Bull. Org. mond. Santé / *Bull. Wld Hlth Org.* 1962, 26, 579-584

Epidemiology of Leukaemia

Background for Future Studies

BRIAN MACMAHON, M.D.[1]

The author of this paper suggests that the very considerable geographical variations in leukaemia mortality warrant continued investigation. However, studies attempting to relate leukaemia mortality to variation in levels of natural radioactivity might to advantage be confined, for the moment, to areas in which differences in natural radioactivity levels are substantial. The investigation of certain groups of patients exposed to ionizing radiation from medical sources is also important to an understanding of the etiology of leukaemia.

There are other groups in which the leukaemia experience is unusual and which might form the basis for further investigation. These include mongolian idiots and their relatives, children aged 3-4 years, children in certain maternal age and parity groups, certain segments of the population of Israel, and persons occupationally exposed to benzol.

Epidemiological interest in leukaemia is greater than that in many numerically more important neoplasms. In addition to the striking clinical features of this disease that have aroused the general interest of many lay and scientific workers, leukaemia has certain epidemiological features that justify a concern with the disease that may at first sight seem disproportionate. These features include its occurrence in children, the existence of marked racial and geographical variations in occurrence, and its association with exposure to large doses of ionizing radiation.

GEOGRAPHICAL DISTRIBUTION

International variations in leukaemia mortality are considerable, even when data are restricted to countries having reasonably accurate diagnostic and registration procedures. Age-specific mortality rates for several such countries have been published by the World Health Organization (*Epidem. vital Statist. Rep.*, 1955).[2] Age-standardized rates calculated from these data indicate that leukaemia mortality is high in the white population of the USA, in Denmark and in the Jewish population of Israel; and relatively low in Finland, France, Ireland, Northern Ireland, Italy and Japan. Clemmesen (1960) has noted that most of this variation occurs in age-groups over 50 years of age. In the thirteen European countries for which data are given in the WHO report quoted above, the average annual death-rate from leukaemia per million in the age-group 25-29 years is 20.7, the range 15.1 to 25.3 and the coefficient of variation 13%; whereas in the age-group 70-74 years the mean is 147.0, the range 61.7-250.5 and the coefficient of variation 44%.

The pattern of international variation in mortality is probably different for the several subgroups of leukaemia, but present mortality data do not distinguish between pathological varieties. Chronic lymphatic leukaemia is said to be rare in several Asian countries, particularly in Japan.

Urbanization is related to leukaemia mortality. In the USA rates for urban residents are about 50% higher than those for rural residents (Meadors, 1956). In Denmark leukaemia incidence rates are higher in the capital than in the provincial towns and higher in the provincial towns than in the rural areas (Clemmesen et al., 1952). In England and Wales leukaemia mortality rates are higher in urban than in rural areas in the north, but the reverse in the south (Hewitt, 1955).

Substantial geographical variations have been reported within countries. Part of this variation is explainable in terms of general demographic variables such as urbanization, economic status and racial distribution, but interesting patterns remain after such factors have been taken into account.

[1] Professor of Epidemiology, Harvard School of Public Health, Boston, Mass., USA.

[2] See also the note by M. Grais on page 683 of this issue.

In the USA, geographical variation in leukaemia mortality has been examined by Walter & Gilliam (1956) and MacMahon (1957). Minnesota has had for some time the highest leukaemia mortality of any state; this appears to be the peak of an area of generally high mortality stretching across the north of the country west of the Mississippi. Rates are generally low in the south-east. Among the eastern states, Vermont has an unusually high rate.

In England and Wales Hewitt reported a fairly regular gradient in leukaemia mortality from a low level in the north to a level about half as high again in the south; this gradient was most marked in rural areas and for older age-groups. Phillips (1959) noted high rates of increase in leukaemia mortality in five mountainous western counties of England and Wales over the period 1950-57. He suggested that these counties experience higher than average strontium-90 contamination by fallout and that this may be related to the high rate of leukaemia increase. Court-Brown et al. (1960) noted that Aberdeen had a leukaemia mortality almost 50% higher and Edinburgh one about 25% higher than the Scottish national average.

The identification of further geographical areas of unusual leukaemia incidence is a potentially useful epidemiological method, and one particularly appropriate for exploitation by WHO. In addition to identification of high-rate areas, exploratory studies should determine the peculiarities of such areas, or of their inhabitants, that might be related to their leukaemia experience. Consideration should be taken of the ethnic characteristics of the inhabitants, their occupational, medical and dietary characteristics, and the physical, chemical and biological characteristics of the environment.

It would be interesting to determine whether areas of high incidence of human leukaemia coincide with areas of high incidence of leukaemia (lymphoma) in cattle and other domestic animals. A WHO Conference on Comparative Studies in Leukaemias held in Philadelphia early in 1961 also made recommendations in this regard.

There should be continued search for episodes, such as the recent " outbreak " in Niles, Illinois, in which the number of cases appearing in a particular locality seems to stretch the probability of chance occurrence beyond credibility. Although such episodes can each be expected to receive intensive local investigation, a central compilation of material by an organization such as WHO might reveal patterns not evident from individual episodes.

INCIDENCE IN AREAS WITH HIGH NATURAL RADIOACTIVITY

Disregarding studies in which leukaemia has not been separated from other forms of cancer, there have been three attempts to relate leukaemia mortality rates to background radioactivity:

Roubault et al. in 1958 reported a sixfold higher adult mortality from leukaemia in a French district located on bedrock rich in granite than in neighbouring communities built on geological formations other than granite. Childhood leukaemia showed no variation. Population parameters were not specified, and it is difficult to evaluate the significance of these findings without more complete data. The authors recommended further investigations in this geographical area, but to date none has been traced in the literature. It may be noted that areas of primitive granitic schistous and sandstone underlie about one-sixth of the French population; the annual radiation dose in these regions is estimated at 180-350 mrem.

Court-Brown et al. (1960) attempted a geographical study of leukaemia mortality in relation to background radiation in Scotland. The investigation provided the setting for careful dosimetry of external gamma-radiation; no evaluation of variation in exposure to internal emitters was undertaken. A major methodological drawback was the choice of a study population within which there were considerable variations in the diagnosis and reporting of leukaemia. Even though concomitant variations in leukaemia mortality and radiation levels were observed, it did not seem to the authors that these could be interpreted in terms of a causal relationship.

Segall (1961) investigated the relationship between terrestrial background radiation and leukaemia mortality in northern New England. Equivalent uranium concentrations of underlying bedrock were used to estimate population exposure to natural radiation in each of some 1000 townships. No association between estimated radiation level and population income, urbanization, availability of medical care, ethnic composition or population mobility was present. Some differences between radiation levels in the proportion of foreign-born persons was present. Age-adjusted leukaemia mortality rates were determined for four background radiation categories. No statistically significant association between level of background radiation and leukaemia mortality was demonstrated, nor were any trends discernible. Findings were the same when analysis was confined to the acute and myeloid forms of leukaemia.

Segall also computed the minimum population size required to demonstrate a leukaemogenic effect of background radiation under conditions prevailing in northern New England, on the basis of available radio-geological data. The number of person-years available to the study (approximately 50 million) was found to be sufficient to test only the upper limit of the possible range of dose-effect relationships as postulated in 1957 by Lewis (6 cases per million population per rem per year). If, however, attention were restricted to only the myeloid and acute forms of leukaemia, any leukaemogenic effect of background radiation at Lewis' " best estimate " of the dose-effect relationship (2 cases per million persons per rem per year) would have been demonstrable. Since virtually all the radiation-induced leukaemias have thus far been of either the myeloid or the acute type (Schwartz & Upton, 1958), such a procedure seems reasonable.

The major drawback of the latter study is its reliance on indirect measurement of external gamma-ray exposure. the validity of which has not been demonstrated. Possible concomitant variation in exposure to internal emitters was not evaluated. However, the results do suggest that terrestrial background radiation is not measurably leukaemogenic at the dose rates operative in northern New England.

The shortcomings of the studies described above should serve to indicate factors that must be taken into account in any new endeavour in this field. Specifically, the following must be considered.

(a) Population size. Before a study on a defined population is undertaken, the adequacy of its size should be ascertained relative to the hypothesis being tested. The minimum population required is, of course, a function of the dose-effect relationship assumed to be operative and of the " natural " leukaemia incidence that exists.

(b) Concomitant variation in exposure. Exposure to various sources of external and internal radiation, both natural and man-made, may exhibit concomitant variation. Thus the study of only one source without excluding the possibility of variation in the others may be misleading.

(c) Distribution of demographic characteristics. Populations to be compared should be similar in those demographic characteristics which may act as determinants of reported leukaemia mortality rates (e.g., ethnic group, income, urbanization, medical practices); or the influence of existing differences should be susceptible to quantification.

(d) Type of leukaemia. If further evidence confirms the past observations on the cell types of radiation-induced leukaemia, future studies of background radiation may deal specifically with the acute and myeloid forms. This would considerably reduce the minimum population size required.

(e) Homogeneity of exposure. Populations to be studied should exhibit a maximum intra-category homogeneity of radiation exposure level and wide inter-category differences.

The possibility of studying leukaemogenic effects of background radiation in the Kerala area in India has been widely discussed. Segall has computed the minimum population size necessary to demonstrate a leukaemogenic effect of background radiation under conditions prevailing, or assumed to prevail, in Kerala. Given that the population is resident in areas where the average skeletal dose rate is about 0.910 rem per year (WHO Expert Committee on Radiation, 1959), and that a comparable unexposed group of equal size exists, it would appear that between one and three years of observation of the relevant population should be adequate to demonstrate statistical significance of a radiation-induced rise in leukaemia incidence at the rate of 2 cases per million per rem per year. If the dose-effect constant is assumed to be 1 case of leukaemia per rem per million persons per year (Lewis' lower limit), the period of observation required would be from one to six years. The situation in Kerala would also seem to be favourable in regard to most of the other considerations listed above.

Other populations exposed to high natural radiation include those living on thorium-containing sands in eastern Brazil and in regions in countries where natural water supplies contain unusual amounts of radioactivity.

However, for the reasons given, we should be cautious in the implementation of further studies, particularly in geographical areas in which the differences in exposure between compared groups are not great. A prudent course would be to await the outcome of studies in areas where such differences *are* extreme, as in Kerala and Brazil, before undertaking further studies in areas where the conditions are less favourable. Parenthetically we may note that the existence of highly developed medical services, while initially appearing to ease the task of data collection in such a study, may actually hinder it because of the introduction of confounding geographical variation both in diagnostic accuracy and

completeness and in the distribution of potentially leukaemogenic medical radiation.

Ionizing radiation from medical sources

It is important to improve our understanding of the role of ionizing radiation in the etiology of leukaemia. Certain groups exposed to radiation from medical sources offer opportunities for the study of this question.

(a) Patients who have received radiation therapy. Particular mention may be made of the desirability of a study of the incidence of leukaemia in patients treated for cancer of the cervix uteri with radium or X-rays. Such a study, supported in part by WHO among other agencies, is now in progress as an international co-operative effort.

(b) Patients who have received thorotrast injections. These probably constitute the largest group of human patients having substantial burdens of deposited radioactivity.

(c) Patients given X-rays for medical diagnostic purposes. Patients irradiated in connexion with cardiac catheterization may receive particular mention.

The number of cases in any one of these groups in any one centre is too small for adequate examination of the leukaemia question, so that there is a real need for co-operative studies, probably on an international basis.

Studies in fundamental radiobiology are also important, including low-level radiation and radiotoxicity studies in animals. Encouragement should be given to improvement in national vital and health statistics, dealing particularly with leukaemia and bone tumours.

The importance of these specific studies and general recommendations lies in the derivation of data on the dose-response relationship in radiation leukaemogenesis, and in particular of data or inferences on the leukaemogenic effects of low doses of radiation, in order that estimates can be made as to the proportion of " spontaneous " leukaemia attributable to radiation. When a reliable estimate of this proportion is available, we may be better able to assess the role of other factors.

At the present time estimates of the proportion of leukaemia that is radiation-induced are purely speculative, but, unless low doses of radiation are much more effective in leukaemogenesis than is now suspected, it is clear that other leukaemogenic agents must still be sought. Thus, probably not more than 5% of leukaemia can be attributed to radiotherapy; Lewis has suggested that 10%-20% of leukaemia may be attributed to background radiation, and, on the basis of the same parameters, an approximately equal amount may be attributed to medical diagnostic procedures. There has been criticism of the methodology of these estimates, nearly all critics suggesting that the estimates are likely to be too high. Even with these " high " estimates, however, we are still left with at least half of the total amount of " spontaneous " leukaemia to account for.

In one particular case it is even clearer that leukaemogenic influences other than radiation must be sought—this is in childhood leukaemia. Thus at most 10% of leukaemia in children under 10 years of age can be attributed to prenatal X-ray exposure (Stewart et al., 1958; MacMahon, 1962); post-natal exposure seems to be even less significant (Polhemus & Koch, 1959; Stewart et al., 1958), and accumulated background exposure is trivial. The major leukaemogenic agent or agents must therefore be sought elsewhere.

Other population groups of interest

In seeking etiological agents other than ionizing radiation, epidemiological findings suggest that attention might well be focused on certain population groups whose leukaemia experience is unusual. These include the following.

Mongolian idiots

Leukaemia is much more common in mongols than in normal children—perhaps twenty times as common. Stewart (1961) has suggested that this relationship may be of very recent origin, but the apparent recency may result from changes in diagnostic accuracy. In view of the fact that association with high maternal age at birth is common to leukaemia and to mongolism, and in view of the chromosomal abnormalities found in mongolism, this relationship deserves further study. Because of the infrequency of children exhibiting both disorders, large co-operative studies may again be required.

The relatives of mongolian idiots

The study of the incidence of leukaemia in the relatives of mongolian idiots may help to elucidate the nature of the relationship between mongolism and leukaemia. Thus, if, as has been postulated, certain individuals have an inherited tendency to

abnormalities of somatic chromosome division which may appear as mongolism, leukaemia or both, we might expect to find a high incidence of leukaemia among the relatives of mongols as well as among the mongols themselves. On the other hand, if the high incidence of leukaemia in mongols results from some unusual feature of their environment—for example, exposure to repeated infections in institutions—no increase of leukaemia incidence in their relatives would be expected.

Children aged 3-4 years

Court-Brown & Doll (1961) have pointed out that the peak of leukaemia mortality in children aged 3-4 years is not a universal phenomenon. It first became discernible in British mortality data about 1920 and has become more pronounced since 1940. The same peak is evident in data for the white population of the USA only since 1940. No such peak is seen in data from Japan or for the non-white population of the USA. Attempts to determine under what circumstances this peak is evident may provide important clues to the understanding of childhood leukaemia. Lee (1961) has recently noted a minor peak in leukaemia mortality in adolescence. Although of less practical significance because of the number of cases involved, this peak is of similar research interest.

First-born children and children born of older mothers

In the USA leukaemia mortality decreases with increasing birth order of the child and increases with increasing age of the mother (MacMahon & Newill, 1962). Thus, leukaemia mortality is about twice as high among first-born children of older mothers as among later-born children of young mothers. Pregnancy and obstetric experience would be an obvious place to seek explanations for associations of this type.

Certain segments of the Jewish population of Israel

In New York City, leukaemia mortality is about twice as high among the Jewish population as among either Catholics or Protestants (MacMahon & Koller, 1957). This may be the result of either better diagnosis among the Jewish population or of actual high rates of leukaemia among them; if the latter, the high rates may result from either environmental or genetic factors. Davis and others (1961) have recently noted that leukaemia mortality among the Jewish population of Israel after the age of 45 was lower for the Afro-Asian-born than for the European-born or native-born Israelis. During the period 1950-58, mortality rates, which doubled in children under 15 years of age, more than tripled in Afro-Asian children, so that at the end of the period this group had the highest leukaemia mortality of all. The investigators thought it pertinent that this group had had a high frequency of X-ray therapy to the scalp for ringworm. Although the numbers on which these trends are based are very small and the observations are subject to interpretation in terms of sampling variation, continued study of this population group seems indicated.

Persons occupationally exposed to benzol

Evidence that low-level chronic exposure to benzol may be leukaemogenic derives from case reports of leukaemia occurring in persons occupationally exposed to benzol, localization of benzol in the bone marrow of exposed persons, and the identification of aplastic and hyperplastic reactions, which are frequent precursors of leukaemia, in the blood of benzol workers (Goldwater, 1947). Unlike exposure to ionizing radiation, benzol exposure is mainly occupational and probably does not contribute appreciably to the total incidence of leukaemia. Nevertheless, fuller information on the risk of leukaemia associated with various levels of benzol exposure is needed.

RÉSUMÉ

L'épidémiologie de la leucémie est plus intéressante que celle d'autres tumeurs, pourtant plus fréquentes: elle affecte les enfants; sa fréquence varie selon la race et la région; elle est l'un des dangers résultant de l'exposition aux rayonnements ionisants.

Les statistiques internationales indiquent que la mortalité par leucémie est élevée dans la population blanche des Etats-Unis, au Danemark, dans la population juive d'Israël, et qu'elle est relativement faible en France, en Finlande, en Irlande du Nord, en Italie, dans l'Eire, et au Japon. L'urbanisation contribue aux taux élevés; le statut économique et la race interviennent. Mais d'autres facteurs sont encore à découvrir, et certaines régions sont plus atteintes que d'autres, au sein d'un même pays. Il serait intéressant de rechercher dans le monde les zones géographiques où la leucémie est fréquente, de déterminer

si les leucémies animales y sont aussi très répandues, de noter les cas où des « poussées » soudaines de leucémie surviennent (celle de Niles, Ill., par exemple).

Pour déceler des facteurs étiologiques autres que l'irradiation, l'attention devrait se porter sur divers groupes de population: *a*) les idiots mongols (la leucémie est 20 fois plus fréquente chez eux que chez les enfants normaux); *b*) leur parenté, car s'il se vérifie que certains sujets ont une tendance héréditaire à des anomalies des chromosomes somatiques qui se traduisent par le mongolisme, la leucémie, ou les deux, on peut s'attendre à trouver ces manifestations pathologiques également dans leur parenté; *c*) les enfants de 3-4 ans; le sommet de la courbe de fréquence n'est pas universellement situé à cet âge-là. On l'a signalé dans le Royaume-Uni dès 1920, et surtout depuis 1940; on ne le trouve pas chez les Noirs des Etats-Unis, ni au Japon; *d*) les premiers-nés et les enfants de mères âgées, chez lesquels les leucémies sont deux fois plus fréquentes que chez les derniers-nés ou les enfants de mères jeunes; *e*) certaines fractions de la population juive d'Israël; *f*) les personnes que leurs occupations exposent régulièrement aux vapeurs de benzène.

REFERENCES

Clemmesen, J. (1960) *Acta Un. int. Cancr.*, **16**, 1611

Clemmesen, J., Busk, T. & Nielsen, A. (1952) *Acta radiol. (Stockh.)*, **37**, 223

Court-Brown, W. M. & Doll, R. (1961) *Brit. med. J.*, **1**, 981

Court-Brown, W. M., Spiers, F. W., Doll, R., Duffy, B. J. & McHugh, M. J. (1960) *Brit. med. J.*, **1**, 1753

Davies, A. M., Modan, B., Djaldetti, M. & Vries, A. de (1961) *Arch. intern. Med.*, **108**, 86

Epidem. vital Statist. Rep., 1955, **8**, 81

Goldwater, L. T. (1947) *Occup. Med.*, **4**, 435

Hewitt, D. (1955) *Brit. J. soc. Med.*, **9**, 81

Lee, J. A. H. (1961) *Brit. med. J.*, 1, 988

Lewis, E. B. (1957) *Science*, **125**, 965

MacMahon, B. (1957) *Publ. Hlth. Rep. (Wash.)*, **72**, 39

MacMahon, B. (1962) *J. nat. Cancer Inst.* (in press)

MacMahon, B. & Koller, E. K. (1957) *Blood*, **12**, 1

MacMahon, B. & Newill, V. A. (1962) *J. nat. Cancer Inst.* **28**, 231

Meadors, G. F. (1956) *Publ. Hlth. Rep. (Wash.)*, **71**, 103

Phillips, T. A. (1959) *Lancet*, **2**, 659

Polhemus, D. W. & Koch, R. (1959) *Pediatrics*, **23**, 453

Roubault, M., Pascal, J. & Coppens, R. (1958) *C.R. Soc. Biol. (Paris)*, **247**, 369

Schwartz, E. & Upton, A. (1958) *Blood*, **13**, 845

Segall, A. (1961) *Cancer and background radiation*, Boston, Mass., Harvard University School of Public Health (Thesis)

Stewart, A. (1961) *Brit. med. J.*, **1**, 452

Stewart, A., Webb, J. & Hewitt, D. (1958) *Brit. med. J.*, **1**, 1495

Walter, W. A. & Gilliam, A. G. (1956) *J. nat. Cancer Inst.*, **17**, 475

World Health Organization, Expert Committee on Radiation (1959) *Wld Hlth Org. techn. Rep. Ser.*, **166**