Survey of Childhood Malignancies

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IN ITS original form the survey of childhood malignancies conducted by Oxford University included children under 10 years of age who died of cancers or leukemia during the years 1953–55, but it has recently been decided to extend the survey to include deaths since 1955 (table 1). In the final study population there will be children born in 18 consecutive years, 1943–60, whose deaths were spread over 8 calendar years (1953–60). Data collected during the second part of the survey (1956–60 deaths) will differ in several respects from the data on 1953–55 deaths, but the general plan remains the same, and both investigations fall into the broad category of retrospective surveys. All varieties of malignant disease are included and approximately half the deaths are due either to leukemias or to lymphosarcomas. Most of the children will be under 10 years of age at death, but some older deaths may eventually be included in the new population.

The survey of 1953–55 deaths began in October 1956 and was the work of 2 General Register Offices (notifying centers), over 200 local health authority departments (collecting centers), and 1 university department (coordinating center). The same team will be responsible for the survey of 1956–60 deaths, which began in April 1961. In each survey group the original study population included all children in England, Scotland, and Wales who died before their 10th birthday during the survey years.

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Survey of 1953–55 Deaths

A detailed study of official statistics of mortality preceded the survey of 1953–55 deaths. According to these statistics the risk of dying from a malignant disease after the age of 40 has barely altered in recent years, but the risk of children and young adults dying from these diseases has appreciably increased. In particular, children between 2 and 4 years of age have been more affected by the unfavorable trend of leukemia mortality than any other age group under 70 years (*1*).

These findings suggested that, provided a sufficiently large number of childhood deaths from cancers and leukemias (cases) could be identified and compared, point by point, with suitable controls, there might be a reasonable chance of identifying some of the factors influencing the prevalence of these diseases.

Original aims. Hewitt's critical analysis showed that the recent increase in leukemia deaths happened sooner in technically advanced countries than in other parts of the world and appeared to be more closely related to medical services than to wealth. In Britain the adverse effect of this increase began to be felt at the beginning of the century and received a "postwar fillip"; during the years 1945 to 1953 a striking feature of British and United States statistics was an increase in leukemia deaths in children between 2 and 4 years of age. This was the main reason for deciding to interview mothers of both cases and controls and obtain

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firsthand accounts of the children's medical histories and social background. It was also decided that pro formas should include questions about (*a*) illnesses of the mothers and children and X-rays before and after birth; (*b*) treatments with modern drugs; (*c*) living conditions; and (*d*) relatives.

Shortage of cases. Though Britain has a population of 50 million, less than 700 children die of malignant diseases each year. It was necessary, therefore, to plan the survey on a nationwide basis, and to seek the cooperation of public health departments. All county and county borough health departments agreed to take part and to assume responsibility for the fieldwork. Consequently, there were no regional gaps among the 1,640 traced cases, which were originally obtained from 1,973 death certificates supplied by General Register Offices in London and Edinburgh (table 2).

On receipt of the names and addresses of the dead children, the coordinating center sent to each collecting center a list of local cases and the pro formas for recording case and control data. In the larger centers more than one "survey doctor" was appointed, but it was agreed in advance that whoever interviewed the mother of a case should also interview the mother of the corresponding control, also that controls should be obtained from birth registers and not from other sources. To insure uniformity one doctor from the coordinating center briefed all the other doctors and provided them with a written set of instructions.

Selection of controls. The instructions stated that each dead child, or case, was to be paired off with a live child, or control, matched for sex, age, and district, but otherwise picked at random from a local birth register.

The control selection list shows how the control was chosen for a boy (John Smith) who was born in 1952, lived in Sheffield, and died of leukemia in 1958. The names and addresses are imaginary, but other items are genuine.

The names and addresses of five possible controls were obtained from a register of births in the district which included the home address of the dead child. The list indicated the order of priority of selection and included boys born on the same day as the dead child, the next day, and so on. On this occasion the first family selected had moved to an unknown address, but the second was still living at the same address and the mother was willing to be interviewed. She was eventually seen by the doctor who had already interviewed Mrs. Smith.

Table 1. Calendar years of births and deaths of children dying of malignancies, 1953–60, survey of childhood malignancies, Oxford, England

Cohorts		Age at death		Followup period (0–10 consecutive years)	
Births	Deaths	Years	Months	1953–60	1953–55
1943	1953	9–10	108–119	1	1
1944	1953–54	8–10	96–119	2	2
1945	1953–55	7–10	84–119	3	3
1946	1953–56	6–10	72–119	4	3
1947	1953–57	5–10	60–119	5	3
1948	1953–58	4–10	48–119	6	3
1949	1953–59	3–10	36–119	7	3
1950	1953–60	2–10	24–119	8	3
1951	1953–60	1–9	12–119	8	3
1952	1953–60	0–8	0–107	9	3
1953	1953–60	0–7	0– 95	8	3
1954	1954–60	0–6	0– 83	7	2
1955	1955–60	0–5	0– 71	6	1
1956	1956–60	0–4	0– 59	5	0
1957	1957–60	0–3	0– 47	4	0
1958	1958–60	0–2	0– 35	3	0
1959	1959–60	0–1	0– 23	2	0
1960	1960	0	0– 11	1	0

NOTE: In each set of figures, 1 year is incomplete. For example, among the 1960 births children born in January and dying the following December would be only 11 months old.

Table 2. Regional distribution of deaths from malignant diseases in children 0–10 years of age, 1953–55 and 1956–60, survey of childhood malignancies, Oxford, England

Authority	1953–55		1956–60 (original cases)
	Original cases	Traced cases	
Counties:			
Northern England	69	62	118
Midlands	344	290	619
Southern England	711	568	1, 191
Scotland [1]	118	89	100
Wales	67	58	125
County boroughs and burghs:			
Northern England	77	70	106
Midlands	307	261	488
Southern England	107	92	192
Scotland [1]	152	134	131
Wales	21	16	27
All local authorities:			
England	1, 615	1, 343	2, 714
Scotland [1]	270	223	231
Wales	88	74	152
All regions	1, 973	1, 640	3, 097

[1] 1956 deaths included with deaths for 1953–55.

The definition of a district varied according to the density of the population and in rural areas often included several villages. If necessary, more than one list of possible controls was compiled, but in the survey of 1953–55 deaths two-thirds of the controls were first choice, and over 90 percent were obtained from a list of five names. Far and away the commonest reason for not obtaining a first choice control was the one shown in the selection control list, namely, that the family had left the district.

In the survey of 1953–55 deaths, if the parents of a dead child had moved to a new local authority area, the rule that a case/control pair should be seen by the same doctor was broken. In the survey of 1956–60 deaths each control will be obtained from the district in which the parents of the corresponding dead child are now residing. In the new survey, therefore, there should be no exceptions to the rule that the same doctor sees each member of a case/control pair. If, however, the proportion of "transfers" is the same as in the original survey, approximately 2 percent of case/control pairs will not be exactly matched for district.

Survey of 1956–60 Deaths

In the interval between the two surveys some facts have been discovered for the first time and others have acquired a new significance:

1. Three independent, retrospective surveys, using different types of controls, have shown a raised incidence of prenatal X-rays among children who subsequently died from malignant diseases (*2–4*).

2. One prospective survey (followup) of children irradiated in utero has shown a raised incidence of harmless somatic mutations (*5*);

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CONTROL SELECTION LIST

For John SMITH Sex M Born on 6.9.52 in Sheffield 3

Priority	Name and address			Selected control (X) [1]
1st	8.9.52	JONES	56 School Lane	D MOVED AWAY
2d	9.9.52	STANLEY	40 Stockport Road	H X
3d	10.9.52	WILLIAMS	5 East Street	H
4th	11.9.52	PETERS	20 Clarke Street	H
5th	11.9.52	HIGGINS	2 Woodside Drive	D

[1] State reasons for not selecting the control of choice (first name on list) or other alternative.

Note: D, domiciliary delivery; H, hospital delivery.

another, concerned only with leukemia deaths, has so far produced negative results (*6*).

3. In 1959 it was discovered that mongolism is due to a chromosomal abnormality which is probably caused by nondisjunction or faulty mitosis during the last reduction division of the gamete (*7*). As a result of this unequal division, mongols carry an extra autosome (No. 21) in all their cells.

4. Though pneumonia is still a common cause of infant deaths among mongols, there have been fewer deaths in recent years (*8*). There are also indications of a substantial increase in the number of mongols dying of leukemia since 1954 (*9*).

5. About 20 percent of mongols have atypical leucocytes (*10*, *11*).

6. Hewitt's analysis of leukemia mortality (*1*) covered the period 1930–53. It has since been shown that, in Britain, the peak of leukemia mortality (2–4 years) appeared for the first time in the late 1920's and reached its present height in the mid-1950's (*12*); also, that the pneumonia death rate for children under 5 years began to decline in the late 1920's and reached its present low level in the mid-1950's (*13*).

7. There is a relationship between a child's position in his sibship and his risk of infection, and an exactly opposite relationship between this position and his risk of developing leukemia. Since older children bring infections into their houses, the infection risk is lowest for first-born children and progressively increases as the number of older children increases. Per contra, the leukemia risk is highest for first-born children and progressively decreases as the number of older children increases. Other malignant diseases in childhood do not show this relationship (*14*).

8. Compared with other cancerous children and with healthy controls, the leukemic children in the survey of 1953–55 deaths had a raised incidence of pneumonia and other serious pyogenic infections. The excess was largely due to children who had not been X-rayed in utero and who died before the age of 5 years. These illnesses were exceptionally common among the 19 mongols who died of leukemia, none of whom had been X-rayed before birth.

9. If prenatal irradiation, which usually takes place 7 to 9 months after conception, is a direct cause of leukemia, deaths caused in this way should be directly related, in time, to these exposures. The actual age distribution of such deaths will depend on the incubation period for leukemia, which is not at present known. But unless all childhood leukemias are initiated in the third trimester—an unlikely proposition—it should eventually be possible to demonstrate a difference between the age distribution, at death, of irradiated and nonirradiated cases. A recent study of first-born children in the survey of 1953–55 deaths suggests that leukemias due to prenatal irradiation have a characteristic age distribution, and that these cases die, on the average, 8 months later than nonirradiated cases (*15*). This, in turn, suggests that the vast majority of childhood leukemias are the direct result of events which tend to occur at or near conception.

10. There are several indications that retinoblastomas occur in two forms, one genetically transmitted and one not (*16*, *17*).

11. Expectations of cancer in twins are complicated by the fact that twins are more likely than other children to be X-rayed in utero, but in no large series of childhood cancers has there been any indication of an excess of identical cancers among identical twins (*12*, *14*). Unpublished results from the survey of 1953–55 deaths suggest that there may in fact be a deficiency of monozygotic twins among cancerous children. In the control group two-thirds of the twins had a twin sib of the same sex. This is the expected proportion, and there were no differences as between the twins who were X-rayed before birth and the other twins. In the case group (children who died of leukemias and cancers) there were 36 twins, 24 of whom had been X-rayed in utero. In this group of 24 X-rayed cases, the expected and observed members of twin sibs of like sex were the same (16). Among the remaining 12 cases not X-rayed before birth, there were only 2 twin sibs of like sex, though the expected number was 8.

The ways in which these and other findings have influenced the design of the 1956–60 survey require some explanation.

Working hypothesis. The natural history of cancers in man might suggest that malignant cells arise de novo and are due to specific, localized changes in the nuclei of somatic cells. But

it is becoming increasingly evident that this is only part of the story.

The Rous theory of co-carcinogenesis (*18*), which is now supported by numerous experiments in animals (*19*), postulates different stages in the formation of a malignant tumor. Normal cells are first converted into "latent cancer cells" by the action of carcinogens or "initiating agents," which produce "hereditable cellular changes" in exposed tissues. This action is irreversible and is followed by a long or short "latent period." Eventually, under the influence of a "promoting agent," the latent cancer cells begin to multiply and form a tumor. According to Berenblum (*20*), promoting agents have the dual action of increasing mitotic frequency and delaying maturation, and the type of cell which can lead to a cancer after being acted upon by an initiator is the comparatively rare kind which normally replenishes tissues; that, is stem cells.

This raises the possibility that cancers in man are due to initiation and subsequent promotion of stem cells. This would include pluripotential cells—ova, spermatozoa, and zygotes—in the category of cells which can develop premalignant properties; so it is necessary to ask why familial cancers and multiple cancers in the same individual are not more common, and why one rarely finds identical cancers in identical twins.

At first sight the absence of twin affinities suggests that there are no genetically transmitted cancers in man other than the obvious ones; namely, retinoblastomas, neurofibromas (Von Recklinghausen's disease) and cancers associated with intestinal polyposis. But the early stages of Von Recklinghausen's disease and intestinal polyposis show that tissues derived from premalignant cells may be at a disadvantage compared with tissues derived from normal cells. It is therefore possible that matching cancers in identical twins are rare, not because germ cells cannot develop premalignant properties, but because a fetus, particularly a twin fetus, derived from a premalignant zygote has a very poor chance of surviving.

If, as a result of initiation, a somatic cell produced a line of cells which were inferior to other cells, the inferior cell line might be eradicated before promotion occurred, thus removing all risk of a cancer developing at the site of initiation. But if, as a result of initiation of a germ cell, a zygote produces a line of inferior premalignant cells, it would usually be impossible for all the cells to be destroyed without causing death. Hence, initiation of a twin zygote might more often produce an abortion than twin cancers.

The few exceptions to the rule that there are no familial cancers are important for two reasons. They show that it is possible for a human zygote to survive a premalignant change, and they suggest that this change is due to a single gene substitution or point mutation. If a premalignant state merely reflected a general change in the cytoplasm, or a change which affected the nucleus as a whole, one would expect a premalignant change in a pluripotential cell to produce multiple cancers more often than not. In practice, familial cancers tend to be confined to certain cell types and to organs which are less likely to cause death, if wholly composed of inferior cells, than to other parts of the body.

Nevertheless, a point mutation in a somatic cell or germ cell might be preceded by changes in the cytoplasm and accompanied by other changes in other genes. For instance, a change in the cytoplasm might cause faulty mitosis the next time the cell divided; on one occasion faulty division of the nucleus might involve only one gene, on another occasion, several genes on the same chromosome, and on yet another occasion, several genes in several chromosomes. The risk of immediate death of the cell would be proportional to the number of genes involved, and it is unlikely that any cell would survive an accident which involved more than one chromosome. If, however, the cell survived faulty division of one chromosome, all that would matter, from the point of view of the subsequent development of a cancer, would be whether or not a gene controlling the nature of specific daughter cells had undergone a premalignant change.

If a mitotic aberration happened during formation of a somatic cell and the cell survived, the remote effects of a change in several genes on the same chromosome—deletion, duplication, translocation, or inversion—might be the same as a change in only one gene. But if the

faulty mitosis happened during formation of a germ cell or zygote, that is, a pluripotential cell, all the genes involved in the accident would influence the end result. A fetus possessing only one inferior, premalignant cell system might survive to produce a child who appeared to be normal at birth and subsequently developed malignant changes in the defective tissues; but a fetus possessing several abnormal cell systems would probably die in utero. Even if the pregnancy terminated in a live birth, the child would have several congenital defects and would be unlikely to survive long enough to develop a cancer.

So far as we know, the only congenital disease due to involvement of an autosome in a mitotic aberration which is both common and compatible with several years of life is mongolism. Mongolism, or trisomy of chromosome No. 21, is also the only congenital disease which is consistently associated with one type of malignant disease, namely leukemia; and this association was not discovered until the life expectancy of mongols increased from less than 2 years to over 14 years. Before the discovery of antibiotics, mongols usually died of pneumonia during infancy, and there is no doubt that a low resistance to bacterial infections is part of the mongoloid syndrome. Hence it is reasonable to suggest that one of the genes controlling leukopoiesis is situated on chromosome No. 21, which is also one of the smallest autosomes.

The size of a chromosome sets a limit to the number of genes which can be damaged during mitosis. There should therefore be a correlation between the size of a chromosome and the number of times that faulty division of the said chromosome causes death of the cell. In this way the position of an important leukopoietic gene might influence the prevalence of childhood leukemias. But before developing this theme it is necessary to consider what effects a "preleukemic change" in a germ cell might have and how these would compare with the effects of a similar change in a somatic stem cell (leukocyte precursor).

According to the theory outlined above, a preleukemic change in a germ cell would probably involve several genes on the same chromosome and would in any case impair the efficiency of all circulating leukocytes. Consequently, if the fetus survived, the risk of an infection death during infancy would be exceptionally high, and only children who escaped these early deaths would die of leukemia. Moreover, any reduction in infant mortality, due either to prevention or cure of infections, would adversely affect the leukemia death rate (*1* and chart).

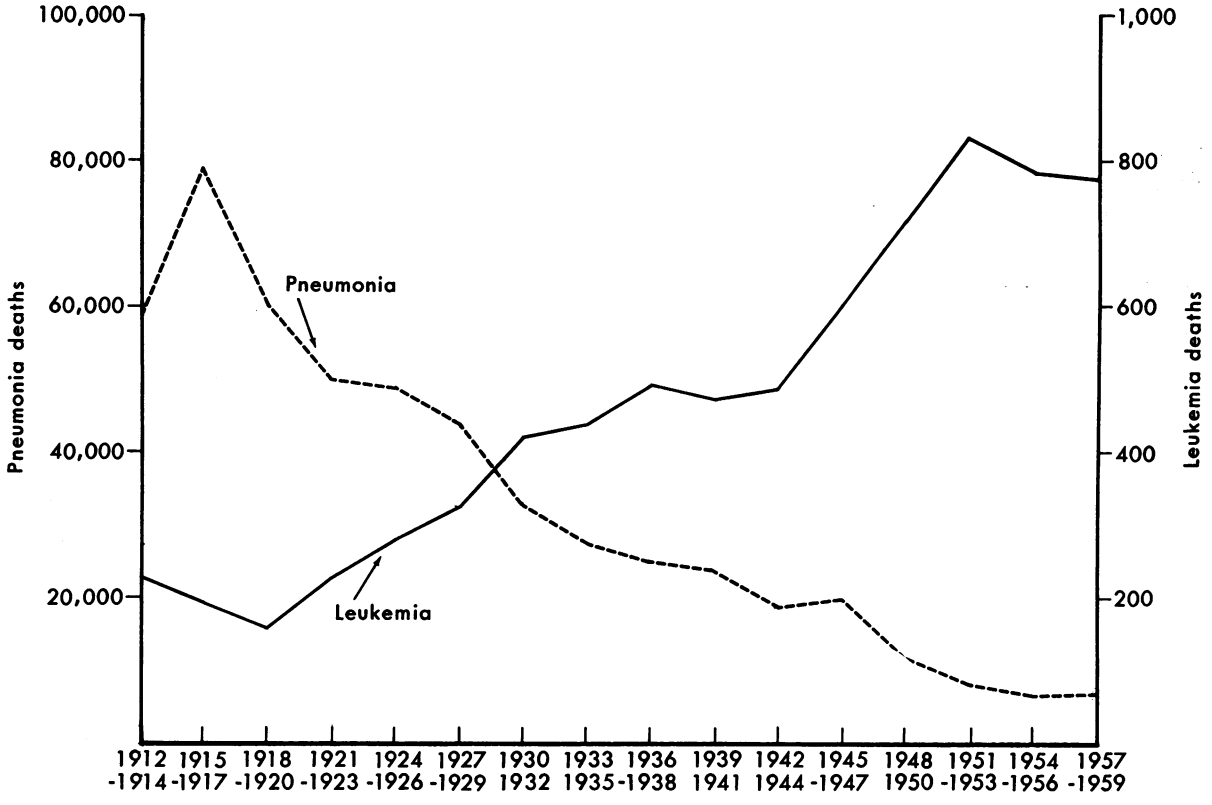
Premalignant conditioning of a leukocyte precursor in an adult, that is, a somatic cell, would also impair the efficiency of daughter cells, but in such cases the existence of healthy leukocytes derived from normal stem cells would provide some protection against infections. Consequently the risk of an intercurrent death should be comparatively small, and to produce an adverse effect on the leukemia death rate there might have to be a substantial decrease in the infection death rate.

Finally, if it is possible for faulty mitosis during the formation of a germ cell to impair the efficiency of leukocytes, and to pave the way for subsequent malignant changes in leukocyte precursors, one would nowadays expect a retrospective survey to reveal a raised incidence of potentially lethal infections among children who subsequently developed leukemia, provided that antibiotics were easily accessible.

In the 1958 report of the survey of 1953–55 deaths from cancer and leukemia (*2*), a raised incidence of pneumonia among the children who subsequently died of leukemia was mentioned. But the possibility that this finding was important and related to the high incidence of mongolism was not considered until 1959, when the origins of mongolism were explained for the first time. Once it was realized that mongolism was due to a chromosomal abnormality which had been present since conception and which predisposed not only to infections but also to malignant changes in the cells which protect the body against infections, the possibility that other cases of leukemia and cancer in childhood were due to lesions which predated or coincided with conception had to be considered.

Reexamination of the data on 1953–55 deaths from cancer and leukemia (*9*) showed that pneumonia was the commonest, but not the only potentially lethal, infection which was

Deaths from leukemia and pneumonia in children 0–10 years of age, England and Wales, 1912–59, by 3-year periods



recorded more often in the medical histories of children who subsequently died of leukemia than in the histories of children who subsequently died of other cancers. Since a raised incidence of these serious infections was a striking feature of mongols and other children who died of leukemia before the age of 5 years and were not X-rayed in utero, it was suggested that there might be two distinct varieties of leukemia in childhood; one initiated at or before conception and associated with a low resistance to infection (common form) and the other initiated in utero or after birth and associated with a normal resistance to infection (rare form).

The family histories of the survey children were scrutinized for evidence of a raised incidence of nonmalignant blood diseases in the relations of leukemic children. The data proved inadequate for this purpose but they did succeed in showing that, despite their rarity, "cancer fraternities," that is, the same malignant disease affecting more than one member of a sibship, were more common than would be expected if they were merely chance phenomena.

There were other indications in the original data that genetically transmitted cancers were not confined to retinoblastomas, but it was not possible to be certain that this was so. Hence the decision to extend the survey and redesign the pro formas so that there would be some possibility of testing the theory that faulty mitosis during or before zygote formation is a common cause of malignant disease in childhood, though these diseases may also be due to mitotic aberrations involving somatic cells. It was also hoped that the new data would help to settle the controversy about prenatal X-rays being a cause of malignant disease in childhood.

This controversy exists because it is impossible to be certain that, in the retrospective surveys mentioned above, the normal incidence of prenatal X-rays was correctly estimated. It is therefore important to obtain evidence which is independent of control data. If all children born in a given period who subsequently died

of malignant disease could be traced, it would be a relatively simple matter to decide whether "irradiated" and "nonirradiated" cases had different age distributions. The survey of 1956–60 deaths will not provide all the facts required, but if it is successful, the data will include an 8-year followup of children born between 1950 and 1953 and may be sufficient for the purpose (table 1).

Other theoretical considerations. The suggested working hypothesis would only be acceptable if it offered a rational explanation of the following facts. First, infants apart, the risk of developing a malignant disease decreases with age before puberty and increases with age after puberty. The age distribution of children with cancers, that is, the age at death, varies with cell type. Cancers of nervous tissues are commonest in the first and second years, renal cancers and retinoblastomas in the third year, leukemias in the fourth year, and lymphosarcomas in the fifth year. Second, compared with other cancers, leukemias have always been relatively common in childhood and are nowadays the commonest variety of malignant disease in childhood. In adults less than 10 percent of malignant diseases are leukemias.

Age distribution. So far nothing has been said about the nature of "promoters" except that there is reason to think that in normal circumstances they do no harm, and merely encourage mitosis. Since it is only in the presence of premalignant cells that a promoter ever produces a cancer, it is possible that "natural promoters" include growth factors (general promoters) and also repair mechanisms and defense mechanisms (local promoters). Assuming that this is so, and that there is a sizable population of premalignant genes in newly formed zygotes, one would expect the risk of promotion during childhood to decrease with age (general promoters) and the risk during adult life to increase with age (local promoters). One would also expect a temporary increase in risk during puberty, but this would be difficult to detect in national statistics because these only show deaths in 5-year age groups. Lee (*21*), who obtained deaths for individual years, has shown that there is a temporary increase in the leukemia death rate during adolescence. Since malignant cells are incapable of maturing much beyond the stage which they have already reached, one would also expect to find that, when promotion occurred within a few weeks of conception, the resulting tumor contained less well differentiated cells than when promotion occurred later. One purpose of the survey is to discover whether there is any correlation between age at the onset of the fatal disease and the maturation phase of the cancer cells.

Preponderance of leukemias. It has already been suggested that the small size of chromosome No. 21 may be related to the fact that leukemia is a relatively common variety of cancer in childhood. According to this theory a gene controlling leukopoiesis should be situated on chromosome No. 21, and leukemia might be the result of this chromosome being involved in a mitotic aberration.

Provided a preleukemic state was the result of faulty mitosis in a leukocyte precursor, that is, in a somatic cell, there might be no obvious side effects due to involvement of other genes on the same chromosome. But if the change affected a germ cell there would be important side effects if neighboring genes were damaged. There are fewer genes at risk in chromosome No. 21 than in other autosomes, and in view of what is now known about mongolism, these genes may be less essential for vital processes than genes on other chromosomes.

The statistical association between mongolism and leukemia was one reason for postulating a leukopoietic gene on chromosome No. 21. Another reason is the so-called Philadelphia chromosome. This is the name which has been given to an abnormality which has been found in the leukocytes of some, but not all, cases of myeloid leukemia in adults (*22*). The chromosome involved is either No. 21 or No. 22, which are difficult to distinguish, and its appearance suggests that during division of a leukocyte stem cell part of the chromosome was lost.

According to the theory outlined above, there would be nothing paradoxical about finding a partial deletion of a chromosome in some cases of leukemia, and a duplication (trisomy) of the same chromosome in other cases. Nor would it be surprising to discover that when the chromosomal abnormality is found in all cells, the leukemia occurs early and is accompanied by

other congenital defects, and when it is found only in leukocytes, the leukemia occurs late, and there are no congenital defects.

Another feature which has probably influenced the prevalence of leukemias in childhood has already been mentioned; namely, the lowering of the infant mortality rate. Thirty years ago cancers of nervous tissues, that is, neuroblastomas and cerebral tumors, more often caused death in childhood than leukemias, and it is only since the discovery of sulfonamides that leukemias have taken first place.

Progress. With these ideas in mind the second part of the survey was launched in April 1961. Once again county and county borough health departments have assumed responsibility for the fieldwork and already arrangements have been made to trace more than three-quarters of the children who died between 1956 and 1960 (table 2). As in the survey of 1953–55 deaths, each dead child will be paired off with a live child of the same age and sex, and doctors will interview mothers. The mothers' descriptions of their children's illnesses, X-ray exposures, and family histories will be recorded on specially printed schedules and the more important items will be checked with hospital records.

Pedigree data. In the survey of 1953–55 deaths some information about the mother's relatives was obtained, but comparatively little attention was paid to the father and his side of the family. Mothers were asked if they knew of any relatives who had died of cancer or leukemia, but their answers showed that they knew, offhand, less about their husbands' relatives than about their own. In the survey of 1956–60 deaths more extensive family histories will be recorded and a new method of collecting pedigree data has been devised.

Each mother will be visited first by a health visitor assigned to her parish. The health visitor's instructions are: (*a*) to obtain the cooperation of the mother; (*b*) to ascertain the date of birth of the dead child (this is needed to obtain the control); (*c*) to explain what is required; and (*d*) if necessary to help the parents to complete schedule X, Enumeration of Relatives.

In general, schedule X will be given to the mother about a week before the doctor calls, together with a covering letter which asks her to record, under printed headings, all that she and her husband know about "the four grandparents of the survey child and all their direct descendants, including stillbirths and miscarriages." The printed headings include position in sibship, illnesses and X-ray experiences (parents), all causes of death and other specified illnesses (other relatives), dates of birth and present state of health or cause of death (sibs), miscarriages and stillbirths (mothers and grandmothers).

Control selection lists. Schedule X is an example of an innovation made in the light of earlier experiences. Another example is the entry alongside each name on the Control Selection List of the letter D (domiciliary delivery) or H (hospital or nursing home delivery). Knowing as we now do that the cases in the survey of 1953–55 deaths had a higher incidence of prenatal X-rays than the controls (*2*), it is clearly important to know whether first choice controls are representative of the population at large in respect of birthplace; also whether failure to obtain 100 percent of first choices has biased the control group in this respect.

Other sources of bias. Retrospective data collected by several doctors direct from mothers of living and dead children are subject both to recording bias (doctors) and to reporting bias (mothers). By insisting from the beginning that the records from each case/control pair be compiled by one doctor, the first type of bias should have affected case and control data equally, and should not have been an important source of error in the earlier reports (*2*, *9*). It is less certain that the second source of error has not affected these reports, and the suspicion still remains that the findings in respect of prenatal X-rays were due to "memory bias" (*23*).

A knowledge of the ways in which the original case and control groups differed from one another should make it possible to collect more convincing data in the new survey. On this occasion answers to questions which are expected to reveal differences between cases and controls will be systematically checked. In addition, several new questions will be asked for the express purpose of discovering whether events which could not possibly have affected

the children, for example, X-rays of the parents after birth of the child, are reported with equal frequency by parents of both cases and controls. In the original survey only positive statements about abdominal X-rays during pregnancy were confirmed by asking X-ray departments to produce the original records. In the survey of 1956–60 deaths addresses of antenatal clinics and X-ray departments will be automatically recorded, and the intention is to check negative statements about X-rays on a sample basis, and positive statements on a comprehensive basis.

Checking records. As soon as the completed pro formas are returned to Oxford they are examined to see if they are internally consistent and to decide what type of postal followup is required. The object of this is to obtain hospital records of the fatal illness and confirmatory evidence about the following statements:

- X-rays and illnesses of the mother during the pregnancy of the survey child, including anemias and threatened abortions.
- Relatives with anemia or other blood diseases, including leukemias.
- Relatives with "matching" cancers; that is, the same type of cancer as the "index" case.
- Relatives said to have died at an early age from an obscure cause.

In addition, approximately 25 percent of negative statements about X-rays and other antenatal events will be checked by asking antenatal clinics to make an abstract of the original notes on a specially printed form (schedule G). If necessary, more information will be obtained from the mothers, and some parents will be asked if they are willing to have sibs of the survey child examined. Twins will be included in this group, also children who have lost more than one sib, or have two or more relatives with blood diseases; for example, leukemia, pernicious anemia, purpura, acholuric jaundice, and aplastic anemia.

Present status. At the time of writing (September 1961), 220 case/control pairs have been completed and 85 "lost" cases have been returned to Oxford. The proportion of lost cases is high, but this is not surprising since it takes longer to complete the records for a case/control than to discover that a family has moved to an unknown address (49 cases), or that the mother is either not willing to cooperate (30 cases), or not in a fit state to be interviewed (6 cases). Already a considerable amount of information about the lost cases has been obtained from other sources, such as hospitals, welfare clinics and schools, and in two cases this was sufficient to justify finding a "matched" control.

The results of the postal followup suggest that the numbers of X-ray records which are still available are larger than the numbers which have been destroyed and may be sufficient to test the accuracy of the mothers' statements. There has been no difficulty in obtaining from hospitals either the original records of the fatal illnesses or abstracts of the original notes on specially printed forms (schedule A). So far none of the mothers who have been interviewed has resented a followup letter and most of them have been able to complete schedule X. We feel confident that, provided they are given sufficient time, the parents of our survey children will be able both to enumerate their relatives and to tell us where to look for hospital records and death certificates. It is too soon to say how many of the children who died between 1956 and 1960 will eventually be traced, but the prospects are at least as promising as they were at the same stage of the survey of 1953–55 deaths.

Summary

The survey of childhood malignancies originally included only children who died between 1953 and 1955 but has recently been extended to include later deaths. In the final study population there will be children who were born in the 18 consecutive years 1943–60 and whose deaths were spread over the 8 calendar years 1953–60.

The method of collecting data and selecting controls for the 1953–60 deaths remains the same, but the pro formas have been revised and there will be more systematic checking of mothers' statements against hospital records.

It is hoped to settle the controversy about the effects of prenatal X-rays by comparing the ages of irradiated and nonirradiated children, and thus obviate the need to place reliance on control data.

It is suggested that the first stage in cancer promotion is a mitotic aberration and that the

commonest cause of childhood cancers is faulty mitosis during division of a germ cell. Following such an accident the risk of death before a tumor has time to develop is much higher than the corresponding risk following faulty mitosis in a somatic stem cell. Consequently there are no "twin affinities" and there is a low incidence of familial cancers.

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Radiation Symposium

A symposium on the technological needs for reduction of patient exposure from diagnostic radiology will be held March 5–6, 1962, in the main auditorium of the Health, Education, and Welfare Building, Washington, D.C. The symposium, sponsored by the Public Health Service, will evaluate present knowledge and discuss future investigation in four main categories: human and phantom dosimeters; radiographic equipment; fluoroscopic and intensifier equipment; and radiographic grids, screens, and films.

For further information and tickets, contact Dr. M. L. Janower, Division of Radiological Health, Public Health Service, Washington 25, D.C.