

TOXAEMIA OF PREGNANCY IN SHEEP*

by

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A syndrome variously called toxæmia of pregnancy, twin lamb disease or ketosis of pregnancy, has been known to occur in pregnant sheep during the latter part of gestation. Clinically this syndrome is characterised by anorexia, disturbances of central nervous system and of vision, oliguria, stupor, convulsion and coma. Blood and urine abnormalities are stated to be: proteinuria, nitrogen retention, ketonaemia, hypoglycaemia, and low plasma CO₂ content. The disease is very often fulminating and occurs more frequently in well nourished pregnant ewes with multiple foetuses which are subjected to a sudden reduction in nourishment. Death of the animal occurs unless the pregnancy is terminated either spontaneously or by caesarean

section. Parry and Taylor have studied renal function in sheep with experimentally induced and spontaneous toxæmia, using the single injection of creatinine and para-amino-hippurate (P.A.H.) clearance. They found a markedly reduced renal plasma flow and glomerular filtration rate in both the conditions.

The present studies were aimed at reproducing the above syndrome by experimentally induced toxæmia in pregnant sheep and investigating the renal haemodynamics and excretion of electrolytes in the same pregnant animal prior to and following the production of toxæmia.

Method

Twenty Suffolk Hampshire cross bred ewes of approximately the same period of gestation were selected for the study. They were confined in the same place, and their basic diet consisted of good quality alfalfa. Control studies were carried out on 10 of the 20 pregnant animals. Thereafter these animals, together with the other pregnant ewes, were subjected to experimental induction of toxæmia. This procedure consisted essentially of increasing the plane of nutrition by feeding the animals with high grade alfalfa and by incorporating

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barley into the ration. During this time which lasted for about 3 weeks, the animals were confined to a small room to prevent undue exercise. Abrupt caloric restriction was then imposed on the animals by substituting straw for the alfalfa mixture.

Of the 20 animals, 8 developed toxæmia within 5 days after caloric restriction was imposed. Four of these 8 animals died before any study could be initiated. Complete renal function studies were obtained from the remaining 4 toxæmic ewes. The diagnosis of toxæmia was made on the basis of clinical signs supplemented by autopsy findings.

The following changes were observed in the affected animals. First stage, abnormal standing posture with asymmetrical head rotation maintained for many hours without movement, stumbling against watering troughs. Abnormal response to an obstruction. Unusual sitting posture maintained on human approach. There was a marked salivary discharge and the animal looked apathetic. Next stage, the animal developed spasticity of limbs and trunk, although the sheep was aware of human approach; it remained immobilised by the rigidity of its limbs. The spasticity and rigidity increased; the animal no longer could maintain the erect position; the eyes remained wide open although bilateral blindness was common to all animals. Finally some of them (3 and 17) developed clonic convulsions immediately, prior to the renal function tests. These convulsions, when observed carefully, were exactly iden-

tical to human eclamptic fits.

One animal (ewe No. 4) was studied early in the disease and later when the toxæmia became more severe.

The studies were all performed in unanaesthetised animals which were maintained in the prone position by keeping them suspended in a hammock with the limbs extended through the openings in the canvas. After the animal was suspended in the hammock, a Foley catheter was inserted into the bladder which was completely emptied. Control blood samples were obtained for assay of glucose CO_2 and eosinophils. Thereafter a priming dose of inulin, P.A.H. and creatinine, calculated for each animal according to body weight, was injected over a period of 2 minutes through a polyethylene tube inserted into the external jugular vein. This was followed by a maintenance solution given by continuous drip and aimed at maintaining a plasma level of approximately 200 mgm/L of inulin, 30 mgm/L of P.A.H. and 10 to 30 mgm/L of creatinine. An equilibration period of 30-45 minutes was followed, after which 3-5 30-minute collections were obtained from each animal. Blood samples were withdrawn at the midpoint of each collection period. Completeness of urine collection was achieved by injecting air into the bladder. A loop of carotid artery was exteriorised under local anaesthesia and mean arterial pressure was measured with a mercury manometer.

Inulin, P.A.H., creatinine, Na, K, C1, glucose, CO_2 , eosinophil and haematocrit were analysed.

Results

Urine flow and solute excretion— In the normally pregnant sheep, urine flow varied from 3.5 to 11.5 ml/min. and solute excretion varied from 607 to 1930 u Osm/min.

The 4 sheep which developed toxæmia excreted urine at a rate of 1.6 to 3 ml/min. and their solute excretion varied from 380 to 690 u Osm/min. These values were significantly lower than the normal group values. Sheep No. 4 which was studied three times excreted urine at a rate of 8.5 ml/min. when normal, 3.4 ml/min. in early toxæmia, and 2.4 ml/min. when toxæmia became severe.

Glomerular filtration rate and renal plasma flow — In the normally pregnant sheep, glomerular filtration rate (G.F.R.) varied from 1.4 to 2.1 ml/Kg/min. and renal plasma flow (R.P.F.) varied from 5 to 12.7 ml/Kg/min. In the sheep which developed toxæmia, G.F.R. was never higher than 1 ml/Kg/min. Even in the sheep with early toxæmia, G.F.R. was still far below the values obtained from the same animal before toxæmia was induced. Likewise, R.P.F. in the toxæmic animals was considerably below those of normally pregnant animals and was statistically highly significant ($P < .01$).

Mean arterial pressure — Mean carotid pressure in the normally pregnant sheep varied from 110 to 128 mm. of Hg. It did not change following the induction of toxæmia.

Plasma and urine electrolytes— During the normal pregnant stage, plasma Na varied between 144 and 154 mEq/L and plasma Cl, between 103 and 109 mEq/L and plasma K, between 3.6 and 5.8 mEq/L. In the toxæmic phase plasma Na rose in each instance, whereas Cl and K remained within the normal range.

The excretion of electrolytes showed a marked variation from animal to animal and in the same animal from one collection to the other, both in normal and toxæmic stages. In general, during normal pregnancy the animals excreted significantly and consistently more K than Na.

There were no significant changes in blood glucose, CO_2 , eosinophils and packed cell volume.

Discussion

From the present data it is clearly shown that a renal disturbance is associated with toxæmia of pregnancy in the sheep. The decrease in urine flow, glomerular filtration rate and renal plasma flow were of same magnitude as were found by some other authors (Parry & Taylor), although the technique followed by them were somewhat different from that of ours. These findings indicate the presence of severe renal ischæmia involving the glomeruli. But since no specific renal pathologic lesion could be demonstrated on autopsy, it appears likely that the disturbance is largely functional.

In view of these findings, it is interesting to speculate about the similarity between the toxæmia of the sheep and that of human.

Similarity Between Human and Sheep Toxaemia

Human	Sheep
1. It occurs sporadically during the latter part of gestation.	Same
2. More frequent in short, obese persons.	Same
3. More frequent with large, or multiple foetuses.	Same
4. Prominent nervous system and visual disturbances, convulsions, coma.	Same
5. Oliguria and proteinuria.	Same
6. Oedema.	Not as frequent
7. Hypertension.	Not present
8. Decreased GFR and RPF.	Same
9. No specific pathology findings.	Same
10. Improvement after delivery.	Same

The present data on renal function add more to the similarity between the two diseases.

The degree of renal ischaemia and decreased filtration rate found in toxaemic sheep was somewhat more marked than that found in women with toxaemia of pregnancy. But this difference could have been due to the more fulminating nature of the disease in the sheep. In one of the sheep, which could be studied during the early toxaemia, the changes in the renal function were found to be closely similar to those of pregnant women.

One striking difference between the two diseases is the lack of hypertension in the toxaemia of sheep. Normal blood pressure was found consistently by Parry and Taylor in spontaneously occurring and experimentally induced toxaemia, regardless of the degree of the disease. Our

findings are in agreement with those of these authors. It is difficult to explain the absence of hypertension in the presence of a marked renal ischaemia such as observed in these animals. Goldblatt and his co-workers were able to produce experimental renal hypertension in the non-pregnant sheep. This could seem to rule out the problem of species difference. A second possibility is that pregnant sheep respond differently from the non-pregnant ones to renal ischaemia or that they may elaborate some antihypertensive substances.

Little can be said about the excretion of electrolytes in either the normal or toxaemic sheep. Despite the effort which was made to keep the diet of these animals constant, a marked variation in electrolyte excretion occurred. Whether the variation was due to a difference in the electrolyte content of the various batches of alfalfa, barley and hay or to inherent properties of the sheep cannot be asserted from these studies, since there are no data available in regard to water and electrolyte excretion in this animal with which ours could be compared. Studies are now in progress to investigate sodium and water metabolism in these animals with radioactive isotopes.

Although it would be difficult to interpret the high levels of plasma sodium observed in the toxaemic animals in view of the irregular behaviour of electrolyte excretion, it is reasonable to assume that these levels reflect sodium retention. Eventually, many studies are necessary to elucidate these various points.

Summary ✓

1. Method of induction of toxæmia in sheep is shown.
2. Renal haemodynamics and excretion of water were investigated in pregnant sheep before and after the experimental induction of toxæmia.
3. A marked decrease in urine flow, renal plasma flow, and glomerular filtration rate was found in the animal which developed toxæmia.
4. Evidence thus obtained support the similarity between toxæmia in human and in the sheep.

References

1. Assali, N. S., Kaplan, S. A., Fomon, S. J., and Douglass, R. A., Jr. *J. Clin. Invest.* 32: 44, 1953.
2. Assali, N. S., Louis Holm and Donald L. Hutchinson: *Circulation Research*, Vol. VI, No. 4, July 1958, U.S.A.
3. Parry H. B.: In *Toxaemia of Pregnancy: Human and Veterinary*. A Ciba Foundation Symposium. The Blakiston Co., 1950, pp. 8-93.
4. Parry, H. B.: *J. Physiol.* 126; 10p, 1954.
5. Parry H. B., and Taylor W. H.: *J. Physiol.* 131: 383, 1596.
6. Parry, H. B., and Taylor, W. H.: *J. Physiol.* 127: 54p, 1955.
7. Phillipson A. T.: In *Toxaemias of Pregnancy: Human and Veterinary*. A Ciba Foundation Symposium. The Blakiston Co., 1950, p. 94.
8. Smith, H. W.: *The Kidney Structure and Function in Health and Disease*. New York, Oxford University Press, 1951, p. 57.