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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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.)

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.)
2 Hall MA. The routine use of vitamin K in the newborn. *Midwifery* 1987;**3**:170-7.
3 Labatut A. Etats de choc lors d'injection de vitamine K. *Therapie* 1988;**43**:57-9.

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