Correspondence

Archives of Disease in Childhood, 1975, **50**, 575.

Ethic of taking blood samples in newborns

Sir,

The Editors have drawn our attention to the ethical justification for taking blood samples from newborns, as was done in our study 'Serum tri-iodothyronine, thyroxine, and thyrotrophin concentrations in newborns during the first 2 days of life' (Similä *et al.*, p. 565) and we are more than glad to discuss this aspect of our study.

The justification for taking blood samples in children has lately been the subject of discussion by several authors (European Society for Paediatric Research, 1973; Editorial, *Archives of Disease in Childhood*, 1973; Illingworth, 1974). In weighing up the ethics of any particular investigation, Illingworth suggests that three questions should be asked: (i) what good may it do? (ii) what harm may it do? (iii) what harm may be done by not doing it? We have tried to answer these questions in the case of our own study

(i) The study was aimed to give, and did give, new information on the adaptation of the pituitary-thyroid axis after birth. The results also showed clearly that screening tests for thyroid functions should not be done until after the age of 24 hours. Clear-cut data giving normal values from the same individual were not available before this study.

(ii) Although not all the venepunctures were undertaken in the course of routine laboratory studies, we stress that a puncture of a scalp vein in experienced hands carries no somatic risk. Neither are there any data in the literature suggesting psychic harm from taking blood samples in newborns. Heel and venous punctures must have been done in millions of newborns without any reports of possible psychic harm.

(iii) Without the detailed data deriving from the 10 newborns in this study, tests for diagnosing and screening congenital hypothyroidism might be wrongly timed and hence misleading.

In summary, we feel that the study gave new information, important both from the theoretical and practical points of view, and did not cause, as far as we can judge, any harm to the babies.

The ethical rules given in the Helsinki Declaration of WMA have been adapted for children by one of us (Kouvalainen, 1974). Rule IV is as follows: 'Consider the study plan from the point of view of the patient: you must *feel* that you have got the child's personal permission, even though he/she cannot speak to you'. In the referred study the authors did feel that in this sense the patients gave their permission for the study. However, we willingly accept that frank discussion of the ethics of paediatric clinical investigation in this connexion are justified and indeed of great importance.

SEPPO SIMILÄ, M.D.
Assistant Chief
KAUKO KOUVALAINEN, M.D.
Professor of Paediatrics
Department of Paediatrics,
University of Oulu,
90220 Oulu 22, Finland.

REFERENCES

Archives of Disease in Childhood, (1973). The ethics of research involving children as controls, **48**, 751.

European Society for Paediatric Research (1973). Annual meeting, Seville.

Illingworth, R. S. (1974). *Modern Trends in Paediatrics*, Vol. 4, p. 329. Ed. by J. Apley. Butterworths, London.

Kouvalainen, K. (1974). *Ethical Rules for Pediatric Clinical Investigation*. Printing House Kaleva, Oulu.

Similä, S., Koivisto, M., Ranta, T., Leppaluoto, J., Reinilä, M., and Haapalahti, J. (1975). Serum tri-iodothyronine, thyroxine, and thyrotrophin concentrations in newborns during the first 2 days of life. *Archives of Disease in Childhood*, **50**, 565.

Haemophagocytic reticulosis

Sir,

We read with interest the views on haemophagocytic reticulosis by Blennow *et al.* (1974). As has been postulated previously (Buist, Jones, and Cavens, 1971), the authors of this present report suggest that a state of chimerism is the cause of this disorder. However, we feel that the evidence presented is far from convincing.

The following observations are all against a state of chimerism. (1) The chromosome analysis in lymphocytes from peripheral blood revealed a normal male karyotype in all metaphases studied. (2) Typing the patient's red cells within the Rh system revealed no mixed field. (3) The antiglobulin test was repeatedly negative, and no irregular red cell antibodies were found in the serum. Previously reported cases of thymic alymphoplasia (Kadowaki *et al.*, 1965; Githens *et al.*, 1969) provide examples of proven chimeras.

Erythrophagocytosis experiments showed that in the presence of the patient's serum, monocytes phagocytosed red cells obtained from the patient and his mother. Phagocytosis of the patient's red cells occurred to a lesser extent. This difference has not been quantitatively recorded and appears from the data given to be based on insufficient experimentation using only one leucocyte donor. Thus, the hypothesis that a host versus graft reaction causes this disorder does not receive firm support from the *in vitro* experiments.

In future cases post-mortem findings would be valuable to show the histopathology of the lympho-

reticular system. These findings could help in the differentiation of the similar histiocytic disorder of Letterer-Siwe disease. Chromosomal analysis should be extended to include bone marrow cells and the histiocytic cell line. The demonstration of an XX cell line in a male patient would obviously be strong evidence of chimerism. These studies might also help to clear up the doubt about the malignant nature of the histocytes.

It has been suggested (Buist *et al.*, 1971) that the disease may be a recessively inherited malignancy. The evidence is from the occurrence of this rare disease in sibs and first cousins (Goodall, Guthrie, and Buist, 1965). It may be of relevance that the patient in this latest report was born of a cousin marriage.

J. S. WAINSCOAT
Department of Experimental Pathology, The Medical School, Birmingham B15 2TJ.
I. M. HANN
Alder Hey Children's Hospital, Liverpool L12 2AP.

REFERENCES

Blennow, G., Berg, B., Brandt, L., Messeter, L., Löw, B., and Söderström, N. (1974). Haemophagocytic reticulosis: a state of chimerism? *Archives of Disease in Childhood*, **49**, 960.

Buist, N. R. M., Jones, R. N., and Cavens, T. R. (1971). Familial haemophagocytic reticulosis in first cousins. *Archives of Disease in Childhood*, **46**, 728.

Githens, J. H., Muschenheim, F., Fulginiti, V. A., Robinson, A., and Kay, H. E. (1969). Thymic alymphoplasia with XX/XY lymphoid chimerism secondary to probable maternofoetal transfusion. *Journal of Pediatrics*, **75**, 87.

Goodall, H. B., Guthrie, W., and Buist, N. R. M. (1965). Familial haemophagocytic reticulosis. *Scottish Medical Journal*, **10**, 425.

Kadowaki, J., Thompson, R. I., Zuelzer, W. W., Wooley, P. V., Brough, A. J., and Gruber, D. (1965). XX/XY lymphoid chimerism in congenital immunological deficiency with thymic alymphoplasia. *Lancet*, **2**, 1152.

Dr. G. Blennow comments as follows:

Drs. Wainscoat and Hann point to three observations that they consider are against a state of chimerism. We would like to comment on their remarks.

(1) In the case of a graft rejection, the peripheral blood lymphocytes are expected to be of host origin as in our patient.

(2) One characteristic feature of haemophagocytic reticulosis is remarkable increase in phagocytic reticuloendothelial cells in various organs. It is possible that grafted, antibody-coated Rh-negative erythrocytes were rapidly eliminated by these phagocytic cells and therefore escaped detection in the mixed field tests.

(3) The antiglobulin test was negative. As mentioned, grafted cells may well be rapidly phagocytosed *in vivo*. However, the results of the erythrophagocytosis experiments *in vitro* may indicate that a few red cells coated by antibody were actually present in the patient's peripheral blood.

We cannot therefore agree that the three observations mentioned are definitely against a state of chimerism. In our report it was not claimed that chimerism was proven in our patient. However, we suggested that future cases of haemophagocytic reticulosis should be examined with such a possibility in mind. As pointed out by Drs. Wainscoat and Hann, karyotype analyses of the bone marrow would then be of great importance.

GÖSTA BLENNOW
Department of Paediatrics, University Hospital, S–221 85 Lund, Sweden.

Phenylalaninaemia

Sir,

The article on phenylalaninaemia by Blaskovics, Schaeffler, and Hack (1974) is timely in that it emphasizes the need for careful evaluation of all suspected cases of phenylketonuria; some patients may be in danger if treatment is too restrictive, others may not need any dietary treatment. The rather complex classification proposed by the authors receives some support from their own observations, but may need to be modified when improved techniques permit more accurate studies of enzyme activities. We prefer the simpler and more practical classification given by Scriver and Rosenberg (1973). They cover 5 types described by Blaskovics *et al.*, in three groups. (1) 'Classical' phenylketonuria. (2) Phenylketonuria ('mild' variant with relaxed phenylalanine tolerance). (3) Phenylketonuria ('transient' variant).

This grouping is more helpful in the clinical context. The authors stress the importance of estimating the daily phenylalanine tolerance of patients on treatment; in the variant forms this is usually over 500 mg/day.

We estimated the daily phenylalanine intake required by 24 of our patients on a low phenylalanine diet at some point between the ages of 11 and 13 months, and at a time when the serum phenylalanine was at an acceptable level. In 18 cases the intake was between 275 and 450 mg/day (mean 365, 2 SD 120). They are all, to the best of our knowledge, cases of classical phenylketonuria. 5 patients were able to tolerate 500 to 600 mg phenylalanine/day. 4 of these returned to normal diet between the ages of 1 year 3 months and 3 years. On normal diet one patient maintains a serum phenylalanine level of 2–3 mg/100 ml, in the other 3 the range is 7–13 mg/100 ml. These 5 children are all developing normally. All show impaired phenylalanine tolerance on a loading test, giving curves above that expected from a heterozygote, but below that of a child with classical phenylketonuria. Perhaps none needed treatment, yet at the time of diagnosis all but one had a serum phenylalanine above 20 mg/100 ml and metabolites of phenylalanine were detected in the urine. The fifth 'atypical' patient tolerated exactly 500 mg phenylalanine/day but was maintained on a diet for 7 years because she had 2 mentally retarded sibs.

Our present practice is to start treatment if the serum