Four patients developed a positive sodium balance during peritoneal dialysis. In one patient this had reverted to a negative balance by the end of the dialysis. The nature of the sodium balance depended partly on the amount of fluid which was removed (Figs. 2–4) and partly on the initial serum sodium level. Where only a small amount of fluid was removed from a patient with a low serum sodium, a positive sodium balance developed. Two patients are omitted from Figs. 2–4. In one a positive fluid balance occurred because of inadequate drainage, and this was responsible for the sodium uptake of 453 mEq, and in the other fluid was removed more rapidly than in the rest of the series (450 ml. per exchange), with a rapidly developing negative sodium balance in excess of 400 mEq.

## Discussion

Urea and electrolytes diffuse along the concentration gradient between fluid within the peritoneal cavity and the serum (Boen, 1961). This process continues until equilibrium is reached after 90 to 120 minutes. During this period the difference in osmolalities determines the volume of fluid absorbed (Shear *et al.*, 1965). The latter workers have shown that subsequently a phase of isotonic absorption occurs when 29.7–39.3 ml. of fluid is absorbed per hour. This latter phase is usually unimportant in peritoneal dialysis, where fluid is not allowed to remain in the peritoneal cavity longer than 45 minutes.

The present study was undertaken to quantify the sodium transfer during the initial period of equilibrium and to determine whether such movement would be physiologically important. The results suggest that significant amounts of sodium are absorbed when a hyponatraemic patient undergoes peritoneal dialysis in which only small amounts of fluid are removed. This may account for the occasional episode of pulmonary oedema during peritoneal dialysis which, as in the case described, may be fatal.

How can this complication be avoided ? One answer would be to lower the sodium concentration of the fluid administered. This would necessitate the preparation of several types of dialysis fluid, containing different concentrations of sodium, making the management of peritoneal dialysis a much more complicated operation. Alternatively, one could reproduce the situation seen in the majority of cases in this series, and withdraw large volumes of fluid from the patient by means of the dialysis. The present series shows that this keeps the patient in negative sodium balance.

Hypertonic dialysis fluid may remove greater quantities of urea than isotonic fluid. This is not merely due to the increased amount of fluid withdrawn, but is also partly attributable to the phenomenon known as "solvent drag." When a large volume of fluid passes through a porous membrane, solute tends to move with it, even against a concentration gradient. It has been postulated that solute particles (in this case urea) are entrained in the solvent stream (Henderson, 1966). In order to determine whether sodium could be withdrawn in such a way by using a hypertonic fluid, peritoneal dialysis fluid containing 6.36 g. of glucose per 100 ml. was administered intermittently and the sodium concentration after each such exchange measured. This failed to produce any increase in the sodium concentration of the dialysis fluid removed (see Table).

*Effect of Varying Glucose Concentration on Sodium Concentration of Fluid Drained from a Peritoneal Dialysis*

| | | | | | |
|---|---|---|---|---|---|
| Dialysis fluid glucose (g./100 ml.) .. | 1·36 | 1·36 | 6·36 | 6·36 | 1·36 |
| Sodium concentration of effluent (mEq/l.) .. .. .. .. | 125 | 126 | 123 | 122 | 125 |

Nevertheless, the present series of cases indicates that if a patient on peritoneal dialysis is kept in a negative fluid balance of several litres there is little danger of excessive sodium absorption.

## Summary

In hyponatraemic patients there is a marked gradient between concentration of sodium in the peritoneal dialysis fluid and the serum. In order to establish whether this causes a positive sodium balance the sodium uptake was measured during dialysis. In 4 out of 13 dialyses there was a positive sodium balance, in one case reaching 400 mEq, despite a negative fluid balance in three of these cases. It is suggested that this may be responsible for acute heart failure during dialysis.

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# Thalassaemia and Hydrops Foetalis—Family Studies

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Stillbirth or neonatal death associated with severe hydrops foetalis, hypochromic anaemia, erythroblastosis, and large amounts of haemoglobin Bart's was first described by Lie-Injo and Jo (1960). In subsequent studies Lie-Injo (1962) and Lie-Injo, Lie, Ager, and Lehmann (1962) reported that the parents of such infants showed haematological changes consistent with $\alpha$-thalassaemia trait, and they thought that the hydropic babies were homozygous for $\alpha$-thalassaemia. Reports by Diamond, Cotgrove, and Parker (1965) and Pootrakul, Wasi, and Na-Nakorn (1966) lend support to this view.

In Hong Kong haematological studies have been made on the families of seven Chinese babies with severe hydrops foetalis associated with over 75% of haemoglobin Bart's, and, while there was evidence that five were homozygous for $\alpha$-thalassaemia, in two a possible interaction between $\alpha$- and $\beta$-thalassaemia was suggested. The purpose of this communication is to report these studies.

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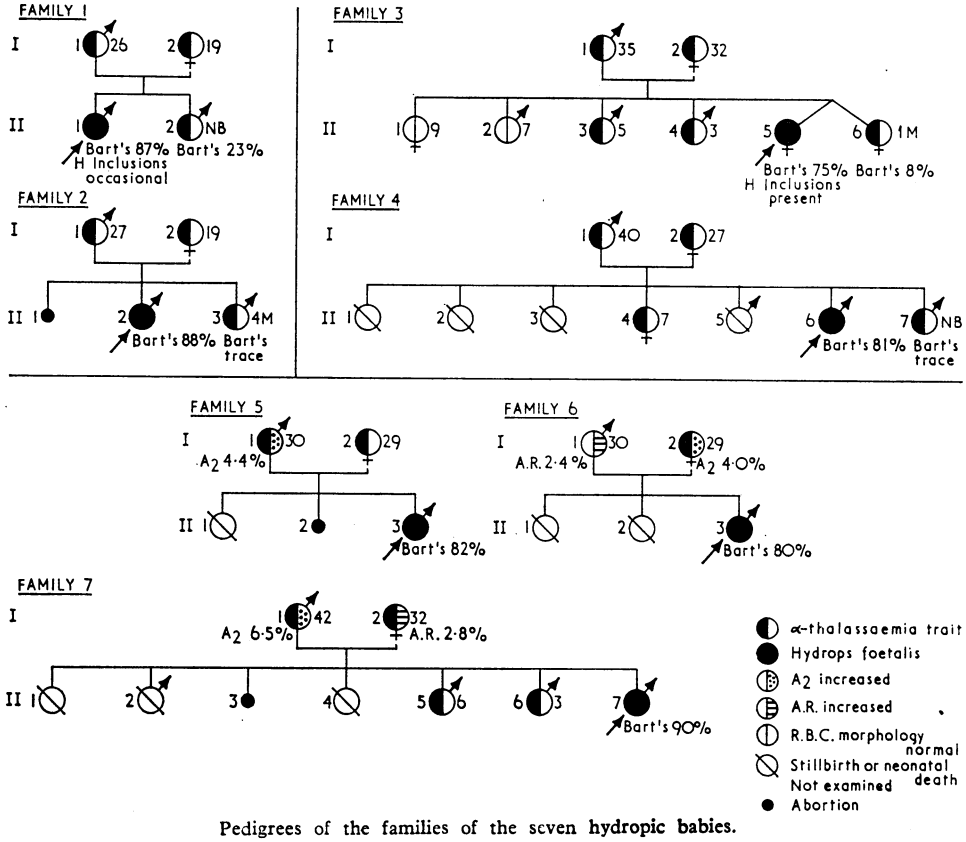
## Material and Methods

All the subjects studied were Chinese and comprised seven stillborn babies with severe hydrops foetalis and over 75% haemoglobin Bart's, and their parents and living sibs. In the case of the hydropic babies, whose periods of gestation had varied from 32 to 38 weeks, cord or cardiac blood was examined. Iron deficiency was excluded in the parents of six of the seven families and the living sibs in Family 3 by the finding of normal serum iron levels; in the remainder the haematological studies were carried out after at least one month of oral iron therapy. The haematological values of the mothers were those obtained after delivery. All parents were Rh-positive.

Standard haematological methods were used throughout. Red cell osmotic fragility was determined by the method described by Flatz, Pik, and Sringam (1965). The direct Coombs test was performed according to Dacie and Lewis (1963). Alkali-resistant haemoglobin was estimated (Singer, Chernoff, and Singer, 1951), and the amounts of haemoglobin A, $A_2$, and Bart's were determined by starch block electrophoresis at *p*H 8.6 (Kunkel, Ceppellini, Müller-Eberhard, and Wolf, 1957). In 56 control subjects the haemoglobin F levels were invariably less than 2% and the haemoglobin $A_2$ levels varied from 1.6 to 3.2%. Starch-gel electrophoresis at *p*H 7.0 was carried out according to Huehns, Flynn, Butler, and Shooter (1960) and at *p*H 8.6 according to Smithies (1959). Red cells were incubated with 1% brilliant cresyl blue at 37° C. for 30 minutes to detect haemoglobin H inclusions (Dittman, Haut, Wintrobe, and Cartwright, 1960), and at least 5,000 red cells were examined.

## Results

In the seven hydropic babies the necropsy findings were similar to those in the cases reported by Lie-Injo (1962). The haemoglobin levels varied from 3.3 to 10.0 (mean 7.4, S.D. 2.3) g./100 ml., and the blood smears showed markedly hypochromic red cells with anisopoikilocytosis, target formation, polychromasia, and numerous normoblasts. In only two instances (Families 1 and 3) were occasional red cells with haemoglobin H inclusions found. The amount of haemoglobin Bart's varied from 75 to 90% of the total haemoglobin (see Family Trees). The remaining 10 to 25% consisted of haemoglobin which migrated like haemoglobin A on starch block electrophoresis at *p*H 8.6 but was not seen in the position of haemoglobin A on starch-gel electrophoresis at *p*H 7.0. This fraction is being further studied by Dr. E. R. Huehns, of University College Hospital, London, and he has confirmed that the main haemoglobin fraction of the hydropic baby of Family 5 is haemoglobin Bart's. The alkali-resistant haemoglobin levels varied from 35 to 77% (mean 59.7%, S.D. 14.9%), and haemoglobin $A_2$ was not found in any. The direct Coombs test was negative in all, and three had the same ABO blood group as their mothers.




Pedigrees of the families of the seven hydropic babies.

The haemoglobin levels in the seven fathers varied from 13.0 to 15.2 (mean 13.8, S.D. 0.7) g./100 ml., and in the seven mothers from 8.5 to 12.6 (mean 10.9, S.D. 1.1) g./100 ml. The red cells were hypochromic and showed decreased osmotic fragility in all except the father in Family 6.

The haemoglobin levels in the eight living male sibs varied from 9.8 to 12.5 (mean 11.7, S.D. 0.7) g./100 ml., and in the three living female sibs from 5.4 (a twin) to 13.0 (mean 10.2, S.D. 3.0) g./100 ml. The red cells were hypochromic and showed decreased osmotic fragility in all except two (Family 3, II 1 and 2).

Other details are set out in the accompanying Fig., in which only abnormal values of haemoglobin F and $A_2$ are shown. Subjects with normal or slightly decreased haemoglobin levels, hypochromic red cells, decreased red cell osmotic fragility, and normal amounts of haemoglobin F and $A_2$ are thought to be carriers of the α-thalassaemia trait (Weatherall, 1965). In four living sibs, all 4 months or younger, relatively small amounts of haemoglobin Bart's were found. No haemoglobin H inclusions were shown in the red cells of the parents or living sibs.

It will be seen that two parents (Family 6 I 1, Family 7 I 2) had slight but significantly raised levels of alkali-resistant haemoglobin which was thought to be haemoglobin F, as haemoglobin Bart's was not shown on starch-gel electrophoresis at *p*H 7.0. With these two exceptions, haemoglobin F levels were normal in the parents and in the seven living sibs aged 3 years or older, varying from 0.6 to 1.8% (mean 1.1%, S.D. 0.3%). In three parents (Family 5 I 1, Family 6 I 2, and Family 7 I 1) the haemoglobin $A_2$ levels were above normal, being 4.4, 4.0, and 6.5% respectively, while in the remaining parents and seven living sibs aged 3 years and older haemoglobin $A_2$ levels were normal, varying from 1.8 to 3.0% (mean 2.4%, S.D. 0.3%).

In Family 3, subjects II 5 and 6 were binovular twins, and subjects II 1 and 2 were haematologically normal. Sibs not studied included three neonatal deaths from unknown cause occurring two to four weeks after birth and one stillborn baby with hydrops foetalis in Family 4; one stillbirth in Family 5; two stillbirths with hydrops foetalis in Family 6; and two stillbirths and one neonatal death from unknown cause in Family 7.

## Discussion

In Families 1 to 4 inclusive both parents showed haematological changes compatible with $\alpha$-thalassaemia trait. Further, the living infants had small amounts of haemoglobin Bart's in addition to a mild thalassaemic blood picture. These findings are similar to those reported by Lie-Injo (1962) and Lie-Injo *et al.* (1962), and are consistent with the hydropic babies being homozygous for an $\alpha$-thalassaemia gene. The relatively high level of haemoglobin Bart's of 23% in Subject II 2 of Family 1 is of particular interest, but unfortunately he has been lost to follow-up.

The finding in Families 5, 6, and 7 of three parents with high haemoglobin $A_2$ levels and two with increased haemoglobin F levels indicates the presence of $\beta$-thalassaemia trait and has not been previously reported among parents of similar hydropic babies. Since the combination of $\alpha$-thalassaemia with either high or normal haemoglobin $A_2$ $\beta$-thalassaemia results in a mild thalassaemia only (Weatherall, 1965), it is unlikely that the hydrops foetalis was the result of double heterozygosity for $\alpha$- and $\beta$-thalassaemia. The hydropic babies may have been, like those in Families 1 to 4, homozygous for $\alpha$-thalassaemia, in which case the parents with the $\beta$-thalassaemia trait were by coincidence doubly heterozygous for $\alpha$- and $\beta$-thalassaemia. However, the finding of a $\beta$-thalassaemia trait in 5 of 14 parents appears to be more than can be accounted for by chance. Further, the obstetrical histories of the mothers in Families 5–7 appear to be particularly bad, for in 13 pregnancies there were six stillbirths and two abortions in addition to the three hydropic babies (see Fig.). It is not clear what part the $\beta$-thalassaemia gene in the father of Family 5 had to play in the production of hydrops foetalis. However, in view of the report by Zuelzer, Robinson, and Booker (1961) that thalassaemia major may result when one parent has a high haemoglobin $A_2$ $\beta$-thalassaemia and the other a normal haemoglobin $A_2$, high haemoglobin F (4.3%) $\beta$-thalassaemia it is possible that the hydropic babies in Families 6 and 7 were the result of interaction between two $\beta$-thalassaemia genes and an $\alpha$-thalassaemia gene, which, in the homozygous state, gives rise to hydrops foetalis. This hypothesis would be supported by the finding among living sibs either of increased levels of haemoglobin $A_2$ or F similar to those in the parents or of $\beta$-thalassaemia major, but unfortunately in the three families concerned out of 13 pregnancies there were only two living children.

The nature of this $\alpha$-thalassaemia gene is not known, but it would appear to lead to a marked suppression of $\alpha$-chain synthesis in the homozygous state. It is probably different from the $\alpha$-thalassaemia gene in Negroes (Weatherall, 1965), as similar hydropic babies have not been reported among that race. It is also probably different from the "mild" $\alpha$-thalassaemia gene of haemoglobin H disease (Huehns, 1965), which is usually not associated with red cell hypochromia, and, furthermore, haemoglobin H disease and hydropic babies with over 75% haemoglobin Bart's appear to occur in different families. It may be identical with the "severe" $\alpha$-thalassaemia gene of haemoglobin H disease (Huehns, 1965). So far this severe $\alpha$-thalassaemia gene has been reported only in Chinese (Lie-Injo, 1962), in Thais (Pootrakul *et al.*, 1966), and in Greek Cypriots (Diamond *et al.*, 1965), in all of whom haemoglobin H disease has also been encountered (Weatherall, 1965).

ADDENDUM.—Since the completion of this paper Kan *et al.* (1967) have reported a case of hydrops foetalis with large amounts of haemoglobin Bart's. The patient's father had an increased level of haemoglobin $A_2$.

## Summary and Conclusions

Haemoglobin studies were carried out on the families of seven Chinese stillborn infants with severe hydrops foetalis and over 75% haemoglobin Bart's. Rh and ABO incompatibility were excluded.

There was evidence that five of the seven cases were the result of the homozygous state for $\alpha$-thalassaemia. In the remaining two there was the possibility of interaction between an $\alpha$-thalassaemia gene and a variety of $\beta$-thalassaemia major.

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