Letters to Editor

Again on Leukemia in Twins

Sir:

In my reply to Professor Steinberg's letter (*Acta Genet. Med. Gemellol.*, 20: 317), I stated that Dr. Brown and I were continuing to review the broad subject of leukemia among twins. The purpose of the present communication is to inform your readers of this continuing survey and to comment additionally on the Steinberg reports (1957, 1960).

Accurate information on the true size of the twin population is not available; therefore, questions regarding leukemia in twins, such as the exact incidence of leukemia among twins, remain open. The apparent tendency to report concordance of any disease among twins may increase the number of clinical reports available for study in the world publications, and ultimately may influence the impressions garnered from reviewing such reports regarding concordance-discordance ratios.

Our report, " Epidemiologic Study of Leukemia in Twins " (Keith and Brown, 1971), cited sixty-two clinical reports published by July 1, 1969 in which there was sufficient material for the type of analysis attempted. Between July 1, 1969 and July 1, 1971, continuing efforts to monitor the world reports have yielded only nine additional clinical studies, one of which, although published in 1965, came to our attention belatedly (Shapetko, 1965). Of these nine new clinical reports, seven of the pairs described were MZ (Shapetko, 1965; Bauke 1969; Kosenow and Pfeiffer, 1969; Fournier et al, 1970; Hilton et al, 1970; Mortier et al, 1970; Raccuglia and Lansing, 1970). One pair was DZ (Wertelecki and Shapiro, 1970); in the remaining pair (UZ) the zygosity was not determined (Greene and Swischer, 1969). Four of these seven MZ pairs were concordant for leukemia (Shapetko, 1965; Fournier et al, 1970; Hilton et al, 1970; Mortier et al, 1970); three MZ pairs were discordant for leukemia (Bauke, 1969; Kosenow and Pfeiffer, 1969; Raccuglia and Lansing, 1970). The DZ and UZ pairs were discordant for leukemia.

So few clinical publications suggest that this disease is under-reported even when concordance is observed. It also suggests that some patients may never have been seen by physicians. That is why a possible solution suggested again was the establishment of regional twin registries, capable of enrolling twins at birth and providing long-term followup. This journal put forth such a suggestion on numerous occasions.

Fraumeni et al (1971) have reported on a series of 1,263 cases of childhood leukemia from the Children's Cancer Research Foundation in Boston. The series included children under age 15 in whom the diagnosis of acute leukemia was made during the years 1957 to 1965. Among those children were 28 twin pairs, 10 MZ and 18 DZ and including only one set of concordant MZ males in whom monocytic leukemia was diagnosed at two and three months of age. The figures noted in that extensive report hardly support the contention of a substantial leukemia concordance rate among twins (Mac Mahon and Levy, 1964; Miller, 1967) nor do they influence the answer one way or the other. Certain questions are immediate.

What was happening in the twin pairs in whom leukemia developed (in one or both members) in the same locality at the same point in time, who did not receive treat-

ment at the Children's Cancer Research Foundation in Boston? It is possible, therefore, that every single case of leukemia of twins was not funneled into this single institution. Fraumeni et al (1971) state that only 50% of the study group came from the state of Massachusetts. They do not mention what percentage of the Boston cases their institution received. They did not provide any clinical information; therefore, we may ask, how long were the discordant members of the pairs followed, if followed at all.

A nonaffected twin presents an excellent patient in whom certain studies can be performed showing possible changes before the onset of clinical leukemia. Chromosomal changes, for example, have been observed in certain types of leukemia in eleven pairs of twins in whom one or both members had leukemia (Keith et al, in press). Those eleven pairs are scattered throughout world publications; but close inspection of the clinical case reports discloses the following: irrespective of zygosity, no nonleukemic twin of a given twin pair has *yet* shown chromosomal abnormalities in the absence of clinically detectable disease. Some of the nonleukemic twins are being followed prospectively for the appearance of chromosomal abnormalities (Bauke, 1969). In most instances, the investigators have not stated their intentions in this regard. Such a method of followup may be useful and should be attempted.

Jackson et al (1969) studied leukemia in a series of California-born twins and collected fifty cases including only two concordant twin pairs. Again, before it can be generally concluded that discordance is the rule among twins with leukemia, several points should be considered: their material was based on death certificates. What about the living patients among twins? Granted that the mortality from leukemia in children is higher than that of adults, it is hardly reasonable to believe that none had survived childhood leukemia in the state of California *during the time of the study*. It is reasonable to assume that among any survivors at that time there may have been twins. Again, we may be dealing with an incomplete population from which it is difficult to draw general conclusions.

Jackson and his coworkers made use of the Weinberg differential method to *estimate* the number of MZ and DZ twins. From this, they concluded that the frequency of MZ pairs in their series was only half that in the general population of twins, although they reminded the reader to interpret this apparent deficit with caution, because their leukemic twin sample was small. The use of the Weinberg formula (necessitated by the lack of more accurate information) cannot substitute for an accurate determination of zygosity by one of the methods currently available. Granted that this determination is often difficult, it is, nevertheless, important. This type of information is frequently available only in detailed clinical reports and therefore was a crucial factor in the selection of the cases for our tables (Keith and Brown, 1971). According to Benirschke (1961a, b), the accurate determination of zygosity should ideally be made shortly after birth when the placentas are available for study; however, this method may sometimes be misleading. In fact, Myrianthopoulos (1970) has described some placentas of MZ twins which were diamniotic-dichorionic. Nylander (1970) confirmed his observation in Western Nigeria, and suggested that gross and microscopic placental examination alone is frequently insufficient to establish zygosity. He has reasonably also proposed that placental enzyme studies be done.

Another provocative comment by Jackson et al (1969) pertains to the possible effects of antenatal X-rays in the induction of childhood leukemia. If intrauterine irradiation of the fetus can influence later childhood cancer, then concordance should be equal among MZ and DZ twins exposed to in-

trauterine X-ray. That supposition presupposes that X-ray alone is the important initiating factor. Only if a genetic predisposition to leukemia were activated by exposure to an exciting agent would differences between MZ and DZ twins become apparent. Such a genetic predisposition has been referred to by Jackson et al, but has been denied in general in the early Steinberg (1957), but without reference to X-rays as a possible exciting factor. Without doubt the questions of the effect of X-rays and the possibility of a genetic predisposition to leukemia among twins need further clarification (Stewart and Barken, 1971). Jackson and his associates believed that the genetic hypothesis was supported by the absence of reliable reports of childhood leukemia concordance among DZ twins. The cases reported by Gunz, Lundmark, and Denolin-Rubin, discussed in our tables (Keith and Brown, 1971), may not have been known to them. Since DZ twins occasionally share a fused placenta and since there may be varying degrees of blood exchange by way of deep intracotyledonal anastomoses between DZ fetuses, concordance among DZ twin may result from common exposure to an exciting agent (viral?) which is shared by transfusion.

The clinical material on which the Steinberg reports were based was also from the records of the Children's Cancer Research Foundation of Boston. Presumably, some of it was included in the more recent publication from the same institution (Fraumeni et al, 1971). Steinberg's preliminary report (1957) set the stage for the detailed work of 1960. In neither report are all the clinical details of the twin patients given: however, the cotwins did not demonstrate leukemia at the time of the collection of data. The age of onset and the survival time were not stated. The chief point was based on the hereditary aspects (if any) possibly leading to susceptibility to leukemia. Steinberg concluded that in general there was no important genetic component in the causation of leukemia.

Our report submitted other factors than did Dr. Steinberg regarding influence on concordance when present: chromosomal defects, common environmental factors, and conjoined intrauterine circulation. Because the problem is complex, examination from many aspects is mandatory. When a question remains unanswered, there can be no right or wrong point of view. That is why, so far, a record of unanimity of opinion is lacking. The purpose of our article was not to alarm parents, but to bring together a series of facts, seemingly unrelated but possibly greatly interrelated. Dr. Steinberg undoubtedly was similarly motivated. Our appreciation goes to the editors of *Acta Geneticae Medicae et Gemellologiae* for the opportunity to express candid opinions.

Sincerely yours,

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