within 10 percent of one another. The content of RNA in the tissues and the specific activity of the RNA were then calculated. We were unable to find any statistically significant increase of either the RNA content of the brain or the incorporation in vivo of H^3-uridine into brain RNA (Table 1) in response to administration of pemoline. In fact, the pemoline-treated animals may show a slight decrease in RNA content (*5*).

In order to reconcile the seeming discrepancy between our results and those reported by others (*2*), it might be argued that the effect of the drug is to stimulate the synthesis not of the total RNA of the brain, but of a special (rare) class of RNA. It might be supposed that only this special class of RNA is synthesized by the RNA polymerase that was measured in vitro by Glasky and Simon (*2*), and that the RNA polymerase responsible for bulk synthesis of RNA is undetectable under these same conditions in vitro. According to this argument, pemoline would have an effect in vitro but not in vivo, but there is no compelling reason to believe that this may be true. If there is no such special class of RNA, another argument to explain the fact that total brain RNA does not increase in response to pemoline might be that the drug increases the turnover of brain RNA, so that, although there is increased synthesis of RNA, it is balanced by rapid breakdown. If this were so, however, one would expect that the RNA from the drug-treated animals would have substantially higher specific activities than the controls. This was not observed. Although it is difficult to draw firm conclusions on the basis of negative findings, the data presented in this report suggest that much more work needs to be done before magnesium pemoline can be regarded as a drug that stimulates the synthesis in vivo of RNA in the brain.

N. RONALD MORRIS
GEORGE K. AGHAJANIAN
FLOYD E. BLOOM
Departments of Pharmacology, Psychiatry, and Anatomy, Yale University, New Haven, Connecticut

References and Notes

1. For recent reviews see *Macromolecules and Behavior*, J. Gaito, Ed. (Appleton-Century-Crofts, New York, 1966).
2. A. J. Glasky and L. N. Simon, *Science* **151**, 702 (1966).
3. N. Plotnikoff, *ibid.*, p. 704.
4. We thank R. K. Richards of Abbott Laboratories for providing us (through N. J. Giarman of the Department of Pharmacology) with samples of magnesium pemoline.
5. When all control and all treated animals were grouped and compared as two larger samples by Student's *t*-test, the value of P for the significance of the apparent decrease in total brain RNA for the pemoline-treated group was $0.1 < P < 0.5$. There was no statistically significant difference for the RNA specific activity measurements between the two combined samples.
6. We are grateful to Donna Reno for technical assistance. Supported by American Cancer Society grant P333 and PHS grant 5-T1-CA5055.

10 October 1966

Leukemia Mortality: Downturn Rates in the United States

Abstract. *A decline, the first ever observed, has recently occurred in leukemia mortality rates for the white population of the United States between the ages of 1 and 74. Possible explanations include diminished exposure to medical x-rays following the release in the United States and Great Britain in 1956 of widely publicized reports on the biologic effects of ionizing radiation.*

A progressive rise in leukemia mortality rates over time has been described in the United States (*1*), England (*2, 3*), and elsewhere (*4*). Among possible reasons for the increase are better diagnosis and reporting, improved survival from infections in the preleukemic phase, and increasing exposure to environmental leukemogens. To determine the extent to which these influences are still operative, we have examined recent leukemia trends in the United States and in England and Wales.

To U.S. leukemia-mortality rates for 1921–60 (*1*) we added data through 1965 (*5*); Fig. 1A illustrates the trends for the white population, on semilogarithmic scale to enable visualization of the rate of change with the passage of time. In the most recent 5-year period, 1961–65, the leukemia rates were for the first time lower than those for the previous period in all age groups from 1 through 74 years, the decline being greatest among children aged from 1 to 4. The downturn was preceded by a variable interval of decelerated climb, such as would occur if improvements in case-detection were approaching their limits while other factors changed little. The earlier fall in leukemia mortality among children under 1 year has been attributed to reduction in wrong diagnoses, which are much more common among infants than for older patients (*6*).

The trends for U.S. nonwhites between 1921 and 1965 (Fig. 1B) were less regular because of the small number of deaths in each category considered. Generally, the rates for the last decade tended to level off, but there was no consistent recent downturn as shown by the white population.

To determine whether the decrease noted for U.S. whites also occurred elsewhere, we examined statistics for England and Wales from 1921 to 1964 (*7*); in availability of published data and in characteristics of medical practice and population, this area resembles the United States. Because deaths from leukemia were fewer in England and Wales, the rates were more variable than among U.S. whites. While the trends for the two populations were similar until 1960, a decline in rate during the last time-period in England and Wales occurred only among children under 5 years. The rates for persons from 5 to 49 years have leveled off, but for the older age groups a slight rise has continued.

If the long-term increase in mortality from leukemia was partially the result of environmental factors, the recent decline among the U.S. white population suggests that these factors have become less prevalent or less effective with time. Since the rates for U.S. nonwhites and for England and Wales are still in the process of stabilizing, it appears that any decrease in environmental factors was greater, or occured earlier, among U.S. whites. In explaining the racial differences in the United States one should consider the probability that, in the past, diagnosis and reporting of leukemia were more complete among whites than nonwhites, so that the recent trends among nonwhites may reflect a narrowing of this gap.

It is of interest that the largest reduction in rates among U.S. whites, and the only decline in rates for England and Wales, occurred in children under 5 years. Although this phenomenon may have resulted from lengthening of the duration of survival of leukemia, with a shift in mortality to greater ages, certain laboratory (*8*) and epidemiological (*9*) observations suggest that the mortality experience of young children is the most sensitive indicator of environmental leukemogens.

While factors responsible for the downturn in mortality from leukemia among U.S. whites are unknown, one may suspect environmental exposures which have varied concomitantly with

changing leukemia rates. In 1956 the National Academy of Sciences–National Research Council in the United States and the Medical Research Council in Great Britain issued reports on the biologic effects on man of ionizing radiation (*10*); the wide publicity seems to have led to more conservative use of medical x-rays. Over the past decade there has been a downward trend in exposures to medical radiation as measured by the gonad dose per capita (*11*). Although no comparable data are available on bone-marrow dosage, in the United States there appears to be much more care taken now than 10 years ago in radiation protection, wider use of radiologic devices (such as image-intensification) that greatly reduce radiation exposure, and concerted effort to employ fluoroscopy only when it is essential.

There is convincing evidence that radiation in sufficient dosage induces leukemia in man (*9, 12*). Study of changes in national mortality from leukemia, by cell type, should indicate the role of radiation in the genesis of the disease. Radiation is known to induce acute leukemia or chronic myelogenous leukemia, but not chronic lymphocytic leukemia (*9, 12*). Court-Brown and Doll (*2*), studying time trends of mortality in England and Wales from 1945 to 1957, observed that persons younger than 60 had increasing rates for acute leukemia and, to a lesser degree, chronic myelogenous leukemia, but not for chronic lymphocytic leukemia; they regarded these patterns as compatible with the hypothesis that the rising mortality from leukemia in the years under study was a consequence of increasing exposure to ionizing radiation.

With the probable decline in exposure to medical radiation since their report, one would expect a fall in the rates for acute leukemia and chronic myelogenous leukemia, with the rate for chronic lymphocytic leukemia remaining unaffected. In practice, an adequate study is handicapped at present. Only since 1958, by revision of the International Classification of Diseases, have separate code numbers been available for differentiating leukemia by cell type in a fashion appropriate to our purpose; such data are published for England and Wales but not for the United States. The results in England and Wales provide no conclusion yet regarding mortality trends by cell type. In the future, as data from the United States become available, one may possibly resolve this question. Should reduction in exposure to medical x-rays be responsible for the decline in occurrence of leukemia, the effects might be seen more readily in the United States if, before 1956, protection from radiation was, as has been suggested (*13*), less stringent here than in England. A decline in occurrence of leukemia would be expected within 10 years of a decrease in exposure to radiation, on the basis of the occurrence of peak leukemia rates within this period among survivors of atomic bombs (*9*) and among patients with radiation-treated ankylosing spondylitis. (*12*).

One must, of course, consider other explanations for the decrease in rate, including changes in diagnostic allocation, refinements in diagnostic accuracy, or lag in mortality consequent to improvements in leukemia therapy. From the data available it is difficult to discriminate between these several alternatives. Clarification should come from leukemia-mortality patterns over the next decade.

JOSEPH F. FRAUMENI, JR.
ROBERT W. MILLER
Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014

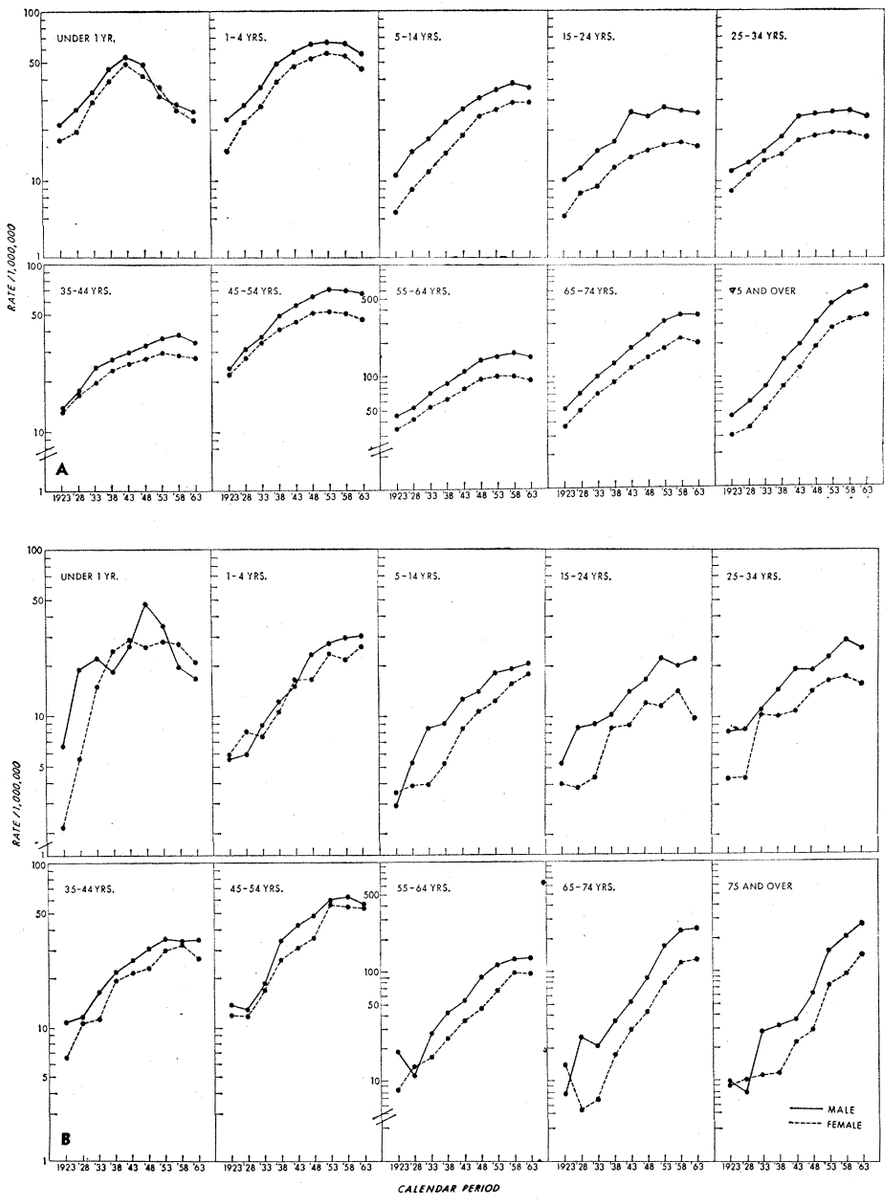

Fig. 1. Trends in average annual age-specific leukemia death rates among males and females in the United States from 1921 to 1965, (A) white and (B) nonwhite.

References and Notes

1. J. F. Fraumeni, Jr., and J. K. Wagoner, *Public Health Rep.* **79**, 1093 (1964).
2. W. M. Court-Brown and R. Doll, *Brit. Med. J.* **1959I**, 1063 (1959).
3. ———, *ibid.* **1961I**, 981 (1961).
4. M. Grais, *Bull. World Health Organ.* **26**, 683 (1962).
5. Numbers of leukemia deaths were learned

from National Center for Health Statistics annual reports (*Vital Statistics of the United States*) for 1961–64; prepublication mortality data for 1965 were supplied by courtesy of National Center for Health Statistics, Washington, D.C.; population data were obtained from the U.S. Bureau of the Census population estimates (*Current Population Reports*), series P-25, No. 321, Washington, D.C. (1965).
6. D. Hewitt, *New Engl. J. Med.* **270**, 933 (1964).
7. A. McKenzie, R. A. M. Case, J. T. Pearson, *Studies on Medical and Population Subjects No. 13* (H. M. Stationery Office, London, 1957); Registrar-General, *Statistical Review of England and Wales* (Annual reports for 1956–64) (H. M. Stationery Office, London).
8. L. Gross, *Oncogenic Viruses* (Pergamon, London, 1961), pp. 359–68.
9. O. J. Bizzozero, Jr., K. G. Johnson, A. Ciocco, *New Engl. J. Med.* **274**, 1095 (1966).
10. NAS–NRC, *The Biological Effects of Atomic Radiation: Summary Reports* (Washington, D.C., 1956); Medical Research Council (U.K.), *The Hazards to Man of Nuclear and Allied Radiations* (H.M. Stationery Office, London, 1956).
11. United Nations, *Report of United Nations Scientific Committee on the Effects of Atomic Radiation* [official records of the 17th session, suppl. 16 (A/5216)] (New York, 1962).
12. W. M. Court-Brown and R. Doll, *Brit. Med. J.* **1965-II**, 1327 (1965).
13. ———, *ibid.* **1958-II**, 181 (1958).

6 December 1966

Early Receptor Potential: Photoreversible Charge Displacement in Rhodopsin

Abstract. *When the eye is illuminated by an intense flash, the visual pigment rhodopsin begins to pass rapidly through a series of intermediate states, eventually becoming bleached. If a second flash is delivered during the lifetimes of these intermediates the rhodopsin can be photoregenerated. A fast electrical response of the visual receptors, the early receptor potential, is elicited by the first flash. A similar response is elicited by the second flash, but the polarity of this response is reversed. Moreover, this response can be separated into three components, each arising from the action of light on a different intermediate. It is likely that all these fast responses, including the early receptor potential, arise from charge displacements in the visual-pigment molecule.*

The absorption of a single photon by the visual pigment rhodopsin can excite a rod (*1*). We do not yet know how the excitatory signal is initiated nor how it is transmitted to the synaptic end of the receptor. Recently, by using intense light flashes, Brown and Murakami discovered in the retina a new electrical response with no detectable latency (*2*). They named this response the early receptor potential (early RP) to distinguish it from a later electrical response, which is presumably generated at the synaptic end of the receptor. The later response arises just before the early RP is fully completed.

The early RP is a biphasic response consisting of an initial cornea-positive phase (R1) followed by a slower cornea-negative phase (R2), lasting for a few milliseconds after the flash (*3, 4*). These two phases can be isolated by cooling the eye to near-freezing temperatures, in which case R1 remains but R2 is reversibly abolished (*5*). The spectral sensitivities of both R1 and R2 match the absorption spectrum of rhodopsin, and the amplitude of each phase is linearly proportional to the fraction of rhodopsin bleached by the stimulus flash (*3, 5*). These characteristics strongly imply that the early RP is generated by processes closely linked to rhodopsin.

That the early RP is not generated by changes in membrane permeability which in turn initiate passive ionic currents has now been almost conclusively demonstrated (*5–7*). Therefore, the early RP is most likely generated by the net displacement of electric charge (electrons, ions, and charged groups) as rhodopsin or neighboring molecules undergo changes in configuration. Since only R1 survives freezing temperatures, the early RP probably arises from two independent or sequential charge displacements (*5*). Brindley and Gardner-Medwin have suggested that changes in the waveform of the early RP produced by salts and by glycerol can all be accounted for by probable changes in the electrical filtering characteristics of the retina, if it is assumed that the early RP is generated by two successive movements of charge (*7*). That the first charge displacement must originate in or very near the rhodopsin molecule is indicated by the rapidity with which R1 arises during the stimulus flash. Using a spark gap with a flash duration of 0.7 μsec, I have found no indication of a latent period between the flash and the rising phase of R1 (*8*). Any latent period that does exist is definitely shorter than 0.5 μsec at 25°C. In addition, as will become clear from what follows, both R1 and R2 develop concurrently with the initial stages of the bleaching process in rhodopsin. Therefore, the presumed charge displacements that generate these responses must be intimately related to the bleaching process in the rhodopsin molecule.

A photon initiates the bleaching process in rhodopsin by stereoisomerizing the 11-*cis* chromophore of rhodopsin to the all-*trans* configuration (pre-lumirhodopsin) (*9*). The molecule then proceeds through a series of intermediate states (lumi, meta I, and meta II) to the end products, retinal and opsin. Each intermediate is a strongly absorbing pigment. This is of primary concern because, by exposing these intermediates to light, the course of bleaching can be manipulated. In particular, rhodopsin can be photoregenerated. Light can apparently isomerize the chromophore of any of these intermediates to the *cis* configuration present in rhodopsin or isorhodopsin (*10, 11*), and this isomerization initiates a reaction leading back to rhodopsin or isorhodopsin (*9*). Clearly, if the early RP depends closely upon rhodopsin, it too should be photoregenerated.

The photoregeneration of the early RP is shown in Fig. 1. The responses shown in this figure were obtained from excised intact eyes of the albino rat. Saline solutions were used to make electrical contact with the cornea and back of the eye. Light was delivered to the eye through a microscope condensing lens to provide uniform illumination of the entire retina, and stimulus flashes lasting 150 μsec were produced by a xenon flash tube. The width of the amplifier band was set at 0.1 to 10,000 hz. All electrical and photovoltaic artifacts were eliminated by appropriate shielding; and, since albino eyes were used, all observed responses can be attributed to the visual pigment in the retina (*3, 12*). For the test flash in Fig. 1, an interference filter with peak transmission at 560 nm was placed in the stimulus beam. With this wavelength the test flash elicited responses primarily from rhodopsin, because at the times when this test flash was delivered only long-lived intermediates would be present, and these absorb maximally in the blue region of the spectrum. Each test flash bleached about 10 percent of the rhodopsin present in the eye.

The top trace in Fig. 1 was obtained from the first test flash presented to the dark-adapted eye. It shows the typical biphasic waveform of the early RP, an initial positive phase (R1) followed by a slower negative phase (R2). After this response was obtained, the eye was exposed to strong tungsten light through a cutoff filter that eliminated all wavelengths shorter than 520 nm. This source delivered at least one photon to each rhodopsin molecule within 10 seconds. Hence, after a 1-minute exposure to this light, little or no rhodopsin remained in the eye. I veri-