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Intracerebral Aneurysms

Epidemiology of Leukemia

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CONTENTS

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Staff Meeting Report

Management of Aneurysms of the Anterior Communicating Artery*

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The purpose of this report is to present the experience of the Division of Neurological Surgery at the University of Minnesota Hospitals in the surgical treatment of aneurysms involving the anterior communicating artery. For the 25 consecutive cases¶ treated prior to July 1961, such topics as the optimal time of surgical intervention, the method of the surgical approach, and the use of hypothermic and hypotensive techniques in anesthesia will be discussed. Because of the considerable controversy about the preferred form of therapy of aneurysms in this location, we have felt it advisable to record and review our experience so that it can be used by others in comparative reports. We recognize that there is no single universally acceptable method of therapy.

LYLE A. FRENCH

Anterior communicating artery aneurysms are notoriously difficult to treat either by nonoperative or by operative methods. The mortality and morbidity rates with either type of management vary greatly in the reports in the literature. McKissick[1] found, in a series of 62 aneurysms involving the anterior communicating artery treated nonoperatively, a mortality rate of 52 per cent within approximately one month of the hemorrhage, and a morbidity rate of 17 per cent among surviving patients.

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*This report was presented at the Staff Meeting of the University of Minnesota Hospitals on February 23, 1962.

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¶Includes all cases representing consistent selection criteria. Not included are data on those few patients for whom other surgical methods were used.

Ask-Upmark[2] in a series of 138 patients observed that approximately three out of five died within a short time following the acute episode, and 50 per cent of the survivors were permanently disabled. However, with more recent therapeutic adjuncts, such as hypotensive therapy, the mortality rate during this acute episode for nonoperative therapy may be reduced. Slosberg[3] reported a mortality rate *during the acute episode* of only 33 per cent in a series of 15 patients. When patients have been followed for a longer period of time, however—up to 5 to 10 years—the mortality rate has been observed to rise to approximately 66 per cent (Ballantine[4]). In addition, these patients face the ever-present threat of a recurrent hemorrhage.

Careful evaluation by Poole[5] and Gillingham[6] has shown that equivalent cases treated surgically have a lower initial mortality rate and an equally good if not better morbidity and prognosis; in addition, the apparent danger of fatal recurrent hemorrhage is removed. But while surgical treatment seems preferable to nonsurgical therapy, opinions differ as to the optimal time of surgery, the selection of patients, the surgical technique to be employed, and the relative usefulness of hypothermia and hypotension in anesthesia.

Clinical Material

The patients included in this study were referred by their family physicians; in most of them, therefore, the diagnosis of subarachnoid hemorrhage was confirmed by the presence of blood in the cerebrospinal fluid prior to their admission to this hospital. Further confirmatory diagnostic tests were not performed after admission to this hospital unless (as rarely happened) the clinical history or course seemed to warrant it. Occasionally, repeated lumbar punctures were used as therapeutic measures to tide the patient over the acute episode, i.e., while awaiting the most propitious moment for angiographic studies and surgical intervention.

The general policy was: 1) to obtain angiographic studies only when the patient's condition was sufficiently good to permit a surgical approach; and 2) always to perform angiographic studies about the first week or 10 days after the initial episode of subarachnoid hemorrhage. This principle is based on data reported in a previous communication.[7] These studies were generally made on about the seventh or eighth day following the last hemorrhage. Obviously, however, the time of angiographic studies varied somewhat with the condition of the patient. In a seriously ill individual, one who was going downhill clinically, the angiographic studies were made immediately

following hospitalization. But if the patient's general condition was quite good, the studies were delayed several days. One factor influencing the time of angiography is the greater frequency of non-filling of the aneurysm as a result of adjacent vasospasm during the acute stage.

Bilateral angiographic studies were performed on all patients in this series except two on whom only unilateral studies were obtained. We firmly believe that bilateral angiography (including collateral circulation studies) is an essential prerequisite for this type of surgical treatment.

It was not always possible to demonstrate unequivocally that adequate cross-circulation was present on contralateral carotid artery compression studies. It was rare, indeed, to find that the interior circle of Willis was entirely intact. This may well have been due to temporary arterial spasms, but usually we felt it was due to some anomalous formation of the circle of Willis, such as was often observed during surgical intervention.

Three of the patients in this series had multiple aneurysms: one had an associated supraclinoid internal carotid aneurysm; another had associated bilateral posterior communicating artery aneurysms; and the third had an associated aneurysm of the middle cerebral artery. Five of these 25 patients gave angiographic evidence of intracerebral hematomas (marked displacement of the anterior or middle cerebral vessels), and in addition one patient had an associated large subdural hematoma.

Three of the 25 patients had complications that arose as a result of the angiographic studies. Shortly after the angiogram, hemiparesis developed in two patients, and aphasia and quadriparesis supervened in a third. The duration of these disturbances varied from 3 to 48 hours, all patients reverting to their pre-angiographic status. No late complications resulted from these angiographic studies.

From Table 1, showing ages of the patients in half-decades, it is apparent that a peak incidence occurs during the fifth

TABLE 1

AGES OF PATIENTS PER HALF DECADE

Age	*No.*	*Age*	*No.*
20-24	1	45-49	5
25-29	1	50-54	0
30-34	1	55-59	2
35-39	3	60-65	4
40-44	8		

TABLE 2

FREQUENCY OF MAJOR HEMORRHAGES IN THIS SERIES

No. with one hemorrhage	14
No. with two hemorrhages	9
No. with three or more hemorrhages	2

decade. This series represents an age group similar to that observed in other series.[8] Increased age is reported to be unfavorable prognostically,[1] and in this series the oldest patient did not survive. In general, however, such an age correlation is not apparent; but our series is too small to warrant any reliable conclusions relative to this correlation. Among patients with multiple hemorrhages, only one was younger than 38 years, while all the others were older than 40 years.

Patients sustaining multiple hemorrhages, especially within a short time, present a much poorer prognosis. It is sometimes very difficult to determine the frequency of multiple hemorrhages; unquestionably a small hemorrhage can be passed off as an attack of migraine or even severe neuralgia. Obvious multiple hemorrhages did occur, however, in 11 of these 25 patients (Table 2). Nine patients each had two hemorrhages, and two patients each had three or more severe hemorrhages. In the group which had had three or more hemorrhages, the longest time between subsequent hemorrhages was four months. In one patient the hemorrhages recurred at eight weeks, and in the remaining patients the time of recurrences varied from eight days to three weeks.

In Table 3 the duration of time between the last hemorrhage and the definitive surgical therapy is presented. Of the three patients operated on within two days of the hemorrhage, one died; this patient had an acute, severe, recurrent hemorrhage and was moribund prior to surgery. Of the two survivors, one had a hemiplegia and has been unable to work. The other has no

TABLE 3

TIME LAPSE—HEMORRHAGE TO SURGERY

Weeks	*No.*	*Weeks*	*No.*
0-1	6	4-5	0
1-2	7	5-6	2
2-3	5	6-7	1
3-4	2	More than 7	2

TABLE 4

NEUROLOGIC SIGNS IMMEDIATELY BEFORE SURGICAL TREATMENT

Status of Patient	*No.*
State of Consciousness	
Alert	10
Confused	12
Comatose	3
Hemiparesis or Hemiplegia	14
Extraocular Nerve Involvement	8
Papilledema	8
Nuchal Rigidity	24
Hypertension	13

neurologic abnormalities and is working on his own farm. In contrast, of the seven patients who underwent surgical treatment four weeks or more after the last hemorrhage, only one has had a poor result from the surgical treatment; obviously these patients were in better general physical and neurologic condition before receiving surgical therapy.

Table 4 summarizes the neurologic deficits observed in these 25 patients during the immediate preoperative period. (Neurologic deficits include an assessment of the state of consciousness, the presence of such abnormalities as nuchal rigidity, papilledema, cranial nerve palsies, gross asymmetry of reflexes, and motor and sensory deficits.) Table 5 indicates the general preoperative status of this entire series of patients. In Table 6 the data on neurologic defects (Table 4) are related to postoperative morbidity and mortality. All the patients who had more pronounced postoperative morbidity can be seen to have had definite neurologic loss preoperatively, and represented, in general, the poorer operative risks. All patients whose preoperative status was normal did well after surgical treatment.

SURGICAL TECHNIQUE

The surgical procedure in this series of 25 patients involved performing a craniotomy and then attacking the aneurysm directly in an attempt to obliterate it completely. In our method of handling aneurysms involving the anterior communicating artery, a general anesthetic is used, the airway being assured with an endotracheal tube. Artificial ventilation is preferred to any respiratory effort on the part of the patient. An osteoplastic transfrontal craniotomy is performed on the right side irrespec-

TABLE 5

PREOPERATIVE ASSESSMENT OF PATIENT'S GENERAL STATUS

Severity of Deficit	*Symptoms or Signs*	*No.*
Normal	None	4
Moderate	Mental confusion lethargy, coma or definite neurologic loss	10
Severe	Symptoms of moderate deficit, plus cardiorespiratory problems	11

tive of whether the aneurysm fills better from the left or the right. The inferomedial trephine is placed as low as possible over the sagittal sinus without entering the frontal sinus. At the inferomedial aspect of the bone opening, the dura is opened in a triangular fashion over to the sagittal sinus and as far forward as possible. A wedge section of anteromedial frontal lobe is removed with the apex at the area of the anterior communicating artery. This wedge generally is about 2 cm. wide and about 4 cm. long. The removal is accomplished by aspiration of the brain tissue with a small suction apparatus. Invariably, the olfactory nerve is inadvertently avulsed. The aneurysm is completely exposed as are also portions of both anterior cerebral arteries leading to and from the region of the anterior communicating artery. Such exposure of the aneurysm by removal of the adjacent, usually softened and hemorrhagic, brain tissue is one of the important aspects of this technique. Since there is no retraction of the aneurysm nor of the vessels leading into the area, premature rupture of the aneurysm seldom occurs and a minimum of vascular spasm results.

The blood pressure is lowered with hypotensive agents as soon as the region adjacent to the aneurysm is encountered. In order to reduce intraluminal pressure to the point at which the aneurysm can safely be clipped, the systolic pressure should be lowered to approximately 60-70 mm. Hg. Pressures appreciably higher than this do not permit appropriate handling of the aneurysm by the surgeon. On occasions a temporary clip has been applied to the vessels leading into the aneurysm to facilitate clipping of the aneurysm. By careful dissection the brain tissue around the aneurysm is removed. The aneurysm is then incised and the blood permitted to go up a sucker, thereby collapsing the aneurysm and making it possible to put silver clips across the neck of the aneurysm or onto the anterior communicating artery adjacent to the aneurysm. Without opening the aneurysm, it is often simply impossible to place the clips properly. These defects are frequently so large that one cannot

successfully dissect around them; adequate visualization of the vessels leading into the aneurysm cannot be obtained without collapsing it. This hemorrhage from the aneurysm is seldom of any serious technical consequence since it is created deliberately and is controlled by permitting the aneurysm itself to pull up into the sucker. As an additional safety factor, however, a second suction apparatus is available for clearing the field of any blood that might not enter the larger sucker placed over the aneurysm. By this technique the aneurysm, of course, is opened into and thus any vessel not visualized at the time of angiography or even at the time of surgical intervention is visualized; thus one is assured of complete obliteration of the abnormality.

This technique of exposure of the aneurysm and of the feeding vessels was employed in nine of the 25 patients. In ten others clips were applied to the apparent feeding vessels and the aneurysm was then opened to insure that there was no occult circulation into the aneurysm. This procedure is recommended because in four of the ten aneurysms so opened, fairly brisk blood flow was observed even though all the entering vessels had been occluded previously. Since aneurysms occur at sites of developmental malformation, small and aberrant feeding vessels may exist; the situation is not always identical to that visualized on angiographic studies. For this reason, the aneurysms were opened in a total of 19 of the 25 patients; in the other six the surgeon considered, for varying reasons, such opening inadvisable or unnecessary. It was necessary in 4 of the 25 patients to occlude permanently the anterior cerebral artery in addition to the direct approach to the aneurysm. In one of the four some damage (short of total occlusion) undoubtedly was done to the contralateral anterior cerebral vessel; this patient had a permanent neurologic defect. In another of the four, both anterior cerebral arteries were occluded, and this patient also suffered a permanent severe neurologic deficit.

Before the craniotomy flap is closed, the blood pressure is restored to normal. The period of hypotension generally lasts for less than 20 minutes. It has not been necessary with this technique to re-open any wound because of postoperative blood clots or edema. If the necessity for proximal ligation of vessels entering the aneurysm is anticipated, hypothermia by means of the cooling blanket is also used in addition to hypotension. This combined technique was used in 4 of the 25 patients. Hypotension alone, however, usually offers sufficient advantage to the surgeon, and it certainly entails less complicated operative and anesthetic preparation. As Semmes has cogently pointed out, there is much to be said for simplicity in surgical approach.[9]

TABLE 6

MORTALITY AND MORBIDITY ACCORDING TO PREOPERATIVE STATUS OF THE PATIENTS

Preoperative Neurological Deficit	*No.*	*Deaths*	*Morbidity*					
			Early			*Late*		
			None	*Mild*	*Severe*	*None*	*Mild*	*Severe*
Normal	4	0	2	1	1	4	0	0
Moderate	10	0	0	5	5	5	4	1
Severe	11	1	0	0	10	3	4	3

There was one operative death in this group of 25 patients (Table 6). Of the surviving 24 patients, there were 7 with gross and 4 with minor neurologic deficits apparent immediately after surgical intervention. These were permanent in four patients, in one they lasted for a period of six months and in the others they lasted less than a month. Essentially all the patients for a short time postoperatively exhibited definite mental confusion. Nineteen of the 24 surviving patients are now working at their previous occupations or their equivalents.

DISCUSSION

The preference in this clinic for the described obliteration and excision of aneurysms is based on several observations. First, it is believed that carotid ligation offers no advantages in patients with aneurysms of the anterior communicating artery. The morbidity associated with the procedure in the presence of subarachnoid hemorrhage is now well known, especially in patients with apparent arterial spasm (Hamilton and Falconer,[10] Shenkin et al.[11]). In addition it is probably much less protective than any other procedure (Logue[8]).

Proximal ligation of the principal patent feeding anterior cerebral vessel has also been used. This technique, however, does not insure against recurrent hemorrhage via the contralateral patent artery.

The technique of wrapping aneurysms with muscle or fascia or both has been reported as occasionally resulting in secondary hemorrhages (Norlen et al.,[12] Hamilton et al.[10]). We therefore believe that this procedure is not as protective as the direct approach with obliteration of the aneurysm.

In this series, we have grouped together all patients treated by clipping of the neck of the aneurysm and by ligation of the entering vessels, with obliteration of the sac of the aneurysm. Ligation of the neck of the aneurysm with secondary opening

of the aneurysm to insure non-filling from an aberrant vessel is, we feel, the best form of therapy; but in many patients the aneurysms appeared to involve both the anterior communicating and the anterior cerebral arteries, and hence did not present an appropriate stalk or neck that could be clipped. In this event, since there was no alternative, the aneurysm and the feeding vessel were clipped.

Controlled hypotension has been used quite routinely in this series. Initially, Hexamethonium® was used to produce the hypotensive state, but Arfonad® is now preferred because of its shorter duration of action and greater controllability. The hypotensive technique described here is contraindicated in cases of vascular disease or of hepatic, renal, or coronary disease.

The complicated dual technique of hypotension and hypothermia was used only when we anticipated a temporary or permanent occlusion of a large cerebral vessel. Certainly the postoperative morbidity and mortality in these few instances in which hypothermia was used support the preoperative assessment that these cases would present the more complex technical problems. Conversely, in most cases a simple hypotensive technique was deemed sufficient, and this opinon again seems to be confirmed by the low morbidity rate among these patients with the less complicated aneurysmal lesions.

This series differs from others presented in the literature in that resection of the medial and anterior aspects of the frontal lobe was used to provide exposure of these aneurysms. This procedure gives a very excellent exposure without undue traction on the adjacent brain tissue, from which the aneurysm is readily isolated. Frequently these aneurysms will project up into the frontal lobe or down into the region of the optic chiasm. With other techniques the traction necessary to obtain proper exposure is applied directly onto the brain tissue and secondarily onto the aneurysm, or there is stretching and distortion of the vessels leading into the aneurysm. For the same reason the intravenous injection of urea to decompress the brain is felt to be inappropriate in the treatment of aneurysms of the anterior communcating artery because resection of the brain adjacent to the aneurysm is made very difficult after the brain has been contracted down by the use of urea. The question that arises, of course, is whether or not any symptoms of frontal lobe deficit occur as a result of resection of this tissue. Those patients on whom reasonably extensive psychological tests were obtained postoperatively showed no significant deficit. Moreover, such deficit has not been apparent in patients who underwent similar

resection to permit surgical approach to the pituitary gland at the time of hypophysectomy for breast cancer. It is believed that postoperative symptoms of frontal lobe deficit more often result from arterial spasm than from resection of the frontal lobe. With few exception, the observed changes have been transient. Only those patients with large intracerebral hematomas and the one patient in whom both arterior cerebral arteries were occluded showed symptoms consistent with a frontal lobe syndrome.

A second real difference in this series compared to others is the use of hypotensive techniques of anesthesia. Hypotension must be used judiciously. The pressure should be reduced adequately to decrease the chance of inadvertent rupture of the aneurysm, and, by the same token, the duration of the hypotension must not be so prolonged as to permit irreversible ischemic alterations. The pressure must be reduced at the precise time of exposure of the aneurysm, on the well-founded assumption that only a short period of hypotension is necessary.

Summary

1. Findings are presented for a series of 25 patients treated consecutively with a specific surgical technique for aneurysms of the anterior communicating artery.

2. A method is described for exposure of aneurysms involving the anterior communicating artery by means of wedge resection of the frontal lobe, along with the use of hypotensive techniques in anesthesia.

3. Following this procedure, one patient died immediately, and three patients (approximately 15 per cent) showed postoperative morbidity. Nineteen of the 25 patients returned to their former occupation.

4. We have concluded that surgical treatment of aneurysms in this location clearly offers a distinct advantage over nonoperative management.

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Staff Meeting Report

An Epidemiologic Study of Childhood Leukemia*

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An increase in age-adjusted leukemia death rates in the United States since 1900 was first described in detail by Sacks and Seeman in 1947.[1] Subsequent studies by Cooke in 1954[2] and Gilliam and Walter in 1958[3] indicate that the rise in leukemia death rates has continued, although Gilliam and Walter have reported that the rate of increase of leukemia death rates in the white population has tended to decline since about 1940. The older age groups have shown the greatest increase in mortality from leukemia, but no age group has escaped the general upward trend.[1–3] Improvement in diagnosis, increasing availability of medical care, increasing accuracy in death certification, changes in classification and other factors all have contributed to produce an increase in leukemia death rates which may, in part, be somewhat more apparent than real.[1–4] It is difficult, however, to accept the astounding increase in the incidence of this group of diseases as being due solely to these factors. Between the years 1930 and 1950 the age-and race-adjusted leukemia death rates in the U. S. rose from 24.7 per million to 58.2 per million.

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*Presented at the Staff Meeting of the University of Minnesota Hospitals on February 9, 1962

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When any group of diseases of obscure etiology, such as leukemia, gives evidence of an increasing incidence, attention is naturally directed to the possibility that some environmental factor or host attribute has been responsible for the observed change. Thus, for example, the increasing use of ionizing radiation for diagnostic and therapeutic purposes has been the subject of considerable interest. Exposure to a variety of newer chemical agents, including drugs, has also been suspected of contributing to the development of leukemia. Apart from environmental factors, certain host attributes may be significantly associated with the development of leukemia, and factors may have been operative which have increased the susceptibility of segments of the population.

A number of published epidemiologic studies have been designed to test associations of environmental factors and host characteristics with the occurrence of leukemia. Unfortunately, the conclusions of studies testing the same hypothesis have not always agreed. Although sampling variations may have been responsible for inconsistencies in results in some cases, certain unrecognized biases in sampling techniques or in methods of data collection also may have led to contradictory findings. In any case, additional studies are clearly needed in order to provide adequate data for a collective test of each likely hypothesis.

Study Design

The Minnesota childhood leukemia study, initiated in 1958, had two main objectives: 1) to determine whether or not an association exists between exposure to ionizing radiation and the development of leukemia; and 2) to evaluate the relationship of certain other environmental and host factors to childhood leukemia. The data to be reported consist of that interview information which has been verified by careful inspection of medical records and other information which is likely to possess a high degree of inherent validity.

The population studied consisted of Minnesota residents in the 0–4 year age group who died of leukemia during the five-year period (1953–57) immediately prior to the inception of the study. By restricting the population to recently deceased children of a young age group, we hoped to maximize recall and amount of available relevant data. It should be pointed out, however, that events in the lives of some of these children dated back about a decade before the study was begun. A search of Minnesota death certificates of children in the 0–4 age group for the period 1953–57 yielded 131 on which leukemia or aleukemia was listed. Only 112 of these cases were ultimately in-

cluded in the study. In Table 1 are noted the reasons for excluding 19 cases.

TABLE 1

REASONS FOR EXCLUSION OF 19 DEATHS ATTRIBUTED TO LEUKEMIA OR ALEUKEMIA IN THE 0-4 AGE GROUP, MINNESOTA, 1953-57.

Not residents of Minnesota	3
Not verified as leukemia	2
Families moved to other states	10
Families not located	3
Family refused to participate	1
Total	19

The three patients who were not residents of Minnesota were children who had been brought to medical centers in this state for treatment. The two cases discarded because the diagnosis could not be verified are of interest. One, certified as dead from congenital leukemia, was shown at autopsy to have died of erythroblastosis fetalis. The other, certified as dead from acute leukemia, actually died of pneumonia complicating aplastic anemia, according to autopsy findings. Families of ten patients had moved to other states after death of the patients and could not, therefore, be personally interviewed by the investigators. Intensive search failed to turn up three families, two of which were thought by neighbors to be evading creditors. The mother of one patient (a mongoloid child) could not be persuaded to participate in the study.

Since the analysis was to involve a comparison of selected characteristics of matched pairs of cases and sibling controls, and matched pairs of cases and neighborhood controls, two control children were sought for each leukemia patient. The selection of a sibling control child was made by the investigator, using the following formula: That sibling was selected who was of the same sex, whose birthdate was closest to the leukemic child and who, at time of family interview, had attained an age in months at least equal to the age at death of the leukemic child. If no child meeting these criteria existed in the family, the child of the opposite sex meeting the above criteria was selected. If no child of either sex fulfilled the age requirement, no sibling control was considered to exist.

In 75 matchings a child of the same sex was obtained. In 30 matchings the sibling control was necessarily of the opposite

sex, and in seven families no sibling control child was available. Although a dead sibling was not to be excluded from the control group provided such a child had attained an age equal to that of the leukemia victim, only one such sibling came into the study. This sibling control child also died of leukemia, but outside of the period (1953–57) under study. Since we did not plan in the study to follow other siblings for possible ultimate development of leukemia, this child had to be included in the control group.

A neighborhood control child was selected for each case according to a detailed procedure. Simply stated, the matched neighborhood control was the child of the same sex, who lived in closest proximity to the family of the leukemia victim and whose birthdate was within one year of that of the leukemia patient.

To locate such a child, the investigator was directed first to the dwelling to the right of that of the leukemia case. This failing, he inquired at the dwelling to the left, followed by the second dwelling to the right, etc., until the block had been exhausted of possibilities. If necessary, he then used a similar strategy across the street, and in blocks to the right and to the left of the block containing the index dwelling. Procedures for selection from apartment buildings and farm communities were somewhat similar, floors in apartment buildings being treated as equivalent to city blocks in single-dwelling neighborhoods, and crossroads in rural areas as street dividers of blocks. These procedures were designed to remove operator bias in the selection of neighborhood control children. Fortuitously, perhaps, no situation was encountered which had not been anticipated in the protocols. In no case was an eligible neighborhood control child lost because of parental refusal to participate in the study. All 112 neighborhood control children were living at the time of the investigation.

Whether or not the matching of neighborhood control children with the leukemia patients actually served to control confounding variables in this study is, of course, debatable. Admittedly, this manner of matching can best be defended with intuitive assumptions. It is hoped that some degree of control on socioeconomic, environmental and ethnic variables was achieved, but since these variables were not measured in the study, the validity of this assumption could not be assessed.

The mother of each leukemia patient was interviewed, and questionnaires were completed for the patient and for the sibling control child. In addition to data concerned with the relevant pregnancies and the lives of the children, the names and addresses were sought for all physicians, dentists, and other practitioners who had attended the mother during pregnancy or the child after birth. Identical questionnaires were completed for the neighborhood control children.

The interviews were designed to elicit, in addition to the usual vital data, information regarding the relevant pregnancies, including radiation and chemical exposures, infectious diseases, metabolic disturbances, trauma, complications of previous pregnancies; and, for the pertinent child, exposures to radiation and chemicals, allergies, infectious diseases, congenital anomalies,

pica, trauma, metabolic disturbances, developmental abnormalities, and use of medications. Although large amounts of data were obviously collected, only verified items were analyzed.

Attempts were made to verify collected data by visits to physicians, dentists, osteopaths, chiropractors, and hospitals throughout Minnesota and in neighboring states. Almost 400 practitioners and 42 hospitals were visited in order to review records. In a few cases data were verified by correspondence with physicians and hospitals in distant states, but in no case was medical or dental information considered verified without personal contact or correspondence with the practitioner or hospital. All interviews and verifications were made by the senior author or one of several medical students in his clinical years at the University of Minnesota. The completion of questionnaires and verification necessitated approximately five man-days of work for each leukemia patient and the two controls.

Results

The diagnosis of leukemia in each of the 112 cases in this study had been made either from bone marrow biopsy, or from autopsy findings, or from both. Lymphatic leukemia, as expected, was most common in this series, representing 93 of the 112 cases. Eleven cases were classified by pathologists as myelogenous leukemia. In eight cases, the degree of cellular differentiation was not regarded by pathologists to be sufficient to classify the disease on the basis of cellular morphology. Most of the cases were considered by pathologists to represent acute leukemia. In a few, the clinical course was thought to be more properly termed subacute, but diagnoses of subacute leukemia based on cellular morphology were made in only four cases.

TABLE 2

Deaths from Leukemia in the 0-4 Age Group by Sex and Year of Death, Minnesota, 1953-57

	Males	Females	Totals
1953	14 (3)*	13 (2)	27 (5)
1954	13 (2)	9 (2)	22 (4)
1955	6 (3)	9	14 (3)
1956	13	13 (1)	26 (1)
1957	13 (1)	10	23 (1)
Totals	59 (9)	53 (5)	112 (14)

*Additional reported but unverified cases are shown in parentheses; three deaths of nonresident patients are excluded.

Deaths in Minnesota from leukemia in the 0–4 year age group during the years 1953–57 were not distributed uniformly over the period under study, as seen in Table 2. The small number of deaths which occurred in 1955 may, of course, represent a chance variation, but it is remarkably different from the death rate in the two preceding and two following years.

The sex ratio for this series is 1.11 males to each female for verified cases and 1.17 including the unverified cases. The death rate for leukemia in males of all ages in the United States as a whole is approximately 1.5 times that in females, both among whites and nonwhites.[5]

A peaking of reported deaths occurred in the third year of life for females, as seen in Table 3. This peak appears to have been delayed in males, however, until the fourth and fifth years (possibly later, if all the childhood cases had been studied). Of the 128 residents whose deaths from leukemia were reported in Minnesota in 1953–57, only one was nonwhite. He and his siblings were the only two nonwhite children in this study. All neighborhood control children were white.

TABLE 3

DISTRIBUTION OF LEUKEMIA DEATHS IN THE 0-4 AGE GROUP BY SEX AND AGE AT DEATH, MINNESOTA, 1953-57

Age in Months at Death	Males	Females	Totals
0-11	7 (2)*	5 (1)	12 (3)
12-23	9 (2)	6	15 (2)
24-35	7 (1)	17 (2)	24 (3)
36-47	18 (2)	14 (2)	32 (4)
48-59	18 (2)	11	29 (2)
Totals	59 (9)	53 (5)	112 (14)

*Additional reported but unverified cases are shown in parentheses; three deaths of nonresident patients are excluded.

The observation by Cooke[2] that the age distribution of leukemia deaths shows a peaking in the third and fourth years of life has been made also by Hewitt.[6] Walter and Gilliam reported, however, that this peaking tendency was present only for the white population of the United States, during the years 1949–51.[7] The increasing risk of death from leukemia is apparent in both white and nonwhite populations in this country, although the age-adjusted death rate is twice as high for whites as for nonwhites.[5]

The possibility of genetic susceptibility in the etiology of leukemia has been suggested by a number of authors. In 1947, Videbaek reported that 8.1 per cent of families of leukemia patients contained another leukemia victim, as compared with 0.5 per cent of families of control subjects.[8] Anderson's report of leukemia in five of eight siblings[9] and reports of leukemia in twins[10,11] lend support to a genetic factor theory in the development of leukemia. These excessively high leukemia death rates among relatives of leukemia patients, however, might conceivably be associated with common and, as yet, undetermined environmental factors or, for that matter, may represent artifactual results of deficiencies in reporting the data on the control subjects.[12]

Multiple occurrence of leukemia was seen in two families in this study. In one of these families, each of a pair of monovular twins died of acute leukemia, one at 9 months and the other at 14 months of age. These cases have been described elsewhere.[11] In another family the sibling control child died of leukemia outside the study period (1953-57). Two other leukemia victims each had twin siblings who were alive and well at the time the family was visited. Leukemia was reported in a relative (outside of the immediate family) of each of four leukemia patients and not among such relatives of any of 112 controls. The diagnoses of leukemia for the relatives outside of the immediate families were not verified by the authors.

Stewart and co-workers[13] and Manning and Carroll[14] have shown that the risk of leukemia may be greater in children who are born of older mothers. One of thes studies,[13] however, recorded an excess of first-born children among its leukemia cases as compared with control children, while the other study[14] revealed a significant tendency for leukemia patients to be among later-born children. The frequent finding of leukemia in combination with mongolism is closely related to maternal age and its effect upon the occurrence of leukemia in children. (The relationship between increased maternal age and mongolism, of course, is well known). The coexistence of leukemia and mongolism has been reported in far greater than expected frequency.[13–16]

The comparison of maternal ages of mothers of the leukemia patients and mothers of the neighborhood control children (Table 4) reveals an interesting disparity. In 70 matched pairs the mother of the leukemia patient was older than the mother of the matched neighborhood control subject at the time of birth of the child in question. The reverse was true in 39 pairs, and no difference in age was found in three pairs. On the av-

erage, the mothers of leukemia patients were 2.25 years older than were mothers of neighborhood control children. While eleven mothers of leukemia victims were 40 years of age or older at the time of birth of those children, only one mother of a neighborhood control child was 40 years of age, and none was older.

Closely related to maternal age is order of birth. In 48 of these 112 matched pairs, the birth order of the leukemic child was higher than that of his neighborhood control. In 39 pairs the neighborhood control child had the higher birth order, and in 25 pairs the birth order was the same. The net average excess in birth order for the leukemia group was 0.46 births.

TABLE 4

DISTRIBUTION OF MATERNAL AGES AT BIRTH OF LEUKEMIA PATIENTS AND NEIGHBORHOOD CONTROL SUBJECTS
MINNESOTA, 1953-57

Maternal Age	Entire Series		Exclusive of pairs with Mongolism in Case or Control	
	Leukemia Patients	Neighborhood Controls	Leukemia Patients	Neighborhood Controls
15-19	5	9	5	9
20-24	31	33	30	33
25-29	26	36	25	34
30-34	23	21	21	17
35-39	16	12	13	9
40-44	9	1	7	1
45-49	2	0	2	0
TOTAL	112	112	103	103
Mean Age	29.26	27.01	28.84	26.50
Difference	2.25 years		2.34 years	

Eight cases of mongolism were encountered in the leukemia series and one case was noted in a neighborhood control child. Since mongolism is well known to be associated with greater maternal age and higher birth order, it is appropriate to investigate the maternal age distributions with and without the nine pairs in which mongolism was found in one member. As seen in Table 4, the greater maternal age of mothers of the leukemia patients cannot be accounted for simply by the presence of an excess of children with mongolism in that group.

Actually, after removal of pairs in which mongolism occurred, the excess of the mean maternal age of the mothers of the leukemia cases becomes 2.34 years. The net average excess in birth order for the group of leukemia cases becomes 0.28 births by this exclusion of pairs with mongolism.

Comparisons of maternal age and birth order between the leukemic children and their sibling controls are of little value in this study, because the method of selection of the sibling control required that such a child had reached an age equal to that of the leukemic child at the time of death. In a disproportionate number of cases, an older rather than a younger sibling was therefore selected. As a result, birth rank and maternal age are both lower for the sibling control on the average.

Ionizing Radiation and Leukemia

Efforts to identify the exogenous or environmental factors which may play a role in leukemogenesis have met with disappointment except for studies concerned with benzol[17–19] and with ionizing radiation.[13,14,20–36] Leukemia associated with benzol exposure has mainly been myelogenous, as was the principal type of leukemia resulting from atomic bomb irradiation in Japan.[26–29]

Court-Brown and Doll[20] have reported a small but significant excess of leukemia developing in patients irradiated for ankylosing spondylitis. Studies have shown a significant excess of deaths from leukemia among physicians, and particularly radiologists. March[21] concluded that the risk of death from leukemia among radiologists was nine or ten times that among physicians who were not radiologists. Dublin and Spiegelman[22] have confirmed this observation and have also shown the age-adjusted leukemia death rate for white male physicians to be 1.75 times that for white male nonphysicians.[23] In 1955, Simpson, Hempelmann, and Fuller reported that a tenfold excess of leukemia deaths had occurred in a group of children irradiated in infancy for thymic enlargement.[24] Murray, Heckel, and Hempelmann have reported a similar finding in children irradiated for thymic enlargement and also in those receiving roentgen ray therapy for pertussis and lymphoid hyperplasia.[25] The leukemogenic effect of atomic bomb irradiation has been described in a number of studies.[26–29]

That antepartum irradiation, as employed diagnostically, may significantly increase the risk of childhood leukemia is indicated in a preliminary report by Stewart and co-workers in 1956;[30] this hypothesis is supported in a subsequent study by the same authors[13] and by the work of Manning and Carroll.[14]

Stewart's study also implicated postnatal exposure to ionizing radiation in the development of leukemia in children. Kaplan[31] described a study in which mothers of leukemic children more frequently gave a history of irradiation during pregnancy with the leukemic children than during pregnancies with their other children. However, the incidence of fetal irradiation of playmate control children was found to be almost identical to that among the leukemia patients studied.

Polhemus and Koch[32] found a significant excess of exposures to ionizing radiation experienced postnatally by leukemic children as compared with control children, but only a slight excess in antenatal exposures. Ford and co-workers[33] observed that leukemic children were exposed to X-rays *in utero* significantly more frequently than were control children. Murray and his co-workers,[25] however, found no difference in incidence of fetal radiation among leukemic as compared to control children. In a study reported by MacMahon,[34] the incidence of antenatal exposure to X-rays was shown to be no different among a 1 per cent sample of liveborn infants in 11 New York hospitals than among 114 leukemic children born in those same hospitals. Kjeldsberg, in 1957, reported a higher incidence of antenatal irradiation in a small group of leukemic children than in his control group.[35] Court-Brown, Doll and Hill compared the incidence of leukemia occurring in a large group of liveborn children known to have been exposed to X-rays *in utero* with the expected incidence of leukemia in the general population of persons born during the same period.[36] No significant difference in death rates from leukemia was observed between the two groups.

Thus, accumulated data have failed to establish clearly the existence of an association between antenatal exposure to diagnostic irradiation and the subsequent development of leukemia in the child. Evidence concerning postpartum diagnostic irradiation is equally conflicting.

Maternal Exposure to Radiation

Mere verification of the number of X-ray films on file in an office or hospital will not, of course, serve to quantitate X-ray exposure. Equipment and techniques vary considerably, and unsatisfactory films are usually destroyed without making records of such exposures. For these reasons, diagnostic X-ray data included in this study are best regarded as qualitative estimates of X-ray exposures.

In Tables 5 and 6 maternal exposure (any type) to X-rays forms the basis for comparing the matched pairs of leukemia

patients and control children. The excesses of total X-ray exposure in pregnancy of mothers of leukemia patients over that for the pregnancies with the sibling control subjects (2.8%) and that for the pregnancies with the neighborhood control subjects (1.8%) are not statistically significant.

The number of pregnancies shown in Tables 5 and 6 for which verified data could not be obtained might, of course, be considered significant. However, if in every pregnancy with a control child for which data are missing the mother were assumed not to have incurred X-ray exposure, and if every leukemia patient for which information is missing were assumed to have been exposed to X-rays *in utero*, the rates of exposure

TABLE 5

DISTRIBUTION OF LEUKEMIA PATIENTS AND MATCHED SIBLING CONTROL SUBJECTS ACCORDING TO OCCURRENCE OF MATERNAL X-RAY EXPOSURE (ANY TYPE) DURING RELEVANT PREGNANCY. MINNESOTA, 1953-57

	Leukemia Patients		Matched Sibling Controls	
	No.	%	No.	%
Mother X-rayed during pregnancy	33	29.5	28	26.7
Mother *not* X-rayed during pregnancy	74	66.1	72	68.6
Inadequate data	5	4.4	5	4.7
Total	112	100.0	105	100.0

TABLE 6

DISTRIBUTION OF LEUKEMIA PATIENTS AND MATCHED NEIGHBORHOOD CONTROL SUBJECTS ACCORDING TO OCCURENCE OF MATERNAL X-RAY EXPOSURE (ANY TYPE) DURING RELEVANT PREGNANCY. MINNESOTA, 1953-57

	Leukemia Patients		Matched Neighborhood Controls	
	No.	%	No.	%
Mother X-rayed during pregnancy	33	29.5	31	27.7
Mother *not* X-rayed during pregnancy	74	66.1	78	69.6
Inadequate data	5	4.4	3	2.7
Total	112	100.0	112	100.0

TABLE 7

DISTRIBUTION OF LEUKEMIA PATIENTS AND SIBLING CONTROL SUBJECTS ACCORDING TO OCCURRENCE OF MATERNAL X-RAY EXPOSURE (ABDOMINAL OR PELVIC) DURING RELEVANT PREGNANCY. MINNESOTA, 1953-57

	Leukemia Patients		Matched Sibling Controls	
	No.	%	No.	%
Mother X-rayed during pregnancy	20	17.9	16	15.2
Mother *not* X-rayed during pregnancy	87	77.7	84	80.0
Inadequate data	5	4.4	5	4.8
Total	112	100.0	105	100.0

TABLE 8

DISTRIBUTION OF LEUKEMIA PATIENTS AND MATCHED NEIGHBORHOOD CONTROL SUBJECTS ACCORDING TO OCCURENCE OF MATERNAL X-RAY EXPOSURE (ABDOMINAL OR PELVIC) DURING RELEVANT PREGNANCY. MINNESOTA, 1953-57

	Leukemia Patients		Matched Neighborhood Controls	
	No.	%	No.	%
Mother X-rayed during pregnancy	20	17.9	16	14.3
Mother *not* X-rayed during pregnancy	87	77.7	94	83.9
Inadequate data	5	4.4	2	1.8
Total	112	100.0	112	100.0

would be 33.9 per cent for leukemia patients, 26.7 per cent for sibling control subjects, and 27.7 per cent for neighborhood control subjects. Thus, even with the most biased possible alignment of the data, disparities of statistically significant magnitudes among the three groups with respect to the incidence of X-ray exposure during pregnancy cannot be demonstrated.

The data in Tables 5 and 6 do not reveal that component of X-ray exposure which could lead to fetal exposure, since maternal X-rays of the teeth, chest, extremities, and skull are included in the data. The extent to which fetal exposure may have occurred in obtaining maternal nonabdominal X-ray films is uncertain, in view of the variations in equipment and techniques

employed in obtaining such films. Thus, theoretically, at least, the more significant fetal exposures should be included and the less significant should be excluded in Tables 7 and 8 in which only X-rays of the maternal abdomen and pelvis have been tabulated. When only abdominal and pelvic X-rays are considered, it is seen that 20 of 112 (17.9 per cent) of leukemia patients were exposed to X-rays *in utero,* as compared with 16 of 105 (15.2 per cent) of sibling control children and 16 of 112 (14.3 per cent) neighborhood control children. A manipulation for the subjects with inadequate data (for the reasons and by the method described above) yielded percentages of 22.3, 15.2, and 14.3 respectively for leukemia patients, sibling controls, and neighborhood controls. These disparities are not statistically significant.

Of the 20 mothers of leukemic children exposed to abdominal or pelvic X-rays, 17 incurred the exposure during the last trimester only. Among the three remaining patients the mother of one was subjected to abdominal X-rays during the second trimester, the mother of another was exposed during both the second and third trimesters, and the mother of the third leukemia patient had been employed in a physician's office during the first trimester, during which time she had taken two hundred or more X-rays of patients without shielding. Of the mothers of 16 sibling control subjects who had been exposed during pregnancy to abdominal or pelvic X-ray, 14 incurred the exposure during the third trimester. One mother was exposed during the second trimester and one other during both the second and third trimester. Only one of the mothers of the 16 neghborhood controls was exposed during the second trimester; the remaining 15 were exposed during the third trimester only.

Children's Exposure to Radiation

In an attempt to assess the magnitude of association of X-ray exposure of the child and the subsequent development of leukemia, a careful distinction must be made between: 1) X-ray exposures occurring during diagnostic procedures for illnesses that ultimately proved to be leukemia, and 2) X-ray exposures which occurred before the onset of the disease process. Review of the initial diagnostic investigation of the leukemia cases revealed that frequently a large number of X-rays had been made some time before the diagnosis was established, and frequently also, X-rays were made during the course of the illness, as intercurrent respiratory infections and gastrointestinal symptoms occurred. It is, of course, very difficult to ascertain the point in time at which the first symptoms or signs of leukemia were present, and one can only speculate as to when the irreversible leukemic process actually had begun. In Tables 9 and 10, only those X-ray exposures are included which occurred prior to one year before death of the leukemia victim and only up to a corresponding point in the life of the sibling and neighborhood control children.

The arbitrary selection of this particular cut-off date is open to some criticism, of course. The diagnosis of leukemia was established by bone marrow biopsy almost a full year before death in a number of leukemia cases included in this study. If the date of onset of symptoms is used to determine the inception of the disease process, one must rely upon parental observations for this information, and assume that early symptoms were, in fact, due to leukemia and not to some other totally unrelated disease process. Retrospective scrutiny of a child's life by bereaved parents would appear to be usual when death from leukemia occurs, and magnification of common childhood complaints is fairly common in these cases. On closer questioning, admissions of similar ailments in siblings and in neighborhood control children were often brought out. Since parents are not uniform with respect to their ability to recognize symptoms at a given level of severity, and since the date of diagnosis may be early or late in the course of the disease, depending upon when the physician is consulted, it becomes very difficult to assign a date of onset based either on symptoms or on professional diagnosis. In the final analysis, the inclusion of X-ray exposures occurring as late as one year prior to death, even if such exposures postdated the onset of the disease in most cases, poses no problem unless a significant excess of X-ray exposures is found to have occurred among the leukemia patients.

Data in Tables 9 and 10 reveal that 22 of 112 (19.6 per cent) of leukemia patients, 17 of 105 (16.2 per cent) of sibling control children, and 20 of 112 (17.9 per cent) of neighborhood control children incurred X-ray exposure during early childhood. The differences between the leukemia patients and each of the sets of matched control subjects are not statistically significant. Again assuming that patients and controls with inadequate data are distributed in such a fashion as to bias the results in favor of X-ray exposure for only the leukemia case, the percentages of X-ray exposures in leukemia patients, sibling control, and neighborhood control subjects, are 22.3, 16.2, and 17.9 respectively—differences which are not statistically significant.

TABLE 9

DISTRIBUTION OF LEUKEMIA PATIENTS AND MATCHED SIBLING CONTROL SUBJECTS ACCORDING TO OCCURRENCE OF X-RAY EXPOSURE DURING EARLY LIFE. MINNESOTA, 1953-57

	Leukemia Patients		Matched Sibling Controls	
	No.	%	No.	%
X-rayed	22	19.6	17	16.2
Not X-rayed	87	77.7	85	80.9
Inadequate data	3	2.7	3	2.9
Totals	112	100.0	105	100.0

If the taking of four or more X-ray films, fluoroscopy, and deep therapy are arbitrarily classed as unusual X-ray exposures, 18 children (of the 329 studied) can be placed in such a cate-

gory. Nine of these were leukemia patients, five were sibling control subjects, and four were neighborhood control subjects. Of the nine leukemia patients who experienced unusually heavy X-ray exposure prior to one year before death, two had symptoms which were almost certainly related to leukemia at the time the films were made. And there is reason for speculation in two other cases. If these four patients, all of whom experienced unusual exposures between 12 and 18 months before death, were actually X-rayed because of symptoms related to leukemia, then even the small differences between the numbers of cases and controls disappear. Two of the nine leukemia patients and one of the neighborhood control children received deep X-ray therapy for thymic enlargement in infancy.

TABLE 10

OCCURRENCE OF X-RAY EXPOSURE DURING EARLY LIFE: LEUKEMIA PATIENTS AND MATCHED NEIGHBORHOOD CONTROLS. MINNESOTA, 1953-57

	Leukemia Patients		Matched Neighborhood Controls	
	No.	%	No.	%
X-rayed	22	19.6	20	17.9
Not X-rayed	87	77.7	90	80.3
Inadequate data	3	2.7	2	1.8
Totals	112	100.0	112	100.0

TABLE 11

TIME OF X-RAY EXPOSURE: LEUKEMIA PATIENTS AND MATCHED SIBLING CONTROL SUBJECTS. MINNESOTA, 1953-57

Time of X-ray Exposure	Leukemia Patients		Sibling Controls	
	No.	%	No.	%
Ante- *and* postpartum	7	6.2	5	4.8
Ante- *or* postpartum	28	25.0	24	22.9
Never X-rayed	72	64.3	71	67.6
Inadequate data	5	4.5	5	4.8
Totals	112	100.0	105	100.0

Combined Radiation Exposure: In Utero and Childhood

Since a combination of X-ray exposure in utero *and* in childhood could have occurred significantly more often among leukemia patients than in control children (despite the insignificant differences noted earlier for the individual analyses of maternal and childhood exposure), the data were analyzed for combinations of ante- and postpartum exposures. Tables 11 and 12 reveal no significant differences in the distributions. It must be recognized, however, that these data on combinations of ante- and postpartum exposure are not quantitative with respect to dosage, and hence, significant disparities could still be concealed.

TABLE 12

Time of Exposure: Distribution of Leukemia Patients and Neighborhood Control Subjects. Minnesota, 1953-57

Time of X-ray Exposure	Leukemia —Patients— No.	%	Neighborhood —Controls— No.	%
Ante- *and* postpartum	7	6.2	3	2.7
Ante- *or* postpartum	28	25.0	28	25.0
Never X-rayed	72	64.3	77	68.8
Inadequate data	5	4.5	4	3.6
Totals	112	100.0	112	100.0

Mongolism and Leukemia

A significant finding in this study was the presence of mongolism in eight of the 112 leukemic children. Consultation with the child's physician revealed that a ninth case of mongolism occurred in the one child whose parents refused to participate in the study. A tenth possible case was not accepted because of a difference of medical opinion on the diagnosis of mongolism. Mongolism did not appear among the sibling control children, but one case did occur among the neighborhood control children. Thus in this study, 126 resident leukemia patients initially surveyed were found to include nine mongoloid children, an incidence of approximately 7 per cent. Since the highest recorded incidence of mongolism in the general population is 1 in 294,[37] the incidence of mongolism among leukemic children in this study is approximately 21 times that which would have been expected if no relationship existed between leukemia and mongolism. This disparity is significant at the 0.00001 level.

The phenomenally high ratio of mongolism in this series of leukemia cases is several times that found by Stewart in England,[13] and though based in part on several cases reported originally by Krivit and Good,[15] is far greater than the ratio observed by them.

Other Defects

Significant recognized anomalies other than mongolism were encountered in only nine children in the entire series. (Lesser conditions, such as nevi, were not recorded.) Distribution of the significant anomalies known to have been present is shown in Table 13.

TABLE 13

Distribution of Significant Anomalies (Excluding Mongolism) Among 112 Leukemia Patients, 105 Sibling Control Subjects and 112 Neighborhood Control Subjects. Minnesota, 1953-57

Leukemia Patients	Sibling Controls	Neighborhood Controls
Genu Valgum (1)	Congenital Torticollis (1)	Congenital Heart Disease (1)
Strabismus (2)	Meningomyelocele (1)	
Genu Varum (1)	Hypospadias (1)	
Congenital spastic infantile quadriplegia (1)		

Prematurity and Leukemia

In five children in this study the birth weight was recorded as under 2500 grams. This finding was noted in three of the leukemia victims and in two of the neighborhood control subjects. No evidence of premature births was found among the sibling control children.

Allergy and Leukemia

An association between leukemia and allergy in mother and child, suggested by Manning,[14] was explored in this study. The analysis presented a special problem. Although many mothers thought their children might have had allergies, they were obviously uncertain about the nature of allergic diseases. A not uncommon assumption was that a transient skin rash, unassociated with fever was, in fact, eczema. Inspection of medical records confirmed all those cases of allergy which the investigators were convinced did truly represent eczema, asthma, or hives; other cases, not diagnosed medically, were not included.

In Table 14 the incidence of allergic disease which occurred in the 329 children studied is compared with that in their matched partners.

TABLE 14

ALLERGIC DISEASES IN LEUKEMIA PATIENTS AND MATCHED SIBLING AND NEIGHBORHOOD CONTROL SUBJECTS. MINNESOTA, 1953-57

Allergic Disease	Leukemia Patients	Sibling Controls	Neighborhood Controls
Eczema	2	5	2
Asthma	2	1	3
Hives	2	0	2
Other, Questionable or None	106	99	105
Totals	112	105	112

Very little can be concluded from Table 14, except that allergic disease (of these three types) was relatively uncommon in all three subject categories, and that distribution of the few allergic manifestations encountered suggests no striking pattern.

INFECTIOUS DISEASE AND LEUKEMIA

In at least one study[38] a suggestive association has been noted between chickenpox and leukemia. An attempt was made in the present study to examine the association with this as well as with certain other common infectious childhood diseases. Obviously, the occurrence of the infectious disease *after* the onset of leukemia would have little or no pertinence here. Therefore the analysis of infectious disease data in this study was limited to those instances of infectious disease which antedated death from leukemia by at least one full year.

Data on all communicable diseases occurring prior to one year before death of the leukemia patients and for a comparable period during the life of control children were collected during interviews and verified wherever possible from medical records.

Only five of the diseases are considered in Table 15 (mumps, measles, chickenpox, pertussis, and rubella). Common colds, sore throats, and cases of "chest flu" and "stomach flu," in addition to ill-defined febrile states were frequently encountered. These presented problems in classification, since even when the children were seen by a physician the diagnosis was often uncertain. The five tabulated diseases were selected for study because there was reasonable certainty of the diagnosis. Although most of these disease occurrences were medically diagnosed, a few additional occurrences were accepted because the

informant's description was convincing and because other cases of the same disease occurring in the home at the same time had been seen and diagnosed by physicians. Nonmedically diagnosed cases, however, are indicated by parentheses in the table.

Total incidence of the relatively common childhood diseases studied is quite low throughout the study group, undoubtedly because of the restriction of time period indicated above—in most instances only the first two or three years of life. A perusal of Table 15 reveals no significant disparities in incidence of the five selected diseases among patients and control subjects.

TABLE 15

COMMON INFECTIOUS DISEASES IN LEUKEMIA PATIENTS AND MATCHED SIBLINGS AND NEIGHBORHOOD CONTROL SUBJECTS MINNESOTA, 1953-57

Infectious Disease	Leukemia Patients	Sibling Controls	Neighborhood Controls
Mumps	9	4	7 (1)
Measles	12 (2)	8 (4)	13
Chickenpox	12	7 (4)	19
Pertussis	5 (1)	9	2
Rubella	9	3	7 (3)

Additional unverified cases are shown in parentheses.

OTHER FACTORS

Information was also collected on the degree to which the leukemia patients and matched control children may have incurred exposure to paints, household solvents, cleaning fluids, floor waxes, furniture polish, liquid fuels, and insecticides. Attempts were also made to obtain data related to usage of various drugs such as antibiotics, sulfonamides, antihistamines, and barbiturates as possible leukemogenic agents or sensitizers. Data collected on these substances were not considered sufficiently reliable to warrant analysis. It is believed that reports of exposures to chemicals were more accurate with reference to the leukemia patients than to the control children, since answers to questions about such exposures tended to be much more detailed and searching when they pertained to the leukemia patient. Some interviews were also attended by the husband, and in such cases disagreement about exposures were commonplace. Drug usage data are considered unreliable because physicians' records were very often incomplete, mothers usually did not know the names of medications, and the medications adminis-

tered were sometimes those which had been prescribed for siblings or even for a neighbor's child.

Comment

A number of design problems and deficiencies in data should be recognized in the interpretation of findings of this study. Significant control of ethnic, socioeconomic, and other variables was, of course, achieved by the use of sibling control children, and possibly also the use of matched neighborhood control children selected on a geographic basis served to provide some control of these same variables. Matched control children, may, in fact, be representative of the same high risk population to which the leukemia cases belonged. Thus, the design employed in this study could conceivably have served to obscure—or at least to minimize—parametric disparities. But since the central purpose of the study was the testing of certain hypotheses, such as those regarding disparities in X-ray exposure histories, rather than a general search for differences between leukemia patients and control children, the use of matched control material would seem to have offered certain advantages, especially with regard to holding constant any unrecognized confounding variables.

Inadequacy of data, because medical records were destroyed when a physician moved, retired, or died, has been indicated in tabular presentations. The fact that unsatisfactory roentgenograms may have been destroyed without record has been mentioned. Hopefully, the names of all medical and dental attendants or other identifying data were obtained by our searching type of interrogation, but there is no guarantee that none was overlooked. Moreover, it cannot be assumed glibly either that the mothers of leukemia cases and neighborhood control children possess equivalent recall, or that recall is the same for events concerning the leukemia patient as for his sibling.

Summary

1. An epidemiologic study of 112 cases of childhood leukemia employing matched sibling and neighborhood control subjects is described.
2. Maternal age at time of birth of the leukemia patients was an average of more than two years greater than maternal age at the time of birth of the neighborhood control children. The excess in maternal age is equally apparent even when the mothers of the leukemia patients with mongolism are excluded.
3. Birth order averaged 0.46 births later in leukemia patients than in neighborhood control children.

4. Mongolism was encountered in eight of the studied leukemia cases, in no sibling control subjects and in one neighborhood control subject. The frequency of association of leukemia and mongolism in this series is significantly greater than has been reported previously.
5. A verified history of antenatal X-ray exposure was shown to be only very slightly more common among the leukemia patients than in either control group.
6. A verified history of X-ray exposure up to one year before death was shown to be only very slightly more common in the leukemia patients than in the matched control children.
7. Histories of allergies and common communicable disease were too infrequent to permit demonstration of a significant disparity in attack rates of these diseases between the leukemia patients and control groups.
8. Data collected on chemical exposures and usage of drugs were not considered sufficiently reliable to warrant detailed analysis. Such information was very difficult to verify, and is thought to reflect considerable parental bias.

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Medical School News

DR. WILLIAM T. PEYTON DIES

Dr. William T. Peyton passed away on March 3, 1962. He was the retired Director of the Division of Neurological Surgery at the University of Minnesota and one of the most able and "loved" members of the faculty.

Bill Peyton, as he was called by his colleagues, was born in Traverse County, Minnesota, on January 11, 1892. He graduated from St. John's High School in Collegeville, Minnesota, in 1911, and matriculated that same year at St. John's College. He entered medical school at the University of Minnesota in the Fall of 1914 and by 1918 he had received B.S. and M.B. degrees. Following his internship at Minneapolis General Hospital he received an M.D. degree. After practicing for two years in Minneapolis he returned to the University as an Instructor in the Department of Anatomy. He received a Ph.D. degree in anatomy in 1926, following which he became a fellow in general surgery at the University of Minnesota. He was appointed Instructor in Surgery in 1929, received a Ph.D. degree in surgery and became an Assistant Professor in the department in 1930. He served in this capacity until 1934 when he was promoted to Associate Professor. In July 1937 he was appointed Director of the Division of Neurosurgery, which appointment he held until his retirement on June 30, 1960. Following his retirement he worked as Consultant in Neurological Surgery at the Minneapolis General Hospital and at the Veterans Administration. Because of his keen interest in academic life he maintained an office at the University Hospitals, attended conferences, clinical rounds, and spent many hours in the University library. In fact, it was while he was in the library obtaining data for a lecture on cervical cord injuries that he suffered the heart attack which eventually lead to his death.

WILLIAM T. PEYTON
1892-1962

It is difficult to delineate the many contributions to medicine that Dr. Peyton has made. He had a tremendous interest in teaching—in giving to others the fruit of his extensive knowledge and experience. To have known and worked with Dr. Peyton is to have enjoyed that stimulating experience of learning surgical principles and techniques from a thoughtful technician, utterly familiar with the anatomical basis of each operation. His surgical

judgment was sound, his technical skill cool and effortless; his overall care of patients was of the very highest quality. Dr. Peyton was always modest, humble, unassuming, content with honest scientific and intellectual achievements. He avoided publicity and personal aggrandizement. Even so, he was recognized nationally and internationally as an outstanding figure in neurosurgery. He was a member of the major neurosurgical societies in America and at the time of his death was Chairman of the American Board of Neurological Surgery.

Dr. Peyton is survived by his wife, Clara, who lives at 64 Barton Avenue, S.E., Minneapolis. There are three daughters and one son all of whom are married. The family prefers memorials to the William T. Peyton Fund for Neurosurgical Research and Training, University of Minnesota. —L.F.

ANESTHESIOLOGY

Dr. Frederick Van Bergen and Dr. Joseph J. Buckley attended the meeting of American University Anesthetists in Dallas, Texas, January 19-21. In February, Dr. Buckley was a Visiting Professor of Anesthesiology at Presbyterian Medical Center, New York City. He lectured on "Postoperative Ventilatory Abnormalities" and "Principles of Preoperative Management of the Open Heart Patient." He also lectured on "Treatment of Severe Systemic Tetanus" at Columbia University College of Physicians and Surgeons.

INTERNAL MEDICINE

Dr. Cecil J. Watson, Distinguished Service Professor and Head of the Department, delivered the annual Thomas Young Lecture on February 15 at St. George's Hospital, London, England, and on February 20 addressed the faculty of Johannes Gutenberg University, Mainz, Germany. There he received an M.D. honoris causa from the University. Mrs. Watson accompanied him to Europe.

Dr. F. W. Hoffbauer, Professor and Chief of Internal Medicine at Minneapolis General Hospital, delivered the Fifth Annual County Supervisors Medical Lecture on January 23rd at the Sacramento County Hospital, Sacramento, Calif. The topic of his lecture was "Fatty Liver Disease: Experimental and Clinical Aspects." He also conducted a clinic on other aspects of cirrhosis for the medical staff of the hospital.

Dr. Wesley W. Spink, Professor of Medicine, addressed the student body and faculty of Augsburg College, Minneapolis, at a special convocation Jan. 4. His subject was "The Challenge of Medical Research."

DR. HENRY MICHELSON TO RECEIVE GOLD MEDAL AWARD

Dr. Henry E. Michelson, professor emeritus of dermatology, has been named to be the first recipient of the Gold Medal Award given by the American Academy of Dermatology. The award will acknowledge his outstanding service and contributions to dermatology, and will be presented at the Academy's annual meeting in December, 1962, in Chicago, Ill.

Dr. Michelson was professor and director of the Division of Dermatology at the University of Minnesota from 1927 until his retirement in 1958. He is now in the private practice of dermatology in Minneapolis, and in 1960 was named winner of the University's Outstanding Achievement Award. He is a 1912 graduate of the Medical School.

The Epilepsy Foundation, Washington, D. C., has granted $4,000.00 to the Medical School for research in epilepsy. Five staff members of the Division of Neurology, directed by Dr. A. B. Baker, will conduct the research. They are Drs. Richard M. Harner, Gilbert S. Ross, Fernando Torres, Lowell Baker, and Kenneth F. Swaiman.

Fourteen medical students at the University of Minnesota have been named winners of University scholarships, made possible by friends of the Medical School. The recipients were Dennis Frisbie, William Bergstrom, John McMillin, Eugene Bagley, Lawrence Pearson, Paul Mertens, John Elstrom, Dennis Jacobsen, Dorr Dearborn, Robert Nelson, Paul Dickinson, Terrill Olsen, Albert Roth, and H. David Knudsen. The awards were administered by the Bureau of Loans and Scholarships of the University.

The Ely-Winton Hospital Association of Ely, Minn., has announced the availability of scholarships worth $200.00 each per year to residents of that school district who pursue studies in Medicine, Nursing, Laboratory or X-Ray Technology, or Medical Library Science, at accredited U. S. schools.

Students at the University of Minnesota will benefit from this permanent new scholarship fund. The Association, a private corporation which operates the Ely-Winton Hospital, anticipates a fund of $10,000 available annually when the program is operating at full level.

MEDICAL SCHOOL GRADUATES PLAN 40th ANNIVERSARY REUNION

Graduates of the Medical School who received M.B. degrees in the years 1921-22 and M.D. degrees the following year are invited to a 40th anniversary reunion planned at the University of Minnesota on Saturday, June 9, 1962.

The reunion will include a tour of the Medical School and University Hospitals, where vast growth and changes have occurred during the passage of 40 years. There will be a luncheon, and the day chosen coincides with the University's Spring Commencement date. Dr. O. Meredith Wilson, president of the University, Dr. Charles Mayo, chairman of the Board of Regents, and Dr. Robert B. Howard, Dean of the College of Medical Sciences, will participate.

LEONARD W. LARSON

Dr. Leonard W. Larson, Bismarck, N.D. pathologist and current president of the American Medical Association, is chairman of the reunion planning committee. Other members are Dr. C. L. Oppegaard, Crookston, Minn., and Dr. O. H. Wangensteen, Minneapolis.

Seventy-eight individuals composed the graduating class of 1921-22. Twenty-four are now deceased, and 54 survive, according to a survey. To commemorate their 40th anniversary, the class plans to present a gift to aid completion of the University's new Bio-Medical Library (Diehl Hall). In 1948, noting their 25th anniversary, class members provided funds to purchase books for the library's medical history collection.

Dr. Larson said wives will be welcome at the 40th anniversary reunion. Inquires regarding the event should be directed to Dr. William Fleeson, Assistant Dean, University of Minnesota Medical School, Minneapolis 14, Minn.

The University of Minnesota MEDICAL BULLETIN will publish a special article about the Class of 1921-22 in its issue of June, 1962.

The School of Nursing has received a grant of $2,800 from the National Fund for Graduate Nursing Education. Miss Edna L. Fritz, school director, said the grant is Minnesota's share of receipts, based on enrollment, of a national campaign in 1961 to supply financial aid to schools of nursing which award graduate degrees. Approximately $100,000 was collected for the National Fund during its 1961 campaign, she said.

Alumni Notes

◆ **1930**

Benjamin A. Weis, an internist in St. Paul for the past 27 years, has been elected president of the Ramsey County Medical Society. He was installed in office January 29, 1962, succeeding Dr. Charles C. Cooper (Med. '34), also of St. Paul.

◆ **1932**

Martin O. Wallace of Duluth is serving as 1962 president of the Minnesota Obstetrical and Gynecological Society.

George E. Cardle is the new president of the Upper Mississippi Valley Medical Society. He practices in Brainerd, Minn.

◆ **1937**

Bernard J. Hughes is now practicing in St. Cloud, Minn. in association with Dr. Henry Broker.

◆ **1939**

Raymond K. Minge of Worthington, Minn. is the current president of the Southwestern Minnesota Medical Society. He is associated with the Worthington Clinic.

◆ **1940**

Fred T. Kolouch is chief of staff at Magic Valley Memorial Hospital, Twin Falls, Idaho. He was featured recently in Time Magazine (1-5-62) for his work in combining surgery and hypnosis.

◆ **1942**

Roger P. Hallin has begun a residency in physical medicine and rehabilitation at the University of Minnesota. He practiced in Worthington, Minn. from 1943 until coming to Minneapolis.

◆ **1943**

Robert E. Nord was elected president of the medical staff at Asbury Methodist Hospital, Minneapolis.

Raymond Sanford of Mankato was named president of the Blue Earth County Medical Society at its annual meeting. Dr. Hobert Setzer (Med. '24) was elected secretary-treasurer.

Harry N. Simmonds, Prior Lake, Minn. physician, is the new president of the Scott-Carver County Medical Society, succeeding Dr. C. R. Heinzerling (Med. '53) of Chaska.

◆ **1944**

Robert Lindell, internist practicing in South Saint Paul, Minn., was elected 1962 chief of the medical and dental staff at St. Luke's Hospital, St. Paul, Minn.

Albert J. Schroeder of Minneapolis was elected chairman of the Minnesota Chapter, American Academy of Pediatrics. Vice chairman is Dr. Robert Bergan (Med. '43), Duluth Minn.

◆ **1945**

Donald G. Bohn, a Minneapolis internist, was elected chief of the medical staff at St. Barnabas (Minneapolis) Hospital, succeeding Dr. Charles R. Peluso (Med. '46).

◆ **1946**

John T. Saidy, an internist practicing in San Mateo, Calif., is now serving as president of the San Mateo County Medical Society. He has practiced there since 1953, and was a fellow in medicine at the Mayo Foundation, Rochester, Minn. from 1950 to 1953.

◆ **1950**

George Rysgaard, Northfield, Minn. physician, is president of the Southern Minnesota Academy of General Practice.

Mark E. Odland was elected chief of the medical staff at St. Mary's Hospital, Detroit Lakes, Minn. Dr. A. S. Midthune (Med. '46), Lake Park, Minn. was named vice chief of staff, and Dr. Robert Watson (Med. '43) was elected secretary-treasurer.

◆ **1954**

Bruce A. Kottke has been appointed to the staff of the Mayo Clinic in Rochester, Minn., as a consultant in internal medicine. He recently completed a residency in medicine at the Mayo Foundation.

◆ **1956**

John C. Richards was awarded the degree of master of science in general surgery from the University of Minnesota on December 14, 1961. He completed a residency in general surgery at the Mayo Foundation, and is now with the U.S. Army, Second Field Hospital, Munich, Germany.

Carl F. Peikert is now associated with the Doctors Clinic at Forest Lake, Minn. He formerly practiced in Elbow Lake, Minn., and interned at St. Luke's Hospital in Duluth, Minn.

◆ **1958**

Floyd J. Swenson, who has been in practice in Cook, Minn., has been appointed a resident in orthopedic surgery in the Mayo Foundation, Rochester, Minn.

◆ **1960**

Lt. Thomas P. Kenefick has entered the U. S. Navy, and is serving as a medical officer aboard the U. S. S. Taconic.

◆ **1960**

Corrin J. Hodgson is now a Captain in the U. S. Air Force medical corps, and is stationed in training at the Aerospace Medical Center, San Antonio, Texas. He interned at St. Mary's Hospital, Duluth, Minn., and was recently a fellow in neurology at the Mayo Foundation, Rochester, Minn.

John E. Larkin, Jr. writes that he ras been accepted as a resident in orthopedic surgery for 1963 in the Massachusetts General Hospital program. He is presently associated with the Harvard Surgical Service, Boston City Hospital, Boston 18, Mass.

ALUMNI DEATHS

◆ **1900**

Dr. Jane F. Kennedy of Minneapolis died January 2, 1962 at the age of 92 years. She had practiced medicine in Minneapolis for approximately 50 years, and served on the medical staff of the University of Minnesota Health Service immediately following her graduation from Medical School. Dr. Kennedy was a life member of the American Medical Association. Survivors include a son, Dr. George L. Kennedy, Faribault, Minn.

◆ **1901**

Dr. Bertram S. Adams, Hibbing, Minn., died November 3, 1961. He was 85 years old. Dr. Adams was founder of the Adams Clinic and Hospital, and served as president of the Range Medical Association and St. Louis County Medical Society. He was a fellow of the American College of Surgeons.

◆ **1905**

Dr. J. C. Jacobs, retired general practitioner who practiced more than 50 years, died January 3, 1962 in Willmar, Minn. He was 83 years old. Dr. Jacobs held several offices in the Minnesota State Medical Association and was former Kandiyohi County coroner. Survivors include his wife, Mattie, a daughter, and three sons, one of whom is **Dr. Douglas Jacobs (Med. '34),** who practices in Willmar.

◆ **1907**

Dr. Earl A. Loomis, retired eye, ear, nose and throat specialist, died January 24, 1962 in Minneapolis at the age of 81. He was a member of the American Academy of Ophthalmology and Otolaryngology, and the American College of Surgeons. A native of Wells, Minn., he is survived by a sister, daughter, and three sons; Dr. George Loomis (Med. '32), Winona, Minn.; Dr. Earl A. Loomis, Jr. (Med. '45), and Dr. Donald Loomis, both of New York City.

◆ **1908**

Dr. Roy N. Andrews, a lifelong resident of Mankato, Minn., and physician in that city since 1908, died December 8, 1961. He was 77 years old, and was among the founders of the Mankato Clinic. Dr. Andrews was Blue Earth county coroner from 1946 until 1961.

◆ **1921**

Dr. Peter E. Peterson, who had been a practicing physician in Minneapolis for 38 years, died February 15, 1962. He had been in ill health for the past year. Dr. Peterson was a native Minnesotan and a member of Phi Rho Sigma medical fraternity. He was 69 years old.

◆ **1922**

Dr. Oscar J. Blosmo, Los Angeles, Calif., died December 8, 1961, at the age of 77 years.

Dr. Reuben H. Waldschmidt, a surgeon, died November 11, 1961 in Bismarck, N.D., where he was associated with the Quain and Ramstad Clinic. He also served on the staffs of both Bismarck hospitals during his medical career. Dr. Waldschmidt was a past president of the North Dakota State Medical Association and a governor of the American College of Surgeons. He was one of the editors of *The Journal-Lancet.*

◆ **1923**

Dr. Leo J. Madsen, Santa Monica, Calif., died November 8, 1961, at the age of 64. He had been an intern at Minneapolis General Hospital and fellow at the Mayo Clinic. Dr. Madsen was a member of the staffs of St. John's and Santa Monica hospitals, and was a fellow of the American College of Surgeons. Born in Rochester, Minn., he was among the founders of the Minnesota Medical Foundation and was a prominent citizen of southern California. Death was caused by a subdural hematoma.

◆ **1927**

Dr. Mildred Warden Couch, a psychiatrist, died October 10, 1961 in Hartford, Conn. She was a member of the American Psychiatric Association, and had practiced nearly 25 years in New England. She was 65 years old.

◆ **1932**

Dr. Robert P. Ewald, who practiced in the St. Paul suburb of Newport, Minn., died October 14, 1961. He was a native of Brownton, Minn., and was on the medical staff of Mounds Park Hospital. Death occurred at the age of 69 years.

◆ **1939**

Dr. Russell George Barnes, Jr., Medford, Ore., died July 13, 1961 of cancer at the age of 46 years. He was a member of the American Academy of General Practice and a veteran of World War II.

◆ **1943**

Dr. Paul M. Brickley, Santa Barbara, Calif., died January 11, 1962. He had been a member of the staff of the Sansum Clinic in Santa Barbara since 1954, and was formerly on the medical staff of the Mayo Clinic. Dr. Brickley was a diplomate of the American Board of Ophthalmology, and a fellow of the American College of Surgeons. He was 44 years old at the time of his death.

Memorial Gifts

Memorial gifts to the Minnesota Medical Foundation have been received recently in memory of:

Mrs. Helen Harrison Hill
Minneapolis, Minn.

Mrs. R. J. Quinlivan
St. Cloud, Minn.

Mr. Chester Riebeth
Minneapolis, Minn.

Dr. Ben Sommers
St. Paul, Minn.

Memorial contributions are a practical means of honoring the memory of a friend or loved one, while helping the Minnesota Medical Foundation in the advancement of medical education and research. Appropriate acknowledgements are promptly sent to both donor and family of the deceased.

Coming Events

University of Minnesota Medical School

List of Continuation Courses for Physicians

University of Minnesota
Center for Continuation Study

1962

All Year	Cancer Detection for General Physicians
April 12-14 . . .	Otolaryngology for General Physicians
April 16-18 . . .	Internal Medicine for Internists
April 26-28 . . .	Surgery for Surgeons
April 30-May 2 . .	Gynecology for General Physicians
May 7-9	Ophthalmology for Specialists
May 14-18 . . .	Proctology for General Physicians
May 31-June 2 . .	Psychiatry for General Physicians

The University of Minnesota reserves the right to change this schedule without notification.

Courses are held at the Center for Continuation Study or the Mayo Memorial Auditorium on the campus of the University of Minnesota. Usual tuition fees are $30 for a two-day course, $50 for a three-day course, and $75 for a one-week course.

Specific announcements are sent out about two months prior to each course to all members of the Minnesota State Medical Association and to any physicians who request information for a specific course. For further information write to:

DIRECTOR
DEPT. OF CONTINUATION MEDICAL EDUCATION
THE MEDICAL CENTER
UNIVERSITY OF MINNESOTA
MINNEAPOLIS 14, MINNESOTA

Memorial Gifts

Memorial gifts are popular means of paying thoughtful tribute to the memory of a relative, friend, or colleague.

Your Minnesota Medical Foundation welcomes memorial gifts, and makes immediate acknowledgment to the family of the deceased, and to the donor.

Contributions are used to help finance the programs of medical education and research conducted by the Minnesota Medical Foundation in behalf of the University of Minnesota Medical School.

Gifts may be sent to:

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University of Minnesota
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