LEUKAEMIA IN CHILDHOOD AFTER ANTENATAL EXPOSURE TO X RAYS.

A SURVEY AT QUEEN CHARLOTTE'S HOSPITAL

BY

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The remote possibility of leukaemia or other malignant disease developing subsequently in the child has been in the minds of obstetricians using antenatal radiography ever since the publication of surveys by Dr. Alice Stewart and her co-workers. Stewart *et al.* (1956) reported that, of 269 children who died of leukaemia under the age of 10 years, 42 had been irradiated antenatally; while of 269 healthy children acting as controls, only 24 had been irradiated. Again, in 1958 Stewart *et al.* reported that direct foetal irradiation had occurred in 13.7% of 1,299 children who died of leukaemia or other malignant disease, but foetal irradiation had occurred in only 7.2% of a similar number of control children. In these two series 6% more of the children who died of leukaemia or other malignant disease had been subjected to irradiation when they were foetuses *in utero* than was the case in the control groups. Because 87% of the leukaemic children were not irradiated and 7% of the control children were irradiated but did not get leukaemia, the greatest possible proportion of children whose leukaemia could be due to antenatal irradiation is 6%. Since the incidence of leukaemia in children under the age of 10 years was 1 in 2,600 births, antenatal irradiation could not be the cause of more than 1 in 40,000 births (6% of 1 in 2,600) in Stewart's two series.

To test the validity of this argument an investigation was undertaken into the incidence of leukaemia in children who were born at Queen Charlotte's Hospital. At the time of Stewart's first paper about 25% of the babies born at Queen Charlotte's were being irradiated *in utero*. Osborn and Smith (1956) estimated that not less than 16% of pregnant women in England and Wales had an obstetric abdominal x-ray examination.

Thus if antenatal irradiation is a cause of leukaemia subsequently in the child there ought to be a greater incidence of the disease in children who had been born in Queen Charlotte's Hospital compared with the national average; and more leukaemic children should be found in those who had been irradiated than in those who had not.

Method

The records at Queen Charlotte's Hospital were searched for each one of 1,548 children who died of leukaemia in England and Wales before their tenth birthday during the six years 1953-8 to see if the child had been born at the hospital. Because any of the children might have been born up to 10 years before death the records had to be searched for the 16 years from the beginning of 1943 to the end of 1958, during which time there were 45,195 live births at the hospital. (Stillbirths were excluded because they could not get leukaemia.)

The names of 26 children who died of leukaemia were found similar to those born in the appropriate

year at Queen Charlotte's. The birth and death certificates were then compared, but only 8 of the 26 children were in fact identical. In order to determine the extent of errors in the recording of leukaemic deaths and of births and in the method of searching, 50 test names of living children known to have been born at Queen Charlotte's were inserted into the lists of leukaemic deaths. These names were unknown to the searchers and were typed at the same time as the lists of deaths, so that there was no way of identifying them. They found 40 test names out of 50, and therefore the number of leukaemic deaths, 8, of those they found were born at Queen Charlotte's should be multiplied by a correction factor of 5/4 if these errors are to be taken into account.

Results

During the six years 1953-8 1,548 children died of leukaemia before their tenth birthday, and 8 of them were born at Queen Charlotte's Hospital (making allowances for errors in the method the number might be 10). If the incidence of leukaemia in the child population is known for each age-group from 1943 to 1958 it can be worked out how many leukaemic deaths of those under 10 years might be expected in 1953-8, given the number of live births in each year and making allowance for deaths from other causes. From the 45,195 live births during the 16 years 1943-58 at Queen Charlotte's Hospital the expected number of leukaemic deaths in 1953-8 is 6 or 7 (best estimate 6.6).

Expected Number of Leukaemia Deaths

Live Births 1943-58	Leukaemic Deaths, 1953-8	
	Expected No.	Actual No.
45,195	6.6	8

During the 16 years 1943-58 11,443 foetuses were exposed to antenatal irradiation; thus 25.3% of foetuses were irradiated. But of the 8 children born at the hospital who died from leukaemia, only one was irradiated; he was exposed to one erect lateral view of the abdomen near term.

In order to find out how many live births are related to the number of deaths in six years of children up to the age of 10 years a calculation has to be made. The total number of live births in 16 years (in this case 45,195) is multiplied by 6/16. This gives an average number of births for six years. The average number of live births for 6 of the 16 years 1943-58 is 16,948, and the average number of foetuses irradiated in six years is 4,291. Thus in six years 12,657 babies were born who were not irradiated (control children) and seven died of leukaemia before the age of 10 years, an incidence of 1 in 1,808. In the same period of time 4,291 irradiated babies were born and one died of leukaemia before the age of 10 years, an incidence of 1 in 4,291.

Incidence of Leukaemia

	Live Births for 6 Years	Deaths from Leukaemia	Incidence
Non-irradiated control cases ..	12,657	7	1 in 1,808
Irradiated cases	4,291	1	1 " 4,291
All cases	16,948	8	1 " 2,118

Conclusions and Summary

Although the figures obtained so far are not large enough to show a tendency for irradiation of the

foetus to cause one case of leukaemia in 40,000 births, they do show that the tendency is not very much greater. The incidence of 8 leukaemic deaths per 16,948 live births, 1 in 2,118, is slightly higher for Queen Charlotte's Hospital than for the country as a whole; but this is due to the much higher incidence of leukaemic deaths in the non-irradiated (control) group, 1 in 1,808, compared with the irradiated group, 1 in 4,291, and cannot therefore have been caused by irradiation.

I thank Dr. Alice Stewart for providing the lists of deaths from leukaemia, Dr. Rohan Williams for the figures on irradiated cases, and the Board of Governors of Queen Charlotte's and Chelsea Hospitals for secretarial aid in searching.

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PHENYLBUTAZONE AND LEUKAEMIA

A POSSIBLE ASSOCIATION

BY

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This paper reports six instances of leukaemia developing in patients who had received phenylbutazone. In the first patient there appeared to be a sequential progression from the development of an early toxic reaction to the patient's death from myeloid leukaemia. In the other five patients a history of administration of the drug was obtained in retrospect.

Case 1

This patient, a man aged 69, had complained of low back pain since 1918. Radiological examination demonstrated marked degenerative spondylitic changes in his lumbar vertebral column. He had not received any x-ray therapy for this.

In February, 1957, he was treated with phenylbutazone. The initial dose was 600 mg. a day, after a few days reduced to 400 mg. a day. Shortly after the treatment was begun he developed a sore throat, and two weeks later a swelling and a rash upon his legs. He was admitted to hospital after three weeks' treatment. Examination showed him to be apprehensive and in poor nutritional state, with a dry, red, glazed tongue. He had a scattered toxic erythematous rash upon his legs and feet, enlarged lymph nodes in his neck and axillae, and a palpable spleen. Blood examination showed a haemoglobin of 13.4 g./100 ml. and total W.B.C. 17,000 c.mm. (polymorphs 75%, lymphocytes 11%, monocytes 9%, eosinophils 4%, and basophils 1%). The red cells showed anisocytosis and poikilocytosis. Platelets were abundant and the lymphocytes and monocytes slightly abnormal, with pale vacuolated cytoplasm. Serum albumin was 3.3 g. and globulin 3.6 g./100 ml.

A left axillary gland was removed, and the report upon the section was: "The architecture of the gland is largely replaced by a medullary disturbance of the reticulum cells together with alteration of age of the lymphoid elements. The picture is consistent with an early reticulosis." The patient was given supportive therapy, including a high-protein diet and parenteral vitamins, and steadily improved. Three months later he was much better, and, although examination still revealed enlarged glands and a palpable spleen, these features were less prominent. His weight had increased. His haemoglobin had risen, and the total W.B.C.

had fallen, but his platelet count had increased to 507,000. There were still 400 eosinophils present.

After a further five weeks he was again admitted to hospital. On this occasion he was very sick, with a generalized bullous rash, conjunctivitis, urethritis, and recurrent glossitis with mouth ulceration. He was thought to be suffering from erythema multiforme and he was again treated symptomatically. His Hb had fallen to 11.25 g./100 ml. His reticulocytes were 3.3% and his platelets had risen to 980,000. A blood film showed a neutrophilia with a shift to the left and toxic granulation. The platelets were predominately large forms. A marrow biopsy showed a normal marrow. He rapidly improved and was discharged approximately four weeks later when his Hb had risen to 12.4 g. However, he had persistent neutrophilia and eosinophilia, and his platelets remained abnormal, being plentiful and showing clumping.

Three months later he had again improved, his spleen was palpable on inspiration and his glands smaller but very firm. His haemoglobin had risen to 14 g., W.B.C. 15,000/c.mm. with 11% eosinophils, and platelets 780,000. The blood film remained abnormal. He was again admitted in January, 1958 (one year after his original treatment), when the findings were much the same, his blood showing neutrophilia and eosinophilia. The zinc turbidity had risen a little higher and a further gland was removed. The biopsy report stated: "Macroscopy: a small hard gland throughout which there are irregular deposits of hard white tissue. Microscopy: areas of caseation accompanied by chronic inflammatory and giant-cell reaction. Probably tuberculous." On this occasion his liver was palpable with a firm edge. He was discharged shortly after this and felt much improved.

He was again reviewed 17 months after his original illness, when he appeared to be again improving. His appetite was good and his weight increasing. Examination revealed that his lymphadenopathy was less, although the glands palpated remained very hard. His liver had also receded and his spleen was not palpable. Examination of his blood gave the following results: Hb, 13.6 g./100 ml.; total W.B.C. 10,700 (polymorphs 71%, lymphocytes 25%, monocytes 1%, eosinophils 3%); platelets, 510,000; E.S.R., first hour 15, second hour 37. Both polymorphs and lymphocytes were atypical, with coarse granular nuclei, and about 30% of the

FIG. 1.—Case 1. Histological appearance of the involved glands.

polymorphs were younger forms. The blood film was consistent with early myeloid leukaemia. His serum albumin was 3.7 g. and serum globulin 3.2 g./100 ml., and zinc sulphate turbidity 10 units.

He was seen three months later, in October, 1958. A marked deterioration had taken place. He complained of recurrent swelling of his glands, weakness, and loss of weight. Examination revealed that he had a generalized lymphadenopathy. The glands were more numerous and