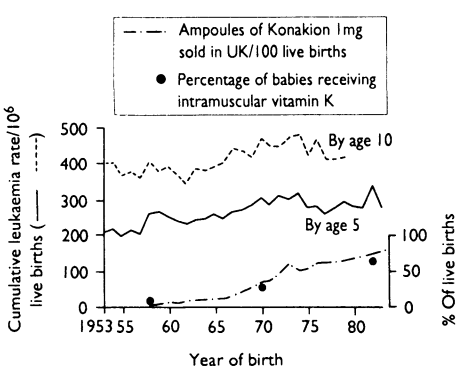
Intramuscular vitamin K and childhood cancer

EDITOR,—Jean Golding and colleagues report an association between neonatal administration of intramuscular vitamin K and the subsequent occurrence of childhood leukaemia.[1] They find a smaller degree of association with other childhood cancer. Oral administration does not show a similar effect. From this, trends in the incidence of childhood leukaemia might be expected to reflect trends in the proportion of babies receiving intramuscular vitamin K.

We estimated the cumulative incidence of childhood leukaemia in Great Britain using data from the National Registry of Childhood Tumours. Our data on the incidence of childhood cancer and the proportion of this due to leukaemia differ considerably from those used by Golding *et al.* Data on the use of intramuscular vitamin K came from three sources. Firstly, Golding and colleagues give estimates for 1958 and 1970 based on the British national birth surveys. Secondly, we estimated use in 1982 by using data from a national survey of special care baby units (J H Tripp, personal communication).[2] Thirdly, we used sales figures for Konakion 1 mg ampoules in Britain during 1958-83; these ampoules seem to have been almost the sole source of intramuscular vitamin K in the United Kingdom since their introduction in 1958 to replace Synkavit. We have assumed that the amount used in any one year is 75% of the sales for that year plus 25% of the sales for the previous year. In the figure the ratio of the estimated number of ampoules used to the total number of live births in the United Kingdom is expressed as a percentage. Some of the Konakion was given orally, and therefore the rates given will tend to overestimate the percentage of babies given intramuscular vitamin K. At least up to and including 1970, however, all of the ampoules used would probably have been given intramuscularly, and even by 1982 only about 10% would have been given orally (J H Tripp, personal communication). The rate for 1958 may be an underestimate as some Synkavit may have been given. The estimates based on sales of intramuscular vitamin K agree well with the independent estimates.

We cannot say with certainty whether trends in the use of intramuscular vitamin K are compatible with the trends in the rates of childhood leukaemia because other factors may influence the rates. For example, we calculate that decreases in antenatal exposure to *x* rays may have led to a 5% decrease in incidence,[3] while improved ascertainment of cases may have led to an increase of a similar magnitude.



Estimates of rates of childhood leukaemia and percentages of babies receiving intramuscular vitamin K, 1953-83

Advice to authors

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Golding and colleagues remark that the increase in incidence of leukaemia between 1962 and 1974 reported previously[4] is compatible with a relative risk of around 2·0 and the increase in the rate of administration of intramuscular vitamin K between 1958 and 1972. Our data on use of intramuscular vitamin K suggest that the trend for the incidence of leukaemia should have continued up to 1982, but there is so far no evidence of any increase among births since the early 1970s. The figure suggests that from the early 1960s to the early 1970s the percentage of babies given vitamin K increased by about 30%, with a similar increase taking place in the next decade. The increase in the incidence of leukaemia in the 1960s is compatible with most of the increase in use of vitamin K being due to intramuscular administration with a relative risk of 2·0, which is similar to the argument presented by Golding and colleagues.

If, on the other hand, we accept their relative risk estimate of 2·65 for leukaemia, we have to assume that about half the increase in use of vitamin K is accounted for by oral administration. This seems unlikely, which suggests that the risk, if it exists, is less. For the remainder of the period under consideration the increase in the level of use of intramuscular vitamin K seems to predict an increase in leukaemia, but no increase was observed. There are several possible explanations for this. Firstly, there may have been a balancing decrease in the completeness of ascertainment of cases; we do not believe that this occurred.[5] Nor is it likely that such a decrease occurred as a result of a trend towards describing cases as non-Hodgkin's lymphoma since registrations for this condition have decreased.[6] Secondly, there may have been a balancing decrease due to the removal of some other leukaemogen; we know of no evidence of this. Thirdly, the increase in use of vitamin K may be attributable entirely or almost entirely to increasing use of the oral route, with a low or zero risk. This last is at variance with Handel and Tripp's report[2] and, in particular, with the estimate given here, based on their survey, of 62% as the minimum percentage of babies who received intramuscular vitamin K in 1982.

We believe, therefore, that the absence of an increase in the incidence of leukaemia in the more recent period studied throws considerable doubt on the risks ascribed to intramuscular vitamin K. To settle this question, large cohort studies of groups of children given intramuscular vitamin K, oral vitamin K, and no vitamin K should be carried out as rapidly as possible.

We have one other comment: table II shows that most of the informative case-control comparisons came from hospital B in the period 1971 onwards. Table I shows that in this hospital in this period almost the only babies receiving intramuscular vitamin K were those who were born following an assisted delivery. This suggested that the excess of cases with intramuscular vitamin K found in this period may have contained a large proportion of babies delivered by these means. The alternative would seem to be that the spontaneous deliveries in which intramuscular vitamin K was administered had an exceptionally high cancer risk. Assisted delivery is not a known risk factor for childhood cancer. This raises the question of whether there could be some artefactual difference arising from the different methods by which the cases and controls were chosen and which might account for the apparent association.

We thank Dr Josef Grüter of Roche, Basle, for providing information on sales of Konakion in the United Kingdom.

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1 Golding J, Greenwood R, Birmingham K, Mott M. Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *BMJ* 1992;**305**:341-6. (8 August.)
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6 Stiller CA, Draper GJ, Vincent TJ, O'Connor CM. Incidence rates nationally and in administratively defined areas. In: *The geographical epidemiology of childhood leukaemia and non-Hodgkin's lymphomas in Great Britain 1966-83*. London: HMSO, 1991.

EDITOR,—Jean Golding and colleagues report a case-control study of the relation between neonatal administration of vitamin K and childhood cancer.[1] Comparing children born in two Bristol hospitals who were given intramuscular vitamin K with those given oral vitamin K or no vitamin K, they estimated an odds ratio for cancer of 2·0 (95% confidence interval 1·3-3·0) using a logistic regression model that also included the variables year of delivery and hospital.

Golding and colleagues made great efforts to check several potential confounders, of which one was type of delivery. When analysing the possible confounding effect of type of delivery, however, they do not take into account the fact that the correlation between type of delivery and vitamin K administration differed drastically between the two hospitals studied. Table I in the article showed that there was little difference in vitamin K administration between spontaneous and non-spontaneous deliveries among controls of hospital A, whereas in hospital B, 81% (56/69) of the non-spontaneously delivered controls and 4% (8/199) of the spontaneously delivered controls had been given intramuscular vitamin K. Furthermore, since in hospital B vitamin K administration showed very little variation given the time period (table I of the article), most of the information regarding the relation of vitamin K and cancer came from hospital B. This was clearly shown in the Mantel-Haenszel analysis reported in table II, in which only two out of 21 informative year strata were from hospital A.

Thus the result obtained comes to a large extent from a comparison in one Bristol maternity hospital between children given intramuscular vitamin K

and delivered non-spontaneously and children given oral vitamin K or no vitamin K and delivered spontaneously. An appropriate way to separate any possible effect of type of delivery from the effect of vitamin K would be a Mantel-Haenszel analysis in which the data are stratified also for type of delivery (or a logistic regression analysis using a model that incorporates interaction terms between the variables hospital and type of delivery, as well as between hospital and year of delivery).

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EDITOR,—We believe the study of Jean Golding and colleagues to be seriously flawed in design, analysis, and (therefore) interpretation. The principal error is of chronological inequality in the acquisition of cases and controls. In the case of any phenomenon with the potential for changes or trends over time it is critical to match cases and controls by time, as well as the other characteristics (hospital, etc) deemed to be potential confounding factors. This is not done. Analytical "fixes" to this problem (such as the inclusion of birth year in the analysis as a potentially important variable) either require a mathematically definable relation between time and outcome (cancer incidence is unlikely to be consistent enough for this), or, if analysed by individual year, a strong influence of year by year changes. Since meaningful temporal trends can exist without either of these conditions being true, analysis cannot deal with this major flaw to the study.

There are more important considerations pertaining to the conclusions of the study. Roche Products believes in providing the best medicines available in the form most useful to medical practice. For this reason, we have been working with paediatric researchers for several years on an oral form of vitamin K that provides equivalent efficacy to the injectable form. This research was undertaken because some physicians believe that the practice of giving an injection to a newborn infant is philosophically wrong if it can be avoided. This research will be concluded soon, and an oral form of vitamin K of sufficient efficacy will then be provided quickly. For the moment, until these studies are complete, injectable vitamin K remains the best treatment for the prevention of haemorrhagic disease.

Finally, we would like to endorse fully the position taken by David Hull in his accompanying comments to the study. Physicians and parents should not be advised to reject the intramuscular use of vitamin K solely on the basis of this study. It would be a tragedy if even one child were unnecessarily put at risk of haemorrhagic disease. A responsible consideration of the study by Golding *et al* and the possibilities it raises should be balanced against the known risks and risk factors for haemorrhagic disease.

Meanwhile, Roche will continue to fulfil its responsibility to investigate the way its medicines are used (as we did by funding Golding *et al*'s study) to make certain that we make only the safest and most effective medicines possible.

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EDITOR,—Jean Golding and colleagues concluded that "Before we change our practice we must be confident that any programme of oral administration [of vitamin K] will be as effective as injected vitamin K and that all infants who need it will receive it."[1] There are many unanswered questions about the widespread use of vitamin K. What is the effect on babies who have normal levels of vitamin K? Is it necessary to give vitamin K to babies who have not had traumatic deliveries? And there are many more questions. These could have been addressed had a randomised controlled trial been undertaken before the medical profession rushed vitamin K into widespread use.

Restricting research to oral vitamin K is not good enough. Women are entitled to full information, and they will not get it until proper trials are undertaken into what is yet another example of the medical profession's failure properly to evaluate its own practice.

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EDITOR,—The probable association between vitamin K given to neonates and subsequent childhood cancer has been convincingly demonstrated by Jean Golding and colleagues.[1] Further studies will be needed to confirm their findings. There is no doubt that vitamin K is a valuable prophylaxis against haemorrhagic disease of the newborn, but it is also important to remember that, on the debit side, it involves other hazards besides malignancy.

These are the risks inseparable from any injected treatment. The first is local infection, which may be life threatening for a newborn baby. I have seen a thigh abscess and osteomyelitis of the femur. (The femur is often impaled by the needle tip.)

The second is damage to deep tissues, mainly muscles, blood vessels, and nerves, particularly the sciatic nerve. A rare but inescapable risk is giving the wrong injection. In the delivery room this is most likely to be an oyxtocic agent, which is presented in a similar ampoule. Deaths have occurred from this error.[2]

Intravenous injection of vitamin K in adults can cause shock and occasionally death.[3] In infants, intravenous injection would be inadvertent but the risk cannot be overlooked.

It is now likely that the prophylactic regimen will revert to that which was the routine a few years ago—namely, to give the drug only to those babies who are at increased risk of haemorrhagic disease because of traumatic delivery (forceps, ventouse, breeches, caesarean delivery, prematurity) but not to those who have easy spontaneous deliveries.

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1 Golding J, Greenwood R, Birmingham K, Mott M. Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *BMJ* 1992;**305**:341-6. (8 August.)
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EDITOR,—Jean Golding and colleagues[1] found a significant association of intramuscular vitamin K with childhood cancer, but not when the vitamin K was given orally. It is noteworthy that the injection of vitamin K was given in a preparation that contained 1 mg of phytomenadione and 5 mg of phenol, together with 10 mg polyoxyl 35 castor oil and 10 mg propylene glycol. The inclusion of phenol is disturbing: at sufficient concentration phenol is said to be both mildly carcinogenic itself and a strong promoter of carcinogenic action.[2] This may not apply if it is given orally, owing to normal detoxification mechanisms, but may be worthy of consideration when injected. It could account for the difference in carcinogenicity of oral as against injected vitamin K—the cancer inducing or promoting mechanism of the injected vitamin K preparation might be due to the phenol, not to the vitamin.

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1 Golding J, Greenwood R, Birmingham K, Mott M. Childhood cancer, intramuscular vitamin K, and pethidine given during labour. *BMJ* 1992;**305**:341-6. (8 Aug.)
2 Clayson DB. *Chemical carcinogenesis*. London: Churchill, 1962: 302-3.

AUTHORS' REPLY,—G J Draper and C A Stiller have produced interesting information on leukaemia rates according to date of birth and compared them with vitamin K sales at the time of birth. The data raise a number of questions which require further clarification.

Firstly, are there other factors relating to the definition of leukaemia which might have an impact on these incidence rates? To cite just one example: the arbitrary distinction between what is lymphoblastic leukaemia and what is non-Hodgkin's lymphoma, usually set at ±25% blasts in a bone marrow aspirate, has altered substantially by practice and custom in the past 20 years. This has been particularly affected by the better definition of T and B cell leukaemia and lymphomas and by the increasing proportion of patients admitted to treatment trials organised by the Medical Research Council and the United Kingdom Children's Cancer Study Group.

Secondly, identification of cases is best undertaken using multiple sources. The Oxford group obtain their data from several sources, including death certificates. As the survival rate for leukaemia has improved over time the chance of picking up from death certificates children who had failed to be registered must diminish. This of itself might contribute towards the flattening of the curve.

Thirdly, there is no reason to doubt the information on vitamin K sales. The crucial question concerns the route by which the vitamin K was given. In 1958 and 1970 almost all was administered intramuscularly. Subsequently the preparation started to be given by mouth. The 1982 estimate of intramuscular use is derived from a study that estimated the number receiving vitamin K by writing in 1988 to the heads of all special care baby units and asking for details of the policy in their catchment maternity hospital in 1982.[1] This method is unlikely to give accurate results. In addition, only 75% of units responded. Presumably also there were no data from district general hospitals that did not have a special care baby units, from general practitioner units, or home deliveries.

These doubts concerning the proportion of intramuscular vitamin K given nationally in 1982 need to be resolved. If the Oxford Cancer Registry data on leukaemia are accurate and the 1982 estimate of intramuscular vitamin K administration is correct then intramuscular vitamin K may not be causally associated with childhood leukaemia. Alternatively, other leukaemogens may be having an effect. Draper and Stiller argue that there is no evidence for this, but without knowing what such potential leukaemogens might be it is impossible to say that exposure might or might have not resulted in a fall in incidence of leukaemia.

J Carstensen suggests that type of delivery is not adequately controlled. True, in one hospital this factor was closely related to use of intramuscular