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RECENT WORK ON LEUKAEMIA IN MAN*

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In this lecture I shall confine myself to human leukaemia, and in particular to recent work on the aetiology, course, and treatment. This work has been mainly inspired by two events. The first is the apparent steep rise in the incidence of leukaemia in Western Europe, North America, and Australasia. The second is the discovery of new and powerful drugs for the treatment of acute and chronic leukaemia. Connecting these two events is the use of the numerical or statistical method to study the incidence of leukaemia at different epochs and in different places, to define the natural history of the disease and its individual variations, and to control the large-scale trials which have proved to be necessary if methods of treatment are to be satisfactorily evaluated.

Classification of Leukaemia

So far I have talked about leukaemia, but in fact we should talk about the leukaemias, for the different forms of leukaemia differ from each other at least as much as the different forms of malaria. The classification of leukaemia offers difficulties, some of which are semantic and others technical. The two parameters used in classification are the acuteness of the disease process and the type of cell involved. Demographers are not fond of the words "acute" and "chronic," and it must be confessed that the definitions given by the Committee for Clarification of the Nomenclature of Cells and Diseases of Blood-forming Organs in 1950 have not proved entirely adequate to deal with the subsequent course of events. With modern therapy an occasional acute leukaemia may last for more than five years, or longer than many patients with chronic leukaemia.

The type of cell involved in acute leukaemia is also sometimes difficult to decide. Fashions in the diagnosis of myeloblastic, lymphoblastic, monocytic, and erythroblastic leukaemia have changed too often for one to have much confidence in *ex cathedra* statements based on a look down the microscope. It is probable that in atypical cases a group of characteristics should be determined before a decision is made—the microscopical appearances of the cells, their physical, histochemical, and immunological reactions, and their cultural characteristics. This would be impracticable as a routine procedure, but it might be of value if it was used as a method of sampling from time to time to keep a check on working diagnoses.

In the seventh revision of the *International List of Causes of Death* leukaemia is classified under the headings of lymphatic leukaemia, myeloid leukaemia, mono-

cytic leukaemia, acute leukaemia, and other and unspecified leukaemias. Acute leukaemia includes all forms of acute leukaemia whether the type of cell is specified or not, with the exception of monocytic leukaemia, which is treated as a separate entity. This is probably as far as the demographers are justified in going at present, and it must be left to the haematologists to discover methods of differentiating the subgroups of acute leukaemia which will stand up to statistical appraisal.

Incidence of Leukaemia as a Whole

With this knowledge in mind we can now turn to recent figures for overall death rates from leukaemia. The rate of increase of leukaemia as a recorded cause of death in Western Europe and North America has been greater than that of any other disease except lung cancer and coronary thrombosis. The figures of the

FIG. 1.—Death rates per million from leukaemia and pernicious anaemia for all persons in England and Wales over the years 1920-55. The data are taken from the Registrar-General's *Statistical Reviews*.

Metropolitan Life Insurance Company of New York (1955) show a rise from 1.8 to 4.7 per 100,000 in their policy-holders between 1930 and 1951. In England and Wales the incidence was more than two and a half times as high in 1953 as in 1931 (Hewitt, 1955) (Fig. 1). Nevertheless, the fear of leukaemia should not blind us to the fact that it is an uncommon disease. In 1955, 2,224 people died of leukaemia in England and Wales, as compared with 17,569 deaths from cancer of the respiratory system and 20,869 from violence. Indeed, something like three times as many children died from accidents as from leukaemia.

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Men and women have been equally affected by the increase in leukaemia, so that the cause is unlikely to be smoking, cosmetics, or occupation. The upward trend has been visible for at least twenty-five years and cannot be explained by recent events such as the introduction of the sulphonamides and antibiotics. The main correlation is with the standard of living. Hewitt noted that as between different countries the incidence followed the order U.S.A. and Denmark; England, Wales, and Scotland; Western Germany and Ireland. As between economic strata, leukaemia is more frequent in the rich than the poor, and in the United States it is more frequent in the white than the non-white. As between different regions of England it was higher in the south than the north, and over the period of observation the south of England had been more prosperous than the north. In the United States the contrary is true, and there leukaemia is commoner in the north than the south.

Incidence of Different Types

It is not easy to demonstrate how changes in the incidence of leukaemia as a whole are related to changes in the incidence of the different types of leukaemia, for until recently the International Classification of Diseases and Causes of Death did not distinguish between acute and chronic forms of the disease. Moreover, crude figures for deaths from leukaemia have little meaning unless we know also the age and sex structure of the population, because leukaemia occurs with increasing frequency over the age of 50 and because males are affected more often than females. Two studies have recently been reported in which a high level of ascertainment and diagnosis of leukaemia was combined with a full knowledge of the structure of the populations under study. MacMahon and Clark (1956) analysed the incidence of leukaemia in the Borough of Brooklyn, a city with a population of 2,700,000, over the ten-year period 1943-52. Hospital records were available in 87% of the cases and marrow puncture or necropsy records in 63%. Gunz and Hough (1956) carried out a similar analysis of deaths from leukaemia over the quinquennium 1950-4 in New Zealand, where the population is just under two million and the level of medical care is high.

In Brooklyn the overall distribution of cases was, acute leukaemia 53%, chronic lymphatic leukaemia 26%, and chronic myeloid leukaemia 21%. Acute leukaemia falls from a level of 44.3 per million in the first decade to 11.9 per million in the decade 20-29. It then rises steadily to

FIG. 2.—Age incidence of the leukaemias in Brooklyn. The data are taken, by permission, from the article by B. MacMahon and D. Clark (*Blood*, 1956, 11, 871).

reach levels over 50 per million in the seventh and eighth decades. Acute lymphatic leukaemia shows an exaggeration of this tendency of the acute leukaemias to occur at the extremes of life. Acute myeloid leukaemia was the commonest form of acute leukaemia except in the first few years of life, but too much reliance should not be placed on the differentiation of the various types of acute leukaemia. Chronic myeloid leukaemia rises steadily from an incidence of 1 per million in the first decade to 39.4 per million in the eighth. Chronic lymphatic leukaemia rises from less than 1 per million in the first three decades to 114 per million in the eighth.

The figures for the relative frequency of acute and chronic leukaemia are in agreement with those of Gunz and Hough, who found that the proportion of acute cases was almost 100% in the first five years of life, falling to about 60% in the forties, and 40% over the age of 75. Noteworthy features in both surveys are the sharp rise in the death rate from all forms of leukaemia over the age of 50, the frequency of chronic lymphatic leukaemia in the aged, and the high proportion of acute leukaemias even in the oldest age groups. Acute leukaemia in later life is often atypical, with few signs pointing to affection of the haemopoietic system, and the diagnosis can easily be overlooked if the blood is not examined. Other observers have confirmed the relative decline in frequency of chronic myeloid leukaemia in the West (Gauld, Innes, and Robson, 1953).

Racial and Geographical Differences

Much less accurate information is available about the racial and geographical incidence of leukaemia, though

FIG. 3.—Mortality rates from leukaemia in males in the U.S.A. and Japan from data collected by the World Health Organization (1955).

there is a general impression that leukaemia is less common in the indigenous populations of Africa and Asia, particularly chronic lymphatic leukaemia. An analysis of the mortality from Hodgkin's disease and leukaemia in different countries has recently been made by the World Health Organization (1955). Unfortunately, the only non-Western country is Japan, but separate figures are given for the white and the non-white population of the United States of America. The contrasts are striking. The overall mortality from leukaemia in men is 7.5 per 100,000 in the white population of the United States, 3.9 per 100,000 in the non-white, and 2.0 per 100,000 in Japan (Fig. 3). In the age group 60-69 the mortality from leukaemia in men is 22.0 per 100,000 in the white population of the United States, 13.8 per 100,000 in the non-white, and 2.5 per 100,000 in Japan.

Causes of Increased Incidence

If these differences in the incidence of leukaemia in time and place are real, they suggest that it resembles cancer of the lung, the liver, and the scrotum, and that environmental factors must be important in its causation. If the differences are spurious, we should have to rank leukaemia with

carcinoma of the breast and the stomach as one of those forms of malignant disease whose incidence we are unlikely to be able to modify until the general problem of neoplastic disease is solved.

Part of the increase is due to the ageing of the population; but this is not the whole story, because not only the absolute numbers but the incidence of leukaemia in the later decades has increased. Cooke (1954) showed that the crude incidence of leukaemia increased from 2.1 to 5.5 per 100,000 in the U.S.A. between 1930 and 1949. At all ages up to 54 the incidence had uniformly doubled, but above age 54 there had been a much sharper increase. In 1949 there were over 23 deaths per 100,000 from leukaemia in patients over 70, which was about four times the figure in 1930. Of these 23 cases one can calculate from MacMahon and Clark's data that 11 were chronic lymphatic leukaemia, 5 acute leukaemia, 4 chronic myeloid leukaemia, and 3 unspecified.

The main correlation of the death rates is with the standard of living. People with a high standard of living have a greater probability of detection of leukaemia owing to better medical attention, and a larger proportion of patients in the older age groups where leukaemia is especially common. I can look back on my own experience as a student and recollect cases which were diagnosed as oral sepsis or haemorrhagic fever, and which would nowadays be almost certainly shown to be leukaemia. A high proportion of acute leukaemias occur at the extremes of life, and if laboratory facilities are not easily available they are apt to be diagnosed as infections in infancy and as cardiovascular or renal disease in later life. It seems certain that a big factor in the increase of deaths attributed to leukaemia is the more frequent recognition of the disease at all ages, particularly in later life.

It is, nevertheless, difficult to believe that enough cases of leukaemia were misdiagnosed in the past, particularly in middle life, to account for the total increase in notifications. In this country a notable improvement in the facilities for the diagnosis of blood disorders was initiated by the expansion of the Hospital Laboratory Service between 1939 and 1948, and this was soon reflected in a fall in the mortality from pernicious anaemia (see Fig. 1). If the increased incidence of leukaemia was entirely a matter of better ascertainment, one would have expected that the curve of deaths from leukaemia would have risen even more sharply about fifteen years ago and then flattened out, but this did not happen.

It looks as if the rise is not just a matter of greater availability of medical care. An improved standard of living seems to contain elements which bring about a real increase in leukaemia. In our discussions together, Alice Stewart has suggested that, as a result of the greatly reduced mortality from infections, people who have sustained leukaemogenic damage to the bone marrow survive to develop leukaemia after the appropriate incubation period. However that may be, it would be complacent at present to assume that the increase in leukaemia is entirely a matter of better notification, and we must continue searching for factors in our greatly changed environment which may have contributed to the increase.

Chronic Lymphatic Leukaemia

The variation in the incidence of chronic lymphatic leukaemia, a disease with manifest clinical signs, is particularly hard to explain by failure of detection. In a recent visit to India and the Far East I saw many cases of acute leukaemia and myeloid leukaemia but none of chronic lymphatic leukaemia. Acute leukaemia and myeloid leukaemia occurred in typical and atypical forms, and it was not unusual to see myeloid leukaemia of the chronic myelocytic type in children. Aplastic anaemia, which is probably related in aetiology to leukaemia, was not infrequent.

Anaemias of all kinds are so common in hospital patients in Africa and Asia that the absence of chronic lymphatic

leukaemia is especially noteworthy. Pernicious anaemia, which is likewise a disease of the later decades, is even less common. Otsuka *et al.* (1956) report that only 309 cases of pernicious anaemia have been described in Japan in the last fifty years. They were atypical in age distribution, occurring most often in the age group 20-40, and a proportion were undoubtedly due to pregnancy or to gross lesions of the intestine. Otsuka and his colleagues emphasize that the Japanese medical profession has been keenly interested in haematology throughout this period and that the rarity of pernicious anaemia contrasts with the frequency of aplastic anaemia.

As already mentioned, the age structure of the populations is very different from ours. In Singapore, for example, 50% of the population are under age 21 and anyone over 45 is described as old. In the absence of written records, the age of middle-aged and elderly people is often unknown to the individual and cannot be determined, but the populations of the Oriental countries are so numerous that in absolute figures there must be large numbers of people in the sixth, seventh, and eighth decades, where chronic lymphatic leukaemia has its greatest incidence with us.

Reasons for a failure to recognize chronic lymphatic leukaemia and pernicious anaemia may be that elderly people are less likely to be referred to hospital for diagnosis or to be admitted for treatment when the pressure of the younger age groups is so great. The proportion of doctors to the population in Eastern countries is rarely higher than one in ten thousand, and certification of the cause of death cannot be expected to be precise, particularly at the extremes of life. Owing to religious prejudices post-mortem examinations are hardly ever made except in persons who have died a violent or unnatural death. In parenthesis, one cannot resist commenting on this failure of Oriental peoples to contribute their quota to our knowledge of the morbid anatomy of disease. When all is said and done, however, one is left with the feeling that there is a real difference in the incidence of leukaemia and pernicious anaemia in elderly people in the West and the East, which might be due to genetic factors or to environmental factors such as differences in diet.

Observations of the kind just made are useful only in so far as they serve as hypotheses for further work. Obviously one thing to be done is to try to improve our statistics of leukaemia. In this country it must be unusual, now, for any patient, however old, to develop a chronic illness like lymphatic leukaemia and die without the blood being examined. In Asia and Africa a comparable standard of diagnostic facilities is unlikely to be achieved for some time, and by then other differences between the two populations, which are at present playing a part in the differing incidence of leukaemia, may have been obliterated. In other words, we are faced with something like Heisenberg's principle of uncertainty. As the incidence of all forms of leukaemia is only about 5 per 100,000 per annum, a pilot survey would be impracticable. In this state of affairs it would be reasonable to act on the hypothesis that there is less chronic lymphatic leukaemia in the East than the West, to enumerate the differences in environment between Asian and Western peoples, particularly in reference to diet, and to study them experimentally.

Aetiological Factors in Human Leukaemia

When a disease occurs in only 5 out of every 100,000 people, it suggests that either the make-up of the patient or his experience has been unusual. The inheritance of leukaemia is still controversial, and it is unusual to find cases in more than one member of a family. Videbaek (1947), who analysed the family histories of 209 patients with leukaemia and a corresponding number of controls, concluded that the chance of a relative of a patient with leukaemia getting leukaemia was 1 in 250 as compared with 1 in 4,000 of the control population. It will be interesting to see if the current survey by Alice Stewart and her co-workers (1956) confirms these ratios. As regards

environmental factors, the only one known for certain is the somewhat unusual one of exposure to large doses of x rays.

This story has so often been recapitulated in the last few years that I shall summarize it briefly. Leukaemia has probably been unduly frequent in doctors and nurses who work with x rays. It has occurred after x-ray treatment of non-malignant diseases such as ankylosing spondylitis in adults and enlargement of the thymus in infants. It is also occurring with abnormal frequency in the survivors of the atomic-bomb explosions in Hiroshima and Nagasaki who were within range of the ionizing radiations. In all these instances there is reason to believe that the dosage was high, usually more than 100 r over a short period of time or more than 200 r over a longer period.

The total normal background radiation over a generation in man amounts to about 3 r. The ordinary chest film exposes the patient to only a fraction of a roentgen, but a gastro-intestinal examination with the apparatus commonly used at present may expose the patient to 15 r a minute if full precautions are not taken. Children are more susceptible to x-radiation than adults, and in their preliminary communication Stewart *et al.* (1956) reported that about twice as many of the mothers of children who died of leukaemia or malignant disease before the age of 10 in the years 1953-5 had had an x-ray examination of the abdomen during the relevant pregnancy as the mothers of a group of control children. Many of these x-ray examinations were probably for pelvimetry, in which it has been stated that a radiation dose of only about 2.5 r is received by the foetus (Rabinowitch, 1956).

While genetic damage is accounted for by a relatively few sites of examination, principally the hip, the lumbar spine, the lower abdomen, and the pelvis, it seems probable that extensive radiation over any part of the trunk or the proximal ends of the long bones would increase the likelihood of leukaemia. The committee appointed by the Medical Research Council (1956) to report on the hazards to man of nuclear and allied radiation considered that there would be little increased risk of leukaemia if an individual received a total dose of 200 r in his lifetime in addition to radiation from the natural background, provided that the dose was distributed over tens of years and that the maximum weekly exposure, averaged over any period of thirteen consecutive weeks, did not exceed 0.3 r. However, there is probably no threshold below which x rays are harmless, and even with small doses ill effects will be seen if a sufficient number of people are observed. In the survivors of the atomic-bomb explosion at Nagasaki who had been most severely irradiated, the incidence of leukaemia has been 1 in 80 or over. At the other extreme of dosage, Court Brown and Doll (1957) suggest that a dose of 1 r averaged over the red bone marrow of the whole body would cause about one case of leukaemia annually in a population of a million people.

It is axiomatic that we should exercise the greatest care in exposing ourselves, our patients, and above all the pregnant woman to x rays and radioactive agents. Nevertheless, it is probable that the contribution made by x-radiation to the total incidence of leukaemia is small. From the figures of Stewart *et al.* (1956) it would appear that 50 children a year may have developed leukaemia or malignant disease because their mothers had an abdominal x-ray examination during pregnancy. All the leukaemias so induced may not yet have appeared, but at the very most the figure for leukaemias induced by x-ray examinations *in utero* is unlikely to exceed 50 per annum. If the number of adults developing leukaemia from diagnostic or therapeutic x-radiation is of the same order as the number of children, x-radiation is unlikely to account for more than 15% of the total deaths from leukaemia.

Most of the leukaemias occurring after radiotherapy for spondylitis have been acute or subacute myeloid leukaemia. Of 92 cases in Hiroshima and Nagasaki, 39 were chronic myeloid leukaemia and only one was chronic lymphatic

leukaemia; the remainder were acute and subacute leukaemias, with the myeloid form predominating and the younger age groups more severely affected (Moloney, 1955). The study of post-irradiation leukaemia thus throws little light on the apparent increase in spontaneous leukaemia, which affects more heavily patients over the age of 50 and which has been largely of the chronic lymphatic type.

Finally, we must balance the risks of x-ray diagnosis and therapy against their benefits. The amount of radiation received by a patient who has a chest film is exceedingly small, and it would be unfortunate if people refused to participate in mass x-ray programmes because of a possible risk of leukaemia. It is protracted screening over the trunk which is dangerous, and the amount of radiation is likely to be greatly reduced by more stringent precautions and improved apparatus. The possible 50 cases of leukaemia a year from x-radiation *in utero* must be set against 439 deaths of mothers in childbirth, 15,829 stillbirths, and 9,750 deaths in the first week of life in 1955. Obstetricians and radiologists believe that the mortality of mother and child may be significantly reduced by appropriate x-ray examinations in pregnancy, and that they can save more lives than are likely to be lost from leukaemia, appreciating as they now do the hazards of x-radiation. Similarly, the death rate from leukaemia after radiotherapy for ankylosing spondylitis is only 3 per 1,000, and, though this is at least ten times as high as the usual incidence of leukaemia in this age group, it is a good deal lower than the mortality of 13 per 1,000 for interval partial gastrectomy for peptic ulcer in the best hands.

Important as has been the discovery of the leukaemogenic effects of x rays in man, their role does not seem to be comparable with cigarette smoking in cancer of the lung or saturated fats in coronary thrombosis. The search for other aetiological factors must be intensified. Alice Stewart and her colleagues are shortly extending their survey to leukaemia in adults, and it is to be hoped that those in charge of patients with leukaemia, especially in hospitals, will give them full co-operation in their important task.

Natural History of Leukaemia

The recent introduction of new remedies for leukaemia and the consequent need for therapeutic trials have attracted the attention of statisticians to the course of the disease and the effect of treatment on it. It is the old story that when we begin the intensive study of a disease we commonly find that we do not know as much as we thought we did about its natural history. For example, a question we want to answer is whether the initial treatment of chronic myeloid leukaemia should be by x rays, radioactive phosphorus, nitrogen mustard, or busulphan ("myleran"), and the data are not yet available.

In leukaemia there are two factors which make therapeutic trials difficult. The first is the great variation in the length of survival in all forms of leukaemia. The second is the occurrence of spontaneous remissions in acute leukaemia. The times of survival in leukaemia, as in other forms of malignant disease, do not have a symmetrical distribution about a mean but are skew—that is to say, the majority of the patients die relatively soon after the onset of the disease but a few live a surprisingly long time. This variable course of the disease is something we are already familiar with in non-lethal diseases such as infective hepatitis, and it means that we require a lot of cases and a long period of observation for therapeutic trials. Numbers required are further increased by the necessity to match cases by type of leukaemia and age of the patient.

The remissions of acute leukaemia are one of the most remarkable phenomena in the natural history of malignant disease. They occur typically in acute leukaemia and they may be complete or partial. In a complete remission all signs and symptoms of the disease disappear and the bone marrow becomes practically normal: a partial remission is substantial improvement but something less than this. Remissions may be spontaneous or induced. Swaen (1954),

who reviewed 97 spontaneous remissions in acute leukaemia, occurring in the days before chemotherapy, thought that the remissions were not, in fact, spontaneous but that they usually followed an infection, probably a virus infection. He thought that the infection caused necrosis of the leukaemic cells, and cancer and leukaemia have been treated by deliberate infection of the host with non-lethal virus diseases, though unfortunately with only scant success.

Spontaneous remissions are not common, at any rate complete ones, occurring probably in less than 5% of cases (Southam *et al.*, 1951). The great discovery of the last decade in leukaemia research has been the ability to provoke remissions by treatment. In acute lymphatic leukaemia in childhood remissions can be induced in 85% of cases. Two main groups of remedies have been used—corticoid hormones, and chemotherapeutic agents which act by blocking the synthesis of nucleic acid. At present three subgroups of the chemotherapeutic agents are available—antagonists to folic acid, purine, and glutamine respectively—but the synthesis of nucleic acid goes through so many stages and research in this field is so active that other agents are certain to be discovered.

The average duration of spontaneous remissions is about four months, and then some of the damaged cells recover and the disease rapidly recurs. Induced remissions may last longer because the therapeutic agent can be continued, but relapse eventually occurs owing to the development of resistance. This may be circumvented by alternating different remedies, and in this way life may be prolonged well over a year, even as long as five or six years. Theoretically, resistance could be postponed by using different drugs in combination. The chemist's dream is that if he can block one stage of the synthesis of nucleic acid so effectively that only, say, one in ten milliard cells becomes resistant, and if he can do the same at other stages, the odds against resistance or recurrence will finally become astronomical.

Nothing quite comparable with the spontaneous remissions of acute leukaemia occurs in chronic leukaemia, though almost all signs of the disease may be temporarily banished by effective therapy. Moreover, the remedies used in acute leukaemia are ineffective in chronic leukaemia, and vice versa. Arsenic, x rays, busulphan do harm and not good in acute leukaemia. Nevertheless, in both types of leukaemia the working hypothesis is that the remedy has a disproportionately lethal effect on the leukaemic cells and works very much as the sulphonamides and the antibiotics do in bacterial infection. The development of strains of resistant cells is likewise used as the explanation of the ultimate failure of treatment. Of course, not all haematologists share these views. Some believe that treatment does something to the defence mechanisms of the body rather than to the leukaemic cells.

Therapeutic Trials

Remedies must first be synthesized, then screened in experimental animals for efficiency in leukaemia and new growth, next studied pharmacologically, and finally tested in human leukaemia. Therapeutic trials are taking on the same shape as in tuberculosis, though it is difficult to get comparable numbers of cases. Survival is estimated from the onset of the first symptom that is identifiable as due to leukaemia—splenomegaly, adenopathy, or bleeding. We may in addition measure survival from the time of diagnosis or the onset of therapy. In analysing and comparing the data the mathematician uses the logarithms of the survival times because these have a normal distribution. For ordinary purposes it is not necessary to make any calculations, as the survival data can be represented graphically by the use of log-probability paper. For comparing different groups of cases, the time at which 50% and 10% remain alive can be read to the nearest half-month. By appropriate statistical methods it is possible to calculate the median survival, the standard deviation of a series, and the standard error of the mean, and in this way to test the significance of the differences between the various groups of cases. If a series con-

tains both living and dead patients, it is necessary to construct a life table such as is used in vital statistics and by insurance companies.

Satisfactory statistical studies of the natural history of the leukaemias are now available. Tivey (1952), who pioneered these studies, showed that of children with acute leukaemia treated only by supportive measures, without antibiotics or specific therapy, 50% will die within a period of approximately four months from the onset of symptoms but 10% will live as long as eleven months. There is no evidence that the prognosis in children with acute myeloid or monocytic leukaemia differs from that of children with the more common lymphatic leukaemia when no specific treatment is given. Haut and co-workers (1955) were unable to find any trials in which patients treated with the new remedies were compared with simultaneous untreated controls, which was perhaps not surprising, but there is good evidence that when patients are treated with the new remedies 50% live for twelve months and 10% for two years.

Tivey (1954) found no difference in survival between chronic myeloid and chronic lymphatic leukaemia. Half the patients will die 1.6 years after beginning therapy or 2.65 years after the first symptom. Ten per cent. will live 7 years after the onset of the disease and 1% will live for 15 years. Treatment has little or no effect on the length of survival, though the period of useful life is almost certainly increased. Additional criteria such as time spent in usual activities, time in hospital, and freedom from pain, could be used to measure the value of treatment.

The position reached in therapeutic research on leukaemia is that we now have full knowledge of the course of the disease and accurate methods for comparing different forms of treatment. Large numbers of cases and long periods of observation are necessary if new remedies are to be promptly evaluated. In England and Wales there were 2,224 deaths from leukaemia in 1955, of which just over half must have been acute leukaemia. No single centre can see enough cases for a therapeutic trial, and co-operative studies must therefore be planned on a national or international basis. Apart from the inertia which affects all of us, resistance to therapeutic trials comes from two quarters. Some physicians believe they can do better for their patients by individual treatment than by including them in a therapeutic trial. As trials in leukaemia nowadays consist in a comparison of remedies or of combinations of remedies this belief is not well founded. Some research workers believe that therapeutic trials mean the expenditure of a great deal of time and money for a relatively small return and that our resources would be better devoted to basic research in the laboratory. However, the expenditure is trifling compared with the national drug bill, and much of the work can be done by practising doctors and public health workers.

Conclusion

The exciting feature of research on human leukaemia in the last decade is that it has passed from the phase of description and classification to a study of the disease as it affects the community as a whole, its apparent increase, and the action of new remedies which relieve the symptoms and, in acute leukaemia at any rate, prolong life. As a side-effect we have learned what a lot can be achieved by co-operative endeavour within the framework of the National Health Service. The work of Abbatt, Court Brown, Doll, Lea, and others on the occurrence of leukaemia after x-ray treatment of ankylosing spondylitis could not have been completed without the help of radiologists, physicians, records officers, and others in widely separated areas. Alice Stewart and her colleagues have shown how much the public health services can contribute to the mass study of a disease like leukaemia, reducing a problem of daunting size to manageable proportions. Therapeutic trials in tuberculosis and ulcerative colitis have shown how cases can be pooled and treated on a central plan.

Leukaemia is a hard nut to crack, and we shall have to wait for further fundamental scientific discoveries before we can greatly modify its frequency and mortality. In the meantime current interest in the incidence of leukaemia and in new forms of therapy can contribute significantly to the welfare of the unfortunate victims of the disease. My experience of therapeutic trials is that they arouse an enthusiasm for treatment which might otherwise be lacking and produce an improvement in results quite apart from the specific remedy. Indeed, as in the famous Hawthorne experiment at the Bell Telephone Works, community studies on the incidence and treatment of disease may sometimes have side-effects which are just as important as the original aim of the investigation.

Summary

Acute leukaemia is becoming commoner than chronic leukaemia, and chronic lymphatic leukaemia commoner than chronic myeloid leukaemia.

Important factors in the increase in the incidence of leukaemia in Western Europe, North America, and Australasia, and in the higher incidence of leukaemia in these countries than in Asia and Africa, are greater availability of medical care with consequent improvements in diagnosis and ageing of the population, leukaemia being more frequent in later life. It is nevertheless unlikely that these factors account for the whole of the increase, and the search for aetiological factors in leukaemia associated with the rise in the standard of living should continue.

Man-made ionizing radiations such as x rays can induce leukaemia, but there is no evidence that they can account for the considerable increase in notifications of leukaemia in the later age groups, which is largely of the chronic lymphatic type, whereas leukaemia after irradiation has so far been predominantly myeloid.

The risks of irradiation may be greater in the foetus than in the adult, and stringent precautions should be taken when x-raying pregnant women. These risks should be carefully balanced against the reduction in maternal mortality, stillbirths, and perinatal deaths which can be secured by the intelligent application of radiography.

Our recently discovered ability to provoke remissions in acute leukaemia, and the accelerating development of powerful chemotherapeutic remedies and new methods of administering ionizing radiations, have made it essential to organize therapeutic trials in leukaemia. Owing to the spontaneous variations in the course of the disease large numbers of cases are required for valid trials, which must therefore be organized on a co-operative basis.

Although we shall have to wait for further fundamental scientific discoveries before we can greatly modify the frequency and mortality of leukaemia, there is no doubt that current interest in the incidence of leukaemia and in new forms of therapy has contributed materially to the welfare of the unfortunate victims of the disease.

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TREATMENT OF STONE IN THE COMMON BILE DUCT

BY

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There are few conditions so disappointing to patients and their doctors as a recurrence of biliary colic following an operation on the biliary tract. I am concerned not so much with the case in which there has been a simple cholecystectomy for stones and a stone has been overlooked in an unopened common duct, as with the case in which there has been a careful exploration of the duct and removal of stones or mud, and at a later date colic has occurred. There is no doubt that surgeons open the common duct much more often than they used to, perhaps because it is easier owing to better anaesthesia and the better general condition of patients, and perhaps owing to information gained from experience and possibly also from cholangiography.

When small stones or biliary mud have been sought and found it is easy to leave some more behind in the lower part of the duct or even in the upper part, be the search ever so careful. They may later pass into the duodenum, though they are more likely to remain in the duct and increase in size or amount and cause further trouble. This may take the form of pain and/or jaundice, or it may only show as recurring attacks of "chills" due to cholangitis. To repeat the operation of exploration and evacuation of the common duct alone is neither sound nor satisfactory, and it is wise to establish some larger opening from the common duct instead of the small lumen at Oddi's sphincter. This may be made at the lower end by some form of sphincterotomy (perhaps combined with a long-armed T-tube) or plastic operation on the duct, or it may be made higher up by a new anastomosis between the common duct and the duodenum. One of the purposes of putting forward this brief communication is to make a plea for the wider use of the latter operation—choledochoduodenostomy. Most surgeons will have done this operation a number of times, some very readily, others less readily, being uncertain of the later results. There are several points connected with the operation about which one may be anxious: whether duodenal contents will get into the common duct and cause infection or other trouble; whether stones or debris may collect in the part of the duct distal to the stoma and set up inflammatory changes or obstruct the main duct of the pancreas; or whether, indeed, the stoma may close.

I have been so well satisfied with the results of the operation over a period of some years that it seemed worth while making a few remarks about it. These are based on an experience of 21 cases.