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advances in acute leukaemia

Reviews in Leukaemia and Lymphoma, 1

Advances in Acute Leukaemia

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ADVANCES IN ACUTE LEUKAEMIA

Reviews in Leukaemia and Lymphoma

Advisory Board

Editor's Preface

The presentation of another review of leukaemia and lymphoma at this time requires some explanation. It is our view that there is at present no satisfactory publication for reviews in depth in an extremely active subject. We felt therefore that each author should be allowed as much space as he required to present the current state of knowledge in a subject and even if this precluded a comprehensive coverage of the field, and we are aware of this defect, we would hope to rectify this in subsequent editions. We are very happy that so many contributors of international repute have agreed to write for us and we hope that their contributions will interest both workers in the laboratory and the clinic. We would especially like to thank Mr. J. Thornton for the preparation of the index.

November 1974

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Chapter 1

On the Epidemiology of Leukaemia

JOHANNES CLEMMESEN

The Danish Cancer Registry, Institute for Cancer Epidemiology under the National Anti-Cancer League, and Department of Pathology, The Finsen Institute, Copenhagen (Denmark)

At a time when the development of new methods in immunology and virology is suggesting new approaches, and thus a new concept of the epidemiology of leukaemia, the time may have come for a critical review, in particular of the rapidly increasing contributions from the last decade. For earlier publications, not least in the statistical field, readers are referred to earlier reviews (e.g. Clemmesen, 1965; Kessler and Lilienfeld, 1969) and to more specific surveys mentioned in the pertinent sections of the following.

The epidemiological research in human leukaemia falls under three main headings: (1) Genetics; (2) Radiation leukaemogenesis, and (3) Cluster analysis, all roughly following the same pattern of stages:

I. At the casuistic, first, stage clinicians report on the observation of groups of cases within some environment such as a family, an occupation, or a village. Such studies will often be extended, e.g. through the collection of pedigrees, case records, or information from other villages. Reports attaining publication at this stage will mostly be in the affirmative, and it may safely be assumed that negative statements will fail to be published.

II. At the second, statistical stage the field of study is extended into more comprehensive statistical efforts which, due to the infrequency of the diseases in question will require fairly extensive investigations with a relatively large staff. Some variation in results from place to place may, therefore, be expected, but few discussions seem to realize this possibility.

III. The final, laboratory stage was first reached in genetics. Here, the absence of a statistically demonstrable excess of cases among relatives of leukaemia patients, appeared to turn the scales against the clinical experience of heredity, although without explaining clinical experience of coincidence in sibs. The association with mongolism and other chromosomal abnormalities, and the demonstration of the socalled ph chromosome introduced new aspects into the discussion, and suggested that the disease is more familial than hereditary. This seems to illustrate that it is incautious to dismiss clinical observation on statistical grounds, unless an explanation of the former is available.

In radiation leukaemogenesis a positive correlation between leukaemia and exposure sufficed to decide the fundamental issue, although some quantitative problems remain unsettled. It seems, however, unnoticed by many authors on the subject that variations in radiological technique may explain minor differences in incidence of leukaemia among exposed persons from different hospitals or hospital groups.

The demonstration of clusters of human leukaemia and of Hodgkin's disease is still at the second statistical stage, meeting with various difficulties. More than once it seems to have been overlooked by investigators that it is epidemiologically irrelevant to express the chance of transfer by contact of leukaemia or Hodgkin's disease by the distance between the habitation of patients as the crow flies, when it is a question of highly industrialized areas where people communicate by mechanical transportation. In rural Africa, however, this method has been useful in the clarification of the semi-continental cluster of Burkitt's juvenile lymphosarcoma.

In the feline species, for which a leukaemia virus has been demonstrated, clusters of lymphosarcoma have suggested horizontal transmission of the virus. By means of an indirect fluorescent antibody test for the demonstration of feline leukaemia virus gs antigen in peripheral leukocytes and platelets of infected cats, Hardy et al. (1973) have demonstrated the presence of infection among apparently normal cats, living in contact with cats infected with the virus, before developing lymphosarcoma. In this species leukaemia epidemiology thus seems to have reached a laboratory stage equalling the epidemiology of infections.

DIAGNOSIS AND STATISTICS

For most practical purposes the relatively short history of leukaemias and lymphomas does not date from Virchow's first description of 1845, but only from Ehrlich's staining of cells from 1879—1880. A safe basis for general statistics on these infrequent neoplasias was, however, not established until the introduction of bone marrow puncture into clinical practice, — in Europe during the late 1930's (Rohr, 1960).

Mortality and other statistics from the early part of the century should, therefore, be taken with some reservation, also because of five subsequent revisions of classification between 1900 and 1945 following concepts of these diseases shifting between infections and neoplasms (Sacks and Seeman, 1947; Alice Stewart, 1972). Even during later years inadequacy in diagnosis has added to these shortcomings, as when the 7th revision of *International Classification of Diseases etc.* (1957) omitted the distinction between the myeloid and lymphoid types of acute leukaemia, due to practical difficulties in diagnosis for the majority of such cases. In consideration of the difficulties encountered even in highly industrialized regions to have all patients subject to adequate treatment, which practically is prerequisite to marrow

puncture and to advanced and uniform specification of diagnosis, it is not surprising that also the editors of modern morbidity data from a series of cancer registries, published with a view to international comparison, (U.I.C.C., 1966, 1970) have been equally unsuccessful in attaining cytological specification for an adequate part of cases.

Much as it should be appreciated that it has been possible in the course of three decades to establish cancer registries from Connecticut to Colombia, and from Denmark to Bombay and Bulawayo, it should, therefore, be realized that data from such different populations, when brought into identical shape and referring to nearly the same years, may treacherously veil differences in technical standard and in clinical tradition. Probably, these differences will not disappear until we have reached such global uniformity of community structure, and consequently of medical standards, that comparison of data will be without interest.

Until the realization of this Utopia it will be practically impossible e.g. to attain the same percentage of histological examinations for various anatomical sites or from different geographical regions, and it will always involve risks to compare data from different areas without direct contact with the institutes or persons which have collected them, knowing their specific qualities.

In the present context attention should also turn to the question to which extent morphological differences in cytology reflects etiological differences.

With such necessary qualifications it will, nevertheless, be possible to obtain some useful data from existing cancer registries, observing the international standards laid down in 1950 by a symposium in Oxford (adopted by a W.H.O. subcommittee, 1952). It follows from the multitude of variables entering international comparisons that we shall stand a better chance of epidemiologically relevant observations by following one population over a longer period with an unchanged technique, particularly for neoplastic diseases with their relatively long periods of induction, than by comparison of simultaneous data from different countries. Such a longitudinal study pattern has little chance if we insist on the revision of international definitions and nomenclature every decade, as is customary to the W.H.O. In demanding simultaneous uniformity we may run the risk of changing enterprising national research into uniform but sterile inter-national administration

It follows from the relatively low incidence rates for leukaemia, i.e. about 8—14 per 100 000 (European Standard Population), that cancer registries, which at most will cover populations up to 5—7 million, must have difficulties in providing sufficient numbers of cases for statistical analysis to the extent applied in the epidemiological study of other neoplasias. Certain problems, e.g. around clusters of cases, may, however, demand larger populations for study, and as mortality data are becoming increasingly inadequate it may become necessary to organize registration of leukaemia alone over larger areas. With the increasing centralisation of therapy and with the limited numbers of patients, such registries should not be too difficult to organize

and administrate, e.g. in Germany, the United Kingdom, or in the United States.

RESULTS FROM GENERAL STATISTICS

Age curves

Whatever the nature of leukaemogenic factors, it will be prerequisite to their recognition that they fit into the pattern of occurrence and distribution, as well as into the secular trends of incidence reported by general statistics.

From the time when national mortality statistics were the main source of information a number of fundamental observations have come to stand (Clemmesen, 1965, pp. 435—475; Kessler and Lilienfeld, 1969). As it appears from the following tables, mortality experience as recorded by W.H.O., 1956, has now been confirmed with morbidity data from a series of cancer registries (UICC, 1970), although the age curves from limited registration

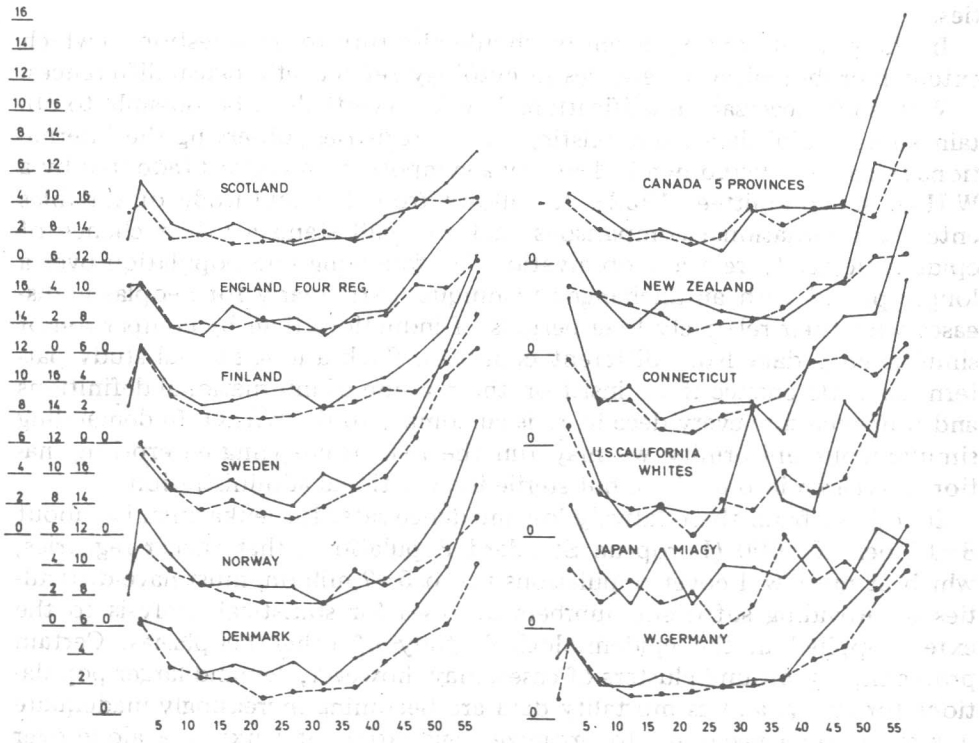

Fig. 1 A. Leukaemia morbidity rates at ages below 60 years for various countries. ———, males; - - - - - -, females. (From U.I.C.C., 1966, 1970)

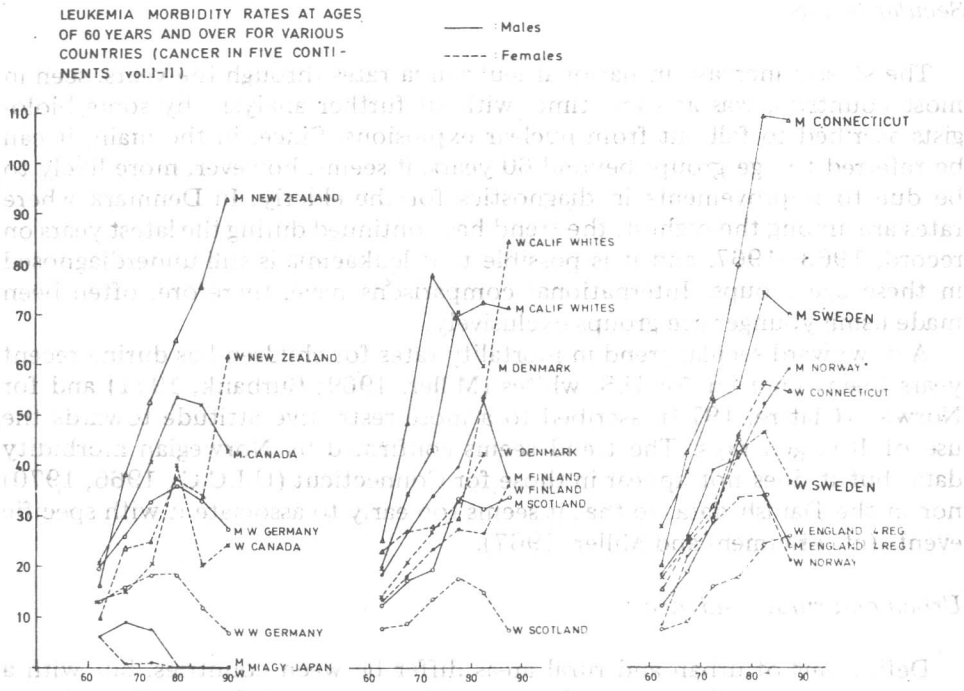

Fig. 1 B. Leukaemia morbidity rates at ages of 60 years and over for various countries. ———, males; - - - - -, females. (From U.I.C.C., 1966, 1970)

areas in some large countries naturally are less regular than the national mortality curves.

For most countries the age curve will show a childhood peak about the fifth year, after which the curve descends until 20—30 years of age, followed by a gradual rise reaching the approximate level of the childhood peak about the age of 50. At 55—60 years begins a steadily steepening rise in rates, perhaps most pronounced in the countries where the childhood level was re-reached earliest in life. This final rise is decisive for the overall national rate and thus for international differences, and it is generally assumed to reflect the accessibility of efficient diagnosis to the elderly (Clemmesen and Sørensen, 1958). In general, curves for men run at a slightly higher level than for women.

Exceptions from the pattern described are: Mortality graphs for Danish, Scottish, Canadian, and U.S. white males showed a slight elevation about puberty (l.c.) also reflected in Fig. 1. In a special analysis Lee (1961), demonstrated its existence also in English data back to at least 1911—15, and referred it to myeloid cases. Another exception is the nearly horizontal curve for Japan, which at no age exceeds the childhood level. Also the rarity of lymphoid leukaemia in Japan, like in South East Asia, differs from most other regions.

Secular trends

The steady increase in national leukaemia rates through the years, seen in most countries, was at some time, without further analysis, by some biologists ascribed to fall-out from nuclear explosions. Since, in the main, it can be referred to age groups beyond 60 years, it seems, however, more likely to be due to improvements in diagnostics for the elderly. In Denmark where rates are among the highest, the trend has continued during the latest years on record, 1963—1967, and it is possible that leukaemia is still underdiagnosed in these age groups. International comparisons have, therefore, often been made using younger age groups exclusively.

A downward secular trend in mortality rates for children has during recent years been reported for U.S. whites (Miller, 1969; Burbank, 1971) and for Norway (Glattre, 1970), ascribed to a more restrictive attitude towards the use of Röntgen rays. The trend seems confirmed by Norwegian morbidity data, but it does not appear in those for Connecticut (U.I.C.C., 1966, 1970) nor in the Danish data, so that it seems too early to associate it with specific events (cf. Fraumeni and Miller, 1967).

Urban and rural residence

Definitions of urban and rural areas differ between countries, but with a few exceptions malignant neoplasms tend to occur more frequently in towns than in the country. The explanation varies with the anatomical site between better access to diagnosis and heavier exposure to industrial oncogens in the urban environment.

Stark and Oleinick, 1966, in an analysis of 21 000 childhood leukaemia deaths in the United States for the years 1950—59, found consistently higher rates for white children than for nonwhite. White children showed higher death rates for urban than for rural areas, while the opposite was found for nonwhites. The urban excess applies elsewhere, e.g. in Denmark, where crude mortality rates from 1930 (Clemmesen, 1965, pp. 528ff.) and morbidity rates since 1943, nearly every year have been slightly higher for the capital than for rural areas, although the difference is smaller than for various other neoplasms. It is worthy of notice that while the urban/rural ratio of mortality rates remained close to 1 from 1931 to 1955 for age groups under 60 years, it was far higher for the rising rates for those aged over 60 throughout the period.

An interesting approach to this question has been taken by Fasal et al. (1968) in a mortality study among 400 000 farm residents in California. While mortality rates for all cancer were significantly lower than for non-farm residents, this was not the case for leukaemia among farm residents, who for both sexes showed a standardized mortality ratio of 114 compared with 99 and 100, respectively, for male and female non-farm residents.

Socioeconomic distribution

Socioeconomic studies into leukaemia were first undertaken by Sacks and Seeman (1947), based on mortality data compared with monthly rental in 157 census tracts of Baltimore, Md. Both for deaths in general and for deaths in hospital they found a rising trend with better socioeconomic status, except for the two lowest income groups, for which rates were higher than for intermediate groups. From England, Hewitt (1955) reported a social gradient of mortality unfavourable to the high income groups, but more uneven at ages over 65 than during working life, and in Buffalo, Pinkel and Nefzger (1959) compared the incidence of leukaemia in economic halves of urban and suburban groups combined. They found a significant difference for childhood cases with higher rates for upper economic halves (urban 79, suburban 98 per 100 000) than for lower economic halves (61 and 44 per 100 000, respectively).

More recently, Githens et al. (1965) in Colorado, made an analysis of death certificates for 258 children aged under 15 years, and found mortality two to almost four times higher for children living in the socially favoured census tracts compared with the poorest.

Racial and ethnic groups

It was originally observed by Panton and Valentine (1929) that among leukaemia patients seen at London Hospital, Hebrews made a ratio of 1 : 1.4 against 1 : 10 roughly estimated for the hospital in general. Later Guasch (1954) had many reports on an increased occurrence among Jews, but found no support for this suggestion in statistics from Israel. Nevertheless, it may be mentioned that Davies et al. in 1961 found an excess among Israeli immigrants from the Near-East, which proved ascribable to the use of Röntgen radiation for epilation of ringworm cases. The problem turned up in a different context, when MacMahon and Clark (1956) and MacMahon and Koller (1957) analyzed 1481 case records for leukaemia from the population of Brooklyn.

They found that Russian born citizens, practically all of Jewish ancestry, constituted 36.6 per cent of the leukaemia group against 26.2 per cent of the general population. A study of 1368 deaths from leukaemia compared with a systematic one in 200 sample of all deaths in the same area, utilized information on cemetry of burial, and showed that leukaemia was recorded twice as frequently among Jews as among others. This applied to native-born as well as to foreign-born, to males and females at all ages, and to all common types of leukaemia. Groups predominantly Catholic or Protestant did not differ from average.

It further appeared that although American Negroes in general show lower leukaemia rates than Whites there was a local trend to similarity in Brooklyn, and the authors pointed out that the Brooklyn income differential between