents, but our routine collection of data on mortality and morbidity will also have to be improved.

Data showing the patterns of drug use in the United States and other nations, by the user's age, sex, geographic location, and purpose of use, should be routinely published. A central agency could develop such data by systematically collecting reports on drug sales and distribution. These data could be supplemented and verified by routine national interview surveys of representative samples of the population. The data would permit epidemiologic studies of the relationship of patterns of use to patterns of disease occurrence.

U.S. data on mortality suffer from an archaic dependence on the reported cause of death. Greater application must be made of the diagnostic and environmental data that are available at the time of a person's death without regard to arbitrary judgments on their contribution to his death, a suggestion made in a recent advisory report to the National Center for Health Statistics (*40*). Analytical methods for applying such information have been proposed (*41, 42*) and should be refined for these purposes.

The routine collection of data on the prevalence of selected disease conditions and of drug use before death, together with routine morbidity surveys to collect comparable information on drug use and morbidity in the general population, would provide a powerful and flexible epidemiologic surveillance system. With such a system, any changes in the degree of association of selected environmental factors with selected disease conditions could be quickly detected.

The many behavioral factors which determine whether a woman becomes a routine user of oral contraceptives or estrogens may be powerful determinants of thromboembolic diseases regardless of any direct physiological effects of the estrogens themselves. Epidemiologic studies must therefore delve into the question of why women request, tolerate, and need oral contraceptives or estrogens for replacement.

The extent of danger from widespread and long-term estrogen use remains largely unknown. We need to give far more attention to improving surveillance of both the health of our populations and their exposure to new agents. We must learn to measure accurately and quickly the beneficial and harmful effects of new environmental factors, of which estrogens are just one example. Exposure of large segments of the population to new environmental agents is a growing fact of modern life. Clinical trials, even of the highest caliber, will not assure the safety of agents which are to be used by healthy populations.

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Existing data on the undesirable effects that widespread use of estrogens may be having on primarily healthy women are inconclusive. Alternative interpretations are possible for the results of epidemiologic studies which have suggested an association between thromboembolic disorders and oral contraception. Comparable studies of the relationship of estrogen replacement treatment to thromboembolic and other diseases are lacking. The long-term effects of either form of estrogen treatment will be especially difficult to determine.

Case-control and prospective studies will continue to provide valuable information. Yet a number of factors, such as the patient's emotional and physical makeup, may influence the use of estrogenic agents and seriously impair the interpretation of even the best of these studies. Furthermore, if any undesirable effects are discovered as a result of such studies, the knowledge may come too late for the millions of women who have been using these agents for many years.

Since this dilemma is pertinent to an increasing number of new environmental substances that man is creating, improvements in epidemiologic surveillance are needed. The improvements must include systems for routine collection and prompt review of data both on the extent and patterns of exposure to new agents and on the patterns of mortality and morbidity in the population. Only by establishing more powerful systems for epidemiologic surveillance will epidemiologists be able to safeguard modern man from the innumerable therapeutic missiles he sends into his midst.