identical on each occasion. In the final episode the rise in plasma uric acid to levels which involved marked supersaturation of the plasma was followed by oliguric renal failure with crystallization in the renal medulla.

FIG. 3.—Post-mortem specimen of kidney showing uric acid and urates in tubule. (Schultz-Schmidt. $\times 500$.)

Removal of a considerable proportion of the excess uric acid from the patient by haemodialysis might be expected to result in a temporary improvement in renal function. Presumably this is the explanation of the return of normal urine output and sustained fall in plasma urea level after the second dialysis, since there was no evidence of haematological improvement at this stage.

The longer and more complete return of renal function after the first dialysis was probably due in part to a remission in the underlying reticulosis, for during the dialysis and following his liver biopsy and laparotomy he received a total of 5 litres of blood. A temporary remission of acute leukaemia is known to occur in about 30% of adults treated by blood transfusion alone (Hayhoe and Whitby, 1955), and during such a remission there is a striking fall in uric-acid output (Dickinson, 1960). As with our patient, the response to a second transfusion is usually less complete.

Conclusions

Haemodialysis has a useful place in the treatment of hyperuricaemic crises. Normal or near-normal renal function may be restored for a few weeks, during which the original cause can be treated. It should therefore be particularly useful in the crises that sometimes follow the start of treatment in polycythaemia vera and chronic myeloid leukaemia. Since older children and adults can now be treated on the artificial kidney with minimal discomfort it may even be indicated in occasional cases of acute leukaemia.

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Preliminary Communications

Transfer of Erythropoietin to Amniotic Fluid in Rh-immunized Pregnant Women

Studies on the plasma erythropoietin (erythrocyte-stimulating factor) levels in cord blood from normal and anaemic infants indicate that the regulatory mechanism of erythropoiesis through erythropoietin is intact in the last part of intrauterine life (Halvorsen, 1963). Normal newborn infants have slightly elevated plasma erythropoietin levels in cord blood, while severely anaemic erythroblastotic infants may have markedly elevated erythropoietin levels (Halvorsen, 1963).

It has previously been reported that erythropoietin is excreted in the urine of anaemic children (Piliero *et al.*, 1956). Whether or not this is true also in the foetus and the newborn infant is unknown, but may be suspected. Although the formation and resorption of the amniotic fluid are only partially understood, there is general agreement that the foetus passes urine into the amniotic fluid. The volume of urine passed and the part this excretion plays in the amniotic fluid balance is, however, unknown.

The prenatal diagnosis of the severity of erythroblastosis has been increasingly important since it has been suggested that induction of labour before term may be essential in reducing the mortality rate of erythroblastosis. Besides the maternal anti-Rh titres, the bilirubin content of the amniotic fluid has been proposed as a useful guide (Walker, 1957), but fails in many cases. It will therefore be of importance if other indices can supplement the present tests used in the prenatal diagnosis of erythroblastosis.

These facts and considerations raise the following questions: Do anaemic erythroblastotic newborn infants excrete erythropoietin in the urine? Does erythropoietin occur in the amniotic fluid in Rh-immunized pregnant women? If erythropoietin is transferred to the amniotic fluid, is it excreted with the foetal urine or transferred through the foetal membranes? Does the amount of erythropoietin in the amniotic fluid have any relationship to the anaemia of the foetus and the severity of erythroblastosis?

MATERIAL AND METHODS

Amniotic fluid was collected from normal and Rh-immunized pregnant women either by trans-abdominal amniocentesis before term or by membrane rupture during delivery or during caesarean section. Cord blood and blood withdrawn during the first part

of exchange transfusions from erythroblastotic infants were investigated, and in a few cases the first urine passed after birth was collected and tested for erythropoietin content. Blood withdrawn shortly before birth from one of the mothers of the erythroblastotic infants was also investigated.

The erythropoietin levels in the body fluids were determined by the use of the 72-hour ^{59}Fe erythrocyte uptake* in transfusion-induced polycythaemic mice (Rosse *et al.*, 1962). As only erythropoietin increases erythropoiesis in the polycythaemic mouse, any increase in ^{59}Fe erythrocyte uptake above the controls indicates the presence of erythropoietin in the material injected. Plasma was given subcutaneously in daily doses of 0.5 ml. on two consecutive days, and urine and amniotic fluid subcutaneously in doses of 1 ml. daily for two days. A well-type scintillation counter (SC-51 Autoscaler, Tracerlab. Inc., Boston, Mass., U.S.A.) was used for counting.

RESULTS

The results of investigations on infants with severe erythroblastosis (cord haemoglobin <13.4 g./100 ml.) are presented in this preliminary report. The clinical data on these infants are shown in Table I. Table II

TABLE I.—Clinical Data on Erythroblastotic Infants

Infant	Anti-Rh Titre		Cord Hb (g.)	Gestation Age (Weeks)	No. of Exchange Transfusions	Outcome
	Coombs	Albumin				
Ol	1/1024	1/2048	?	38	0	Died
La	1/1024	1/1024	7.2	36	1	"
Gu	1/512	1/512	8.2	36	4	Survived
Bo	1/256	1/256	13.4	36	2	"
Pe	1/256	1/256	10.5*	39	2	"
Ha	1/512	1/1024	3.5	38	2	"
Be	1/256	1/256	4.4	36	2	"

* Capillary haemoglobin.

TABLE II.— ^{59}Fe % Erythrocyte Uptake

	Infant	Amniotic Fluid	Cord Plasma	Infant Urine	Mother's Plasma
Rh+ mothers	Da	1.2 ± 0.6 (5)			
Normal infants	Ho	0.9 ± 0.2 (3)			
	Lu	0.5 ± 0.1 (4)			
Rh- mothers	Ol	$19.2 \pm 0.9^*$ (4)			
Anaemic infants	La	1.8 ± 1.2 (4)	0.4 ± 0.1 (4)	0.8 ± 0.2 (3)	
	Gu	2.6 ± 2.1 (3)	15.2 ± 3.7 (4)		
	Bo	2.9 ± 1.8 (4)			
	Pe	34.2 ± 3.8 (5)	26.8 ± 3.3 (6)	26.6 (1)	
	Ha	14.1 ± 2.4 (5)	19.3 ± 2.9 (5)	22.8 ± 3.6 (2)	0.8 ± 0.2 (4)
	Be	4.1 ± 0.6 (3)	3.5 ± 0.2 (5)	2.6 ± 0.4 (7)	
Saline-injected mice		0.67 ± 0.09 (19)			

*0.5 ml. $\times 2$.

The ^{59}Fe % erythrocyte uptake in transfusion-induced polycythaemic mice injected with amniotic fluid from normal pregnant women (mothers Rh positive) and from Rh-immunized pregnant women, with cord plasma, infant urine, mother's plasma, and normal saline. Numbers in parentheses indicate the number of recipient mice.

shows the control material, polycythaemic mice injected with normal saline and with amniotic fluid from Rh-positive mothers, and the results of the investigations on the erythroblastotic infants. Table III illustrates the possible use of the erythropoietin levels in the amniotic fluid as a diagnostic test in pregnant women who have previously given birth to severely diseased erythroblastotic infants and who have heterozygous husbands.

*In a few cases the 48-hour uptake was used.

TABLE III.—Severe Erythroblastosis in Previous Pregnancies. Fathers Heterozygous

Infant	Anti-Rh Titre		Rh Type Infant	Cord Hb (g.)	^{59}Fe % Uptake	
	Coombs	Albumin			Amniotic Fluid	Cord Plasma
Fo	1/128	1/128	—	15.7	$0.5 \pm 0.3^*$ (2)	1.0 ± 0.2 (5)
Be	1/256	1/256	+	4.4	0.9 ± 0.3 (3)	3.5 ± 0.2 (5)
					$4.1 \pm 0.6^*$ (5)	

* Amniotic fluid collected by amniocentesis before term. Numbers in parentheses indicate number of recipient mice.

DISCUSSION

Although the presented data are few they show that the newborn infant may excrete erythropoietin in the preformed urine. They further clearly indicate that erythropoietin may be transferred to the amniotic fluid and in some cases in large amounts. The route of transfer is at least partly through the foetal urine, but it seems unlikely that the high levels of erythropoietin found in some cases may be sustained if foetal urine is the only source of erythropoietin. The possibility of transfer through the foetal membranes may therefore be taken into consideration, although it is generally believed that erythropoietin is non-dialysable.

The high levels of erythropoietin in the amniotic fluid have been found only in patients who have a severe erythroblastosis with grave anaemia. Thus the presented data suggest that the erythropoietin level in the amniotic fluid may be an indicator of the severity of anaemia in the foetus. As the controls did not have any marked elevation of erythropoietin one may postulate that a high level of erythropoietin in the amniotic fluid in Rh-immunized pregnant women indicates a severe degree of erythroblastosis.

Slightly elevated erythropoietin levels in the amniotic fluid may, however, be found in cases of severe erythroblastosis (Table II, Infants La and Gu), and it is possible that only definitely elevated erythropoietin levels may be given significance. This is in accordance with findings in anaemic adults where sometimes low levels of plasma erythropoietin are found even in cases with low haemoglobin levels. The clinical significance and usefulness of amniotic erythropoietin levels in the prenatal diagnosis of erythroblastosis must await further investigations on a larger series of pregnant women at risk of bearing erythroblastotic infants. Increased erythropoietin production is the response to all types of hypoxia, not only anaemia, and is therefore not a specific test for erythroblastosis. In Rh-immunized pregnant women one must, however, be allowed to take elevated erythropoietin levels in the amniotic fluid as a sign of anaemia, although placental dysfunction may be an additional cause of hypoxia. As normal newborn infants may have moderately elevated erythropoietin levels in cord plasma (Halvorsen, 1963), it may be expected that moderately or slightly elevated erythropoietin levels may be found in the amniotic fluid from normal pregnancies.

The observation of erythropoietin in the amniotic fluid may also be useful in the studies on the formation of some of the constituents of the amniotic fluid in the human. In the described situation of Rh-immunized pregnancies there is a high level of a specific protein (erythropoietin) in the foetal plasma and urine and in the amniotic fluid, while the amount in the mother's plasma is negligible. This finding points to the foetal

urine also as a source of some of the protein content of the amniotic fluid.

SUMMARY

The erythropoietin content of amniotic fluid from Rh-immunized pregnant women and of cord blood and foetal urine from anaemic erythroblastotic infants has been investigated by use of transfusion-induced polycythaemic mice as recipients. High levels of erythropoietin have been found in the amniotic fluid in pregnancies with severely anaemic fetuses, and they seem to be correlated with those in cord blood and foetal urine. It is suggested that estimations of the erythropoietin levels in the amniotic fluid may be of help in the prenatal diagnosis of erythroblastosis.

SVERRE HALVORSEN, M.D.

PER HAAVARDSHOLM FINNE, M.D.

Children's Department,
Paediatric Research Laboratory and
Department of Obstetrics and Gynaecology,
Rikshospitalet, Oslo, Norway.

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Medical Memoranda

Fibrosarcoma of Left Atrium

Primary malignant tumours of the heart are indeed rare. There is no constancy of the clinical picture to make the diagnosis certain during life. Most of the cases are diagnosed only after death. We report here one such case.

CASE REPORT

A man aged 40 was admitted to hospital with a three-months history of pain in the left side of the chest, backache, and progressive shortness of breath. Four weeks before admission he coughed up blood on two occasions. There was no history of nocturnal dyspnoea. He was sent by his doctor to the mass x-ray unit for a chest film and was then referred to the chest clinic with a diagnosis of inflammatory lesion in the left lung. He made an apparent recovery with a four-day course of demethylchlortetracycline. A few days later he became more dyspnoeic and was admitted to the hospital on December 6, 1961.

On admission he was dyspnoeic at rest, but not cyanosed; temperature 99° F. (37.2° C.); pulse 112 per minute, rhythm regular. Examination of the chest revealed signs of fluid at the left base and on the right side coarse crepitations were heard. Clinically, the heart was not enlarged. Jugular venous pressure was normal. No increased pulsation could be seen or felt at the left sternal edge. The pulmonary second sound was accentuated; no murmur was heard; B.P. was 140/70; the liver and spleen were not palpable; central nervous system showed no appreciable disease.

Investigations.—Haemoglobin 79%; W.B.C. 15,600/c.mm. (92% polymorphs); E.S.R. 5 mm./hr. (Westergren); P.C.V. 36%; M.C.H.C. 32.5%. Liver-function tests were normal. Urine N.A.D. Sputum showed no significant organisms. The E.C.G. unfortunately was not done. A radiograph taken at the chest clinic on November 8, 1961, showed an enlarged left hilar shadow with unilateral congestion on the left side (Fig. 1). A radiograph on December 7 showed an effusion at the left base with marked congestion on the right (Fig. 2).

On December 7 left pleural aspiration was done and 400 ml. of haemorrhagic fluid was taken off. Cytology showed a large number of neoplastic cells, the origin of which was uncertain. At 6.30 p.m. he coughed up a small amount of bright red blood, and became cyanosed and more dyspnoeic. At midnight he collapsed with a massive haemoptysis and died instantaneously.

The salient findings at necropsy were as follows. The lungs were oedematous and the heart was of normal size, weighing 278 g. A softish white tumour mass measuring 7 by 4 by 3 cm. was protruding from the auricular wall below and anterior to the left pulmonary vein into the lumen

FIG. 1

FIG. 2