Reviews in Leukaemia

Advances in Acute Leukaemia

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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

F.J. Cleton
D. Crowther
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Chapter 1

On the Epidemiology of Leukaemia

JOHANNES CLEMMESEN

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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

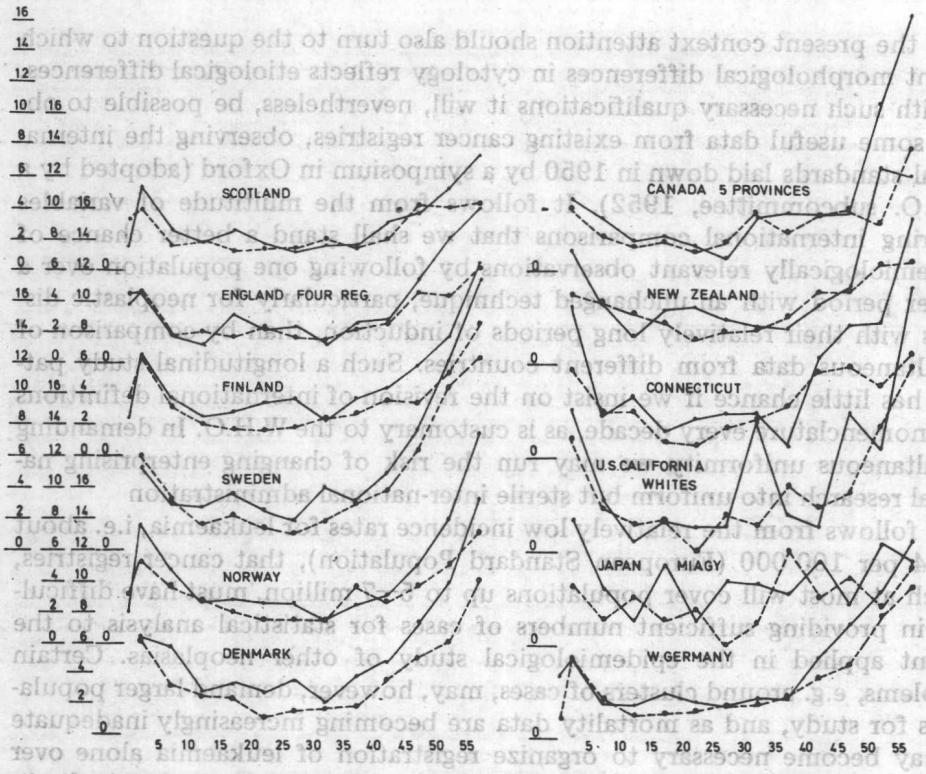

Fig. 1 A. Leukaemia morbidity rates at ages below 60 years for various countries. ———, males; - - - - -, females. (From U.I.C.C., 1966, 1970)

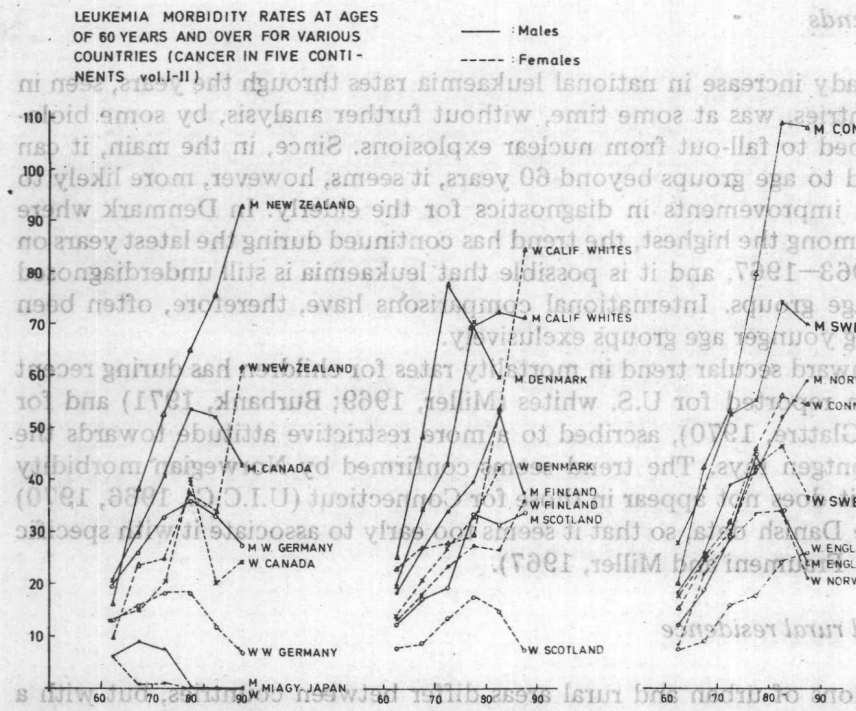

Fig. 1 B. Leukaemia morbidity rates at ages of 60 years and over for various countries. ——, males; - - - - -, females. (From U.I.C.C., 1966, 1970)

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 1868 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

Whites and Negroes was lower than in many parts of the United States. Their analysis supported the view that the higher national leukaemia death rates for Whites in comparison with Negroes was attributable to the social complex of factors measured by income.

Graham et al. (1970) resumed the subject. They covered all leukaemia patients reported from 1959 to 1962 in the metropolitan districts and their surrounding counties in Upstate New York (exclusive of New York City), in Minneapolis, and in Baltimore, partly brought up by registries organized for the occasion.

It appeared that no differences were found among child cases and controls in religious or ethnic background, nor on any demographic parameter. Among more than 1200 adult cases and as many controls, however, Jews, Russians, and Poles all had significantly elevated risks. For Russian Jews the risk was over five times that of non-Jews born in the United States. They exceeded groups culturally different from themselves more than they did those that were more similar. There was no difference in the distribution of leukaemias by cell type between Jewish and non-Jewish cases, which was counted against the assumption of differences in exposure to radiation as cause of the difference in leukaemia risk. Furthermore, the Russian and Jewish relationship appeared to persist in both the irradiated and non-irradiated populations.

GENETICS IN HUMAN LEUKAEMIA

The study of genetics in leukaemia naturally sprang from repeated clinical observations of coincidence of cases among families and in twins.

During the late 1940's and the 1950's attempts at statistical evaluation of such findings resulted in a series of comprehensive interview studies comparing the incidence of leukaemia among relatives of patients with those of control persons: Videbaek (1948) commented by Busk (1948, 1954), Amiotti (1953), Guasch (1954), Morganti and Cresseri (1954), Kaliampetsos (1954) and Steinberg (1960).

The discussion in and around this series (reviewed: Clemmesen, 1965, pp. 497 ff.) may largely be summed up in Steinberg's view that no increased incidence had at that time been convincingly demonstrated among relatives of leukaemia patients in comparison with normal control persons. Nevertheless, Steinberg admitted the existence of exceptional cases, as R.C. Anderson's family of 8 (1951), of which 5 died from acute leukaemia, and two other unpublished family cases.

A number of such observations are now on record from workers with fully reliable diagnostic facilities at their disposal, such as: Hornbaker (1942), Reilly et al. (1952), Johnson and Peters (1957), Gunz and Dameshek (1957), Campbell et al. (1962) and Gunz et al. (1966).

Also, observations of coincidence of leukaemia in twins have been made

repeatedly, most often published as casuistics as reviewed by Guasch (1954), Ioachim (1962) and Iversen (1966), but also studied in series as by MacMahon and Levy (1964) and by Miller (1968) who both estimated a concordance rate of 20 per cent for childhood leukaemia among identical twins. Hewitt et al. (1966) found numbers lower in England and Wales, and pointed out that suspected twin pregnancy used to be a common indication for obstetric X-ray examination, which might influence the occurrence of leukaemia and cancer among twins.

It should be added that also multiple myeloma has shown familial occurrence (Nadeau et al., 1956) and that reticulo-sarcomatosis has been observed in three siblings, two of which were monozygotic twins, and all dying about the age of twelve months (Zachau-Christiansen and Christensen, 1966).

The apparent conflict between the absence of statistically significant results, as underlined by Steinberg, and the clinical experience of familial occurrence, as maintained e.g. by Videbaek (1958), was finally solved by the demonstration of chromosomal anomalies associated with hemopoietic neoplasia.

Originally suggested by Bernard et al. (1955) from clinical findings of an association between leukaemia and Down's syndrome and cardial and other malformations, the statistical evidence of a connection was provided by Krivit and Good (1957). Later it was shown at the same time by Lejeune et al. (1959), Jacobs et al. (1959) and Ford et al. (1959), that Down's syndrome was accompanied by an additional small acrocentric chromosome, and the demonstration in the following year of the ph-chromosome in association with chronic myeloid leukaemia by Nowell and Hungerford (1960) and by Baikie et al. (1960) tended to bridge the gap to chromosomal aberrations caused by ionizing radiation, and brought this branch of research on an experimental level.

The situation has been summed up by Lilly (1972): "It is possible that certain types of human leukaemia or lymphoma will prove to be largely due to single recessive genes with quite incomplete penetrance. More likely, however, is the hypothesis that these diseases occur as a function of the individual's constitution at several gene loci, each of which makes a contribution to susceptibility or resistance to the disease. As with most biological phenomena, the phenotype . . . . is determined by the interaction of the host genotype at these multiple loci and certain environmental factors . . . . which can increase the innate risk of the disease."

ANIMALS AND MAN

History of animal leukaemia

Few if any neoplasias have been studied throughout the animal kingdom like leukaemias, as evidenced by reference works as Schalm's veterinary

haematology (1965) and Loppnow et al.'s special pathological anatomy (1971), or symposia on the Comparative Pathology of hematopoietic neoplasms (1968) and on Comparative Leukemia Research (1965, 1967, 1969, 1971, 1973).

Medical interest in these, largely veterinarian, studies sprang from a hope for results conclusive for the human disease, a hope renewed whenever a new species seemed to differ from earlier experience, and comprehensive reviews by Jármai (1934) and Engelbreth-Holm (1942) listed hundreds of publications from the first decades of this research. According to their information, fowl leukaemia was discovered in 1868, and for mammals they gave the following years: horse 1858, pig 1865, dog and cat 1871, mouse 1874, cattle 1878, goats 1896, elephants 1908, deer and rabbits 1914, monkeys, sea lions, and opossums 1923, squirrels 1925, guinea pigs and sheep 1926—27, and buffalos 1938. To these comes lymphosarcoma reported in skunks, civets, kangaroo rats, pacas, and African clawed toads (Lombard and Witte, 1959; Balls, 1965).

Engelbreth-Holm pointed out, followed by Marshak et al. (1966), that all mammalian cases seem to have been of lymphatic type with the exception of two myeloid cases, reported in one horse and one cat, but doubted by Jármai. According to later investigators, granulocytic sarcomas as well as undifferentiated myeloid leukaemias do occur in cattle, although very rarely (Migaki, 1969; Bendixen, personal communication) — a predominance of lymphocytic leukaemia well in keeping with the percentage of about 60 of circulating lymphocytes in cattle.

After Ellermann and Bang's cellfree transmission of fowl leukaemia (1908) and the corresponding transmission of chicken sarcoma by Rous (1911) and by Fujinami and Inamoto (1914) the deep interest in leukaemia research centered around the question of the applicability of the virus concept to human neoplasia. Numerous negative and unpublished results were vindicated with Shope's discovery of virus tumours in rabbits (1932, 1933) and leukaemia research was encouraged, when Krebs et al. (1930) established the first transmissible strain in mice, originally in universally irradiated animals, but it took till 1949 before Gross (1951) could demonstrate transmission of leukaemia between two strains of mice by means of virus.

Later attention turned to dogs, resulting e.g. in the establishment of a state-wide registry for canine lymphomas in New Jersey (Cohen et al., 1959); and the discovery of viral lymphosarcoma in cats (Jarrett et al., 1964; Rickard et al., 1969) inspired further research.

Meanwhile, since the turn of the century, veterinarians had observed the spread of epizootic cattle leukosis from East Prussia across most of Europe, Russia, and the United States. Some investigators, e.g. Bendixen (1963), found the epidemiological pattern indicating transmission by virus, but experiments seem to have been hampered probably due to economic considerations, until the authorities in various places (e.g. Bendixen, 1973) began literally removing the basis for further study by extermination of affected