

Fetal cells in the blood of pregnant mothers

SIR,

In the August 1980 issue of your Journal,¹ there was a paper dealing with 'fetal lymphocytes' in the maternal blood. Since the paper contains a few mistakes, lacks some important references, and is in contradiction to most existing data, I would like to state the following.

(1) Schröder² has never studied fetal erythrocytes in the maternal blood with immunofluorescent or other techniques (authors' reference 1).

(2) Turunen *et al*³ never studied fetal 'lymphocytes' in maternal blood with a fluorescence activated cell sorter. The group has actually never worked with a cell sorter (authors' reference 26).

(3) The nature of fetal cells in the maternal blood is not known at present. However, all attempts to demonstrate XY mitoses in lymphocyte cultures from pregnant mothers have been unsuccessful,^{4–7} except occasionally after delivery provided the identification has been carried out after quinacrine staining. Since Y chromatin positive cells have been enriched from blood samples of pregnant mothers with HLA antisera and fluorescence activated cell sorting,⁸ it seems reasonable to assume that such cells actually do pass through the placenta during pregnancy. On the other hand, these cells do not seem to divide in lymphocyte cultures and might therefore not be lymphocytes at all.

This was the status of research on fetal cells in maternal blood in August 1980 before the publication of the paper by Kirsch-Volders *et al*. Has the situation radically changed?

JIM SCHRÖDER

*Folkhälsan Institute of Genetics,
PO Box 819, SF-00101 Helsinki 10, Finland*

References

- 1 Kirsch-Volders M, Lissens-Van Assche E, Susanne C. Increase in the amount of fetal lymphocytes in maternal blood during pregnancy. *J Med Genet* 1980;**17**:267–72.
- 2 Schröder J. Transplacental passage of blood cells. *J Med Genet* 1975;**12**:230–42.
- 3 Turunen O, Lundqvist C, de la Chapelle A. Fetal cells in the maternal blood: differential effects of mitogens on maternal and fetal lymphocytes. *Excerpta Medica Int Cong Ser* No 397, 1976:162–3.
- 4 Schröder J, Tiilikainen A, de la Chapelle A. Fetal leukocytes in the maternal circulation after delivery. I Cytological aspects. *Transplantation* 1974;**17**:346–54.

- 5 Schröder J, Schröder E, Cann HM. Fetal cells in the maternal blood. Lack of response of fetal cells to mitogens and mixed leukocyte culture. *Hum Genet* 1977;**38**:91–7.
- 6 Björkbohm S, Turunen O, Lundqvist C, de la Chapelle A. Stimulation of human fetal lymphocytes by lipopolysaccharide B in culture. Studies on cells circulating in maternal blood. *Acta Pathol Microbiol Scand (C)* 1978;**86**:159–64.
- 7 Schröder J, Herzenberg L. Fetal cells in the maternal circulation. Prenatal diagnosis by cell sorting using a fluorescence-activated cell sorter (FACS). In: *Genetic disorders and the fetus*. New York, London: Plenum Press, 1980.
- 8 Herzenberg LA, Bianchi DW, Schröder J, Cann HM, Iverson GM. Fetal cells in the blood of pregnant women: detection and enrichment by fluorescence-activated cell sorting. *Proc Natl Acad Sci USA* 1979;**76**:1453–5.

This letter was shown to Dr Kirsch-Volders, who replies as follows:

SIR,

I wish to thank Dr Schröder for the correction of two references. (1) The second sentence of the first paragraph "Schröder estimated, using immunofluorescent techniques, . . ." should be changed to "Schröder estimated in a review work¹ that from data obtained by immunofluorescent techniques . . .". (2) The congress abstract written by Turunen *et al*² mentioned "the possibility of obtaining enrichment of mitoses of fetal origin". We misinterpreted this sentence as including the use of a fluorescence activated cell sorter. Instead of this reference, Dr Schröder's work³ would have been mentioned, but it had not been published at the time we prepared our paper.

However, I cannot agree with the remark made by Dr Schröder that "all attempts to demonstrate XY mitoses in lymphocyte cultures from pregnant mothers have been unsuccessful". Indeed, as we stated in our paper, many other authors have observed the presence of male fetal cells in the peripheral blood of mothers pregnant with a boy, in interphases and metaphases as well (table).

The fact that Dr Schröder found no male metaphases, except after delivery, in lymphocytes purified from maternal blood on Ficoll—Hypaque gradients and stimulated with PHA or LPS as mitogen and MLC,¹¹ encouraged us to undertake our experiments. We have to confirm that the situation has not radically changed. Some laboratories still find male

TABLE Frequency of mothers pregnant with a male with male fetal cells in their peripheral blood. Data on interphase and metaphase counts are presented separately

	Interphases in uncultured cells	Interphases after PHA stimulation	Metaphases after PHA stimulation
Walknowska <i>et al</i> ⁴			19/21 cases
de Grouchy and Trébuchet ⁵			8/11
Zimmerman and Schmickel ⁶	No good correlation between sex and fluorescent bodies		
Schindler <i>et al</i> ⁷			4/9
Schröder and de la Chapelle ⁸	7/9	7/9	
Grosset <i>et al</i> ⁹		42/45	
Zilliaccus <i>et al</i> ¹⁰	7/11		0/10

metaphases, with quinacrine staining, in the peripheral blood of pregnant women after stimulation with PHA, but no previous purification of lymphocytes. Whether these cells are lymphocytes or not has already been discussed earlier by Schröder and Herzenberg.¹²

M KIRSCH-VOLDERS
Vrije Universiteit Brussel,
Laboratorium voor Antropogenetika,
Pleinlaan 2, 1050 Brussels, Belgium

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TABLE Amniocenteses in South Wales 1974-1980

Amniocenteses	NTD detected				NTD detection rate	NTD undetected	Total NTD rate
	No	An	SBC	E			
Indication							
Previous NTD	927	14	10	—	1:39	7	1:30
Family history of NTD	596	3	2	—	1:119	—	1:119
Parent with NTD	40	—	—	—	—	—	—
Raised serum AFP	774	47	45	1*	1:8.3	5	1:7.9
Other CNS malformations	75	1	1	—	1:37	—	1:37
Anxiety	151	1	—	—	1:151	—	1:151
Cytogenetic	1523	1	3	—	1:508	3	1:218
Other	127	2	—	—	1:63	—	1:63
Total	4221	69	61	1	1:32	15	1:30

A, anencephaly; SBC, spina bifida cystica; E, encephalocele. *A case of Meckel-Gruber syndrome.

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Recurrence risk of neural tube defects

SIR,

With reference to Dr Seller's paper (page 245) on recurrence risks for neural tube defects (NTDs) derived from a population of women presenting themselves for prenatal diagnostic tests,¹ I would like to confirm some of her conclusions from the experience in South Wales. Among the 4221 amniocenteses carried out between 1974 and 1980, the 927 carried out because the mother had had one or more previous children with an NTD led to the detection of 24 recurrences, giving an apparent recurrence risk of 1 in 39 (2.58%) (table). However, a follow-up of all the pregnancies revealed a further seven cases that were missed (in four because the lesion was closed) giving a total risk of recurrence derived from this population of 1 in 30 (3.34%),