expression of the cloned toxin gene indicates that the production of the proposed vaccine strains is a viable prospect.

In addition, we would like to report an observation which may be of importance when considering the evolution of the *V. cholerae* enterotoxin. When radiolabelled *V. cholerae* cloned DNA (17 kb) was hybridised back to restriction fragments of chromosomal DNA separated by gel electrophoresis, two fragments hybridised to the probe. Similar results were also seen when the A subunit of the LT gene was used as probe. However, only one fragment was detected when the B subunit encoding DNA of the LT gene was used. This suggests that there is, within the chromosome, another gene with almost identical sequence which could, therefore, be expected to code for a protein of similar function—i.e., catalysing ADP ribosylation. This observation accords with biochemical studies of Fernandez et al.[4] who showed that *V. cholerae* contains more than one ADP ribosylating enzyme. One might, therefore, speculate that the sequence encoding the A subunit of cholera toxin may have arisen by mutation following duplication of the gene specifying a normal host cell function. Possession of the toxin would have given the organism a selective advantage over non-toxigenic forms. We are now investigating this possibility and are developing the candidate vaccine strains mentioned in this letter.

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PHENOXY HERBICIDES, TRICHLOROPHENOLS, AND SOFT-TISSUE SARCOMAS

SIR,—Your May 8 editorial rightly draws attention to the presence of the toxic contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in both the herbicide 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and in the related 2,4,5-trichlorophenol. TCDD, as the editorial points out, is reported to have genotoxic effects in microbial assays and is also tumorigenic in rats.

Your editorial also notes that TCDD is not seen in the herbicide 2,4-D (2,4-dichlorophenoxyacetic acid). This is true. However, there are other chlorinated dioxins in 2,4-D. A recent report[5] says that 2,7-dichloro, 1,3,7-dichloro, and 1,3,6,8/1,3,7,9-tetrachlorodibenzo-*p*-dioxins are present in 2,4-D ester formulations sold in Canada. The concentrations for the 2,7-dichloro and the 1,3,7-trichloro compounds and for the two tetrachloro isomers are reported as 0·11-23·8, 0·035-2·45, and 0·12-8·73 parts per million, respectively.

Dr Coggon and professor Acheson (May 8, p. 1057) review the evidence for a link between exposure to 2,4,5-T and soft tissue sarcoma and conclude, cautiously, that there may be one. This evidence includes a paper by Hardell et al.[6] who reported an increased risk from malignant lymphoma in workers exposed to several other chlorinated herbicides, including 2,4-D. Thus, although 2,4-D does not have measurable concentrations of TCDD, it might not be entirely in the clear, if Hardell's findings are correct.

We[7] have investigated the mutagenic properties of several chlorinated dioxin isomers, using the cell transformation assay.[8] In this assay both 2,8-dichloro and 1,3,7-trichloro dibenzo-*p*-dioxin were weakly positive (i.e., weakly mutagenic) whereas two samples of TCDD were clearly positive. The unsubstituted dibenzo-*p*-dioxin and the fully chlorinated octachlorodibenzo-*p*-dioxin were both negative in the cell transformation assay. Although we were unable to test the 2,7-dichloro isomer, the 2,8-dichlorodibenzo-*p*-dioxin which we did test is a closely related analogue. A study[9] commissioned and published by the National Cancer Institute concluded that the 2,7-dichloro isomer is probably carcinogenic in male B3C3FI mice where it caused marginal increased incidences of combinations of leukaemias and lymphomas, of haemangiosarcomas and haemangiomas, and of hepatocellular carcinomas and adenomas. The concentration of chemical required to produce tumours in this animal (tumours have not been observed in other species tested so far) is high.

As your editorial points out it is most important that the issue of the link between 2,4,5-T exposure and soft tissue cancer remain under informed scrutiny. It might also be prudent to widen the net slightly and look at some other chlorinated herbicides.

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PHENOBARBITONE AND NEONATAL INTRAVENTRICULAR HAEMORRHAGE

SIR,—Last year we reported promising experience with phenobarbitone for the prevention of intraventricular haemorrhage (IVH) in preterm infants.[1] We have so far enrolled 105 babies in this controlled study, which is continuing. Examination of treatment failures in our first cohort of 60 infants suggested that haemorrhage was occurring before completion of phenobarbitone loading and achievement of anticonvulsant serum concentrations. Therefore, after our first report we modified the dose schedule of treated infants to allow for earlier drug loading. Infants receiving assisted ventilation are given phenobarbitone in a single 20 mg/kg loading dose intravenously over 10–15 min. Spontaneously breathing infants are given two 10 mg/kg intravenous doses 4 h apart. Most of the treated infants received the first dose within an hour of birth; all were treated before 6 h of age. In all instances maintenance doses of 2·5 mg/kg (intravenously) are started 12 h after loading is completed and continued for 7 days. Serum levels of phenobarbitone are measured and dosage adjusted when necessary to maintain concentrations in the serum of 20–30 μg/ml.

The table shows the results of the effect of phenobarbitone on the incidence of all grades of IVH. We continue to find a significant reduction in the incidence of IVH in treated infants. The distribution of IVH by grade[2] is also shown. The major impact of treatment appears to be a reduction in the number of haemorrhages (grades I, II, and III) not extending into brain parenchyma.

Hope et al.[3] and Morgan and Cooke[4] have found no beneficial effect of phenobarbitone on IVH. The major differences between our investigation and theirs are time of first dose, route of administration, and duration of therapy. Morgan and Cooke gave a single intramuscular dose of 20 mg/kg without further treatment. Although the phenobarbitone was usually administered within the first 2 h of life, serum levels were not provided to document the rate and efficacy of absorption from the intramuscular site. Hope et al. gave two 10 mg/kg doses of phenobarbitone parenterally 12 h apart. The timing of the first dose varied from 2 to 46 h of life. The route of parenteral administration (intravenous or intramuscular) was not

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INCIDENCE AND DISTRIBUTION OF IVH

IVH grade	Phenobarbitone (n=51)	Control (n=54)
0	44	31
I	1	7
II	3	7
III	1	6
IV	2	3
Any IVH	7 (*14%*)	23 (*43%*)

$\chi^2 = 10{\cdot}71$, $p < 0{\cdot}005$.

stated. Maintenance therapy was discontinued at 120 h of age. Serum phenobarbitone levels were not provided.

Our reduction in the incidence of IVH in treated babies may be related to a more rapid achievement of peak serum levels which were then maintained for 7 days. Additional controlled investigations are clearly needed to test the hypothesis that early and rapid achievement of anticonvulsant serum levels of phenobarbitone may reduce the incidence of IVH in preterm infants.

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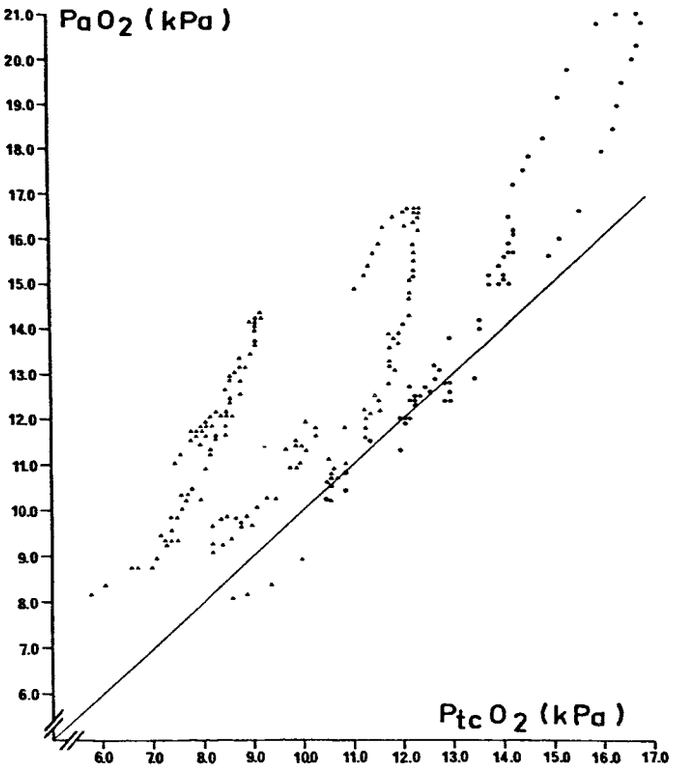
VALIDITY OF TRANSCUTANEOUS PO_2 MONITORING AS COMPARED WITH INTRA-ARTERIAL PO_2 MONITORING IN NEWBORN INFANTS

SIR,—The transcutaneous PO_2 electrode ($tcPO_2$) has become a frequently used tool in the neonatal ward since it was introduced commercially in the mid-1970s. $tcPCO_2$ electrodes are now commercially available too, and could be used as frequently as the PO_2 electrode is, especially if the two electrodes can be combined. Interest in this subject is illustrated by the holding of international meetings devoted solely to transcutaneous gas monitoring (San Francisco 1977, Marburg 1978, Zürich 1981).

We have monitored oxygen with a transcutaneous sensor and a surface heparinised intra-arterial PO_2 electrode simultaneously in infants and found that the transcutaneous electrode often underestimated PaO_2, when the arterial PaO_2 was above 9 kPa (67 mm Hg) (figure). Furthermore, when infants were distressed, as indicated by increased plasma catecholamine levels, the $tcPO_2$ was lower than the PaO_2, probably because of reduced skin perfusion. The transcutaneous oxygen sensor almost lost its sensitivity when compared with a rising PaO_2, but the breakpoint could not be predicted, and was obviously a function of plasma catecholamine concentration. Jensen et al.[1] have demonstrated a successively decreased ratio between $tcPO_2$ and PaO_2 as a function of raising plasma noradrenaline levels in the asphyxiated fetal sheep. A poor correlation between $tcPO_2$ and PaO_2 in severely sick infants has previously been reported.[2,3]

Companies selling $tcPO_2$ electrodes and the proceedings of international symposia give the impression that the $tcPO_2$ when used on infants is very closely correlated with PaO_2. Several graphs have been presented with r values close to 0·9, but in evaluations of individual measurements, the same readout on the $tcPO_2$ monitor corresponds with PaO_2 values which can vary within a wide range.[3,4] A close correlation might hold for ideal clinical conditions and for high electrode temperatures, but the method is not always reliable in the routine care of sick neonates, as indicated above.

Transcutaneous measurements should never be trusted alone:



Corresponding readouts from continuous intra-arterial PO_2 recorders and $tcPO_2$ monitor on eight newborn children in intensive care.

The intra-arterial PO_2 sensor (Hoffman-La Roche, Basle, Switzerland) was surface heparinised (IRD Biomaterial AB, Stockholm, Sweden). The $tcPO_2$ sensor (Radiometer, Copenhagen, Denmark) was placed on the same level as the tip of the intra-arterial PO_2 sensor, to avoid influence from the arterial ductus. The oxygen atmosphere of the infants was determined on clinical grounds. When the intra-arterial PO_2 became high the fraction of oxygen was lowered in order to avoid dangerously high PaO_2 values.

continuous intravascular recordings with non-thrombogenic sensors should be preferred for monitoring PaO_2 in severely distressed infants.

The study was approved by the ethical committee at the Karolinska Hospital, Stockholm.

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IgA AND PRETERM MILK

SIR,—Recent work suggests that the milk of mothers who have delivered preterm infants, so called preterm milk (PTM), differs in constitution from normal-term milk (TM),[1,2] which is the type of milk donated to human milk banks. We have identified an immunological difference between PTM and TM which may be relevant to the management of high-risk low-birthweight infants.

As part of an immunological study (to be published in full) of 115 samples of expressed TM or PTM from healthy mothers in the first 10 days after delivery, we found that during the first 5 post-partum days total milk IgA concentrations (determined by both rocket immunoelectrophoresis and reverse passive haemagglutination) were significantly higher in PTM than in TM (see figure). These findings accord with those of Gross et al.[3] (but not with those of

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