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Domsiekte or Pregnancy Disease in Sheep—I. A Review of the Literature.

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Introduction.

Pregnancy diseases or Domsiekte, as it is called locally, has been known for many years and has been reported from practically every part of the world. There is an enormous mass of literature available on the subject and the object of this paper is to catalogue and evaluate the facts and opinions expressed. A large proportion of the articles published give little more than a description of the symptoms and pathological findings. This can be understood when it is remembered that outbreaks appear spasmodically and are not usually of long duration. Furthermore, prior to 1934, there is apparently no record of successful production of the disease by experimental means. The literature, therefore, consists largely of reports on outbreaks and speculation as to possible causes. A careful study of the recorded facts, however, reveals that much useful knowledge has been gained and it is hoped that this review will prove of value to our fellow workers in other countries.

Synonyms.

Owing to its widespread occurrence and the ignorance of its true aetiology, the disease has acquired numerous designations. The following are listed for the sake of interest, Acute Parenchymatous hepatitis, Acetonaemia, Acute partum eclampsia, Acidosis, Domsiekte, Ewe-paralysis, Eclampsia, Fatty infiltration of

the liver, Ketonaemia, Ketosis, Lambing paralysis, Lambing sickness, Ophaalziekte, Pregnancy disease, Preparturient paralysis, Parturient paresis, Pregnancy toxaemia, Parturient fever, Sleepy sickness, Stercoraemia, Tremblings, Twin tremblings, Uterine acetonaemia and White liver.

It will be seen that many of these names are unsuitable, referring as they do to only one of many clinical manifestations of the disease. The word " paralysis " is entirely misplaced in describing the symptoms of typical domsiekte.

It is considered that, in order to avoid confusion, many of these names should be discarded. The Afrikaans name " domsiekte ", which translated literally means " stupid sickness " is very descriptive. The nearest English equivalent listed above would be " sleepy sickness ". Although pregnancy is not an absolute essential to the development of the condition, the disease nearly always makes its appearance in heavily pregnant ewes and therefore the commonly used term " pregnancy disease " is appropriate. Such terms as Ketonaemia and acetonaemia are not specific as the changes they imply may occur in other conditions, e.g., diabetes.

Occurrence.

The disease appears to be present wherever sheep are kept but the main countries mentioned in the literature are: The United States, Australia, Great Britain, New Zealand, South Africa, Canada, Holland, France, Germany and Austria.

History.

Rosenstein (1874) appears to be one of the earliest workers to describe eclampsia in the human being which he attributed to the infusion of serum into the cerebral tissues. In 1887 Carpenter considered a diminished amount of albumin in the blood to be a predisposing cause to eclampsia. One of the first definite references to Pregnancy Disease in sheep appears to be that of Steele. In 1890 he gave a remarkably accurate description of a disease which he called " Parturient Fever in Sheep ". The symptoms described are without doubt those of domsiekte. Henning (1932) states that the disease domsiekte has been known in the Cape Colony for more than 50 years.

Economic Importance.

Although the disease usually appears in spasmodic outbreaks which do not as a rule cause a high mortality, it can assume the nature of an epidemic. Hull and Dimmock (1935) state that, in Kentucky, pregnancy disease is second only to internal parasites in importance.

Van Rensburg (1931) stated that outbreaks had been assuming alarming proportions in the Karroo areas of the Cape Province since 1926, but actually they have not been of great economic importance in South Africa, except where stud sheep were involved.

There is no doubt, however, that an increasing number of cases have been reported from all over the world in the last two decades and many people attribute this to the more intensified farming conditions which now prevail.

Whatever the economic importance may be, the disease deserves intensive study, if only for the light its elucidation will place on the whole question of the nutrition and metabolism of the ruminant, especially in pregnancy.

Pregnancy Diseases of Other Species.

As it is extremely likely that there are at least common factors in the " pregnancy disease " of different species, short reference will be made to the literature on this category of conditions. The parallel between pregnancy disease in sheep and acetonaemia in the cow would appear to be especially close. This is pointed out by Sampson *et al.* (1933) and by Webster (1935). The latter author states that no similar condition has been seen in goats, pigs or horses. Hudson (1931) describes an acetonaemia, hypoglycaemia and nervous symptoms in cows shortly after calving, all of which closely correspond to the changes seen in domsiekte. It is quite conceivable that the drainage of lactation in the cow would take the place of that of gestation in the sheep in the chain of aetiological factors. Furthermore it must be remembered that cases of domsiekte have been reported after lambing.

The parallel with Milk Fever in the cow does not appear to be so close, especially in that the classical calcium treatment for Milk Fever does not appear to assist in domsiekte (see section on treatment) and also in that the blood calcium during domsiekte is reported to be normal. (See " mineral deficiency ".)

A spontaneous outbreak of " Pregnancy Toxaemia " in rabbits is reported by Greene (1938).

Most of the literature on Eclampsia in the human appears to be devoted to the discussion of renal lesions and malfunction.

It is very difficult to draw any clear-cut comparisons between the pregnancy diseases of the human and those of sheep, but certain statements in the literature on the former appear to be of significance to us. For instance Anderson (1940) suggests a diet low in sodium but with adequate protein and liberal in carbohydrate, as a prohylactic against eclampsia. Bingham (1932) states that toxaemia only developed in his patients with excessive gain in weight. Stander (1929) describes symptoms in human eclampsia which strikingly resemble those of domsiekte. In eclampsia the liver is said to show necrosis which is not the case in domsiekte, where only a fatty infiltration occurs.

Aetiology.

Numerous predisposing and casual factors have been suggested in the literature.

(*a*) *Specific Infection.*

Some of the earlier investigators suspected that the disease might be of an infectious nature and Newsome (1918) supported this view. Glover *et al.* (1919) tried out a vaccine but with very doubtful results. There is no evidence that the condition is infectious and this conception of its aetiology has been dismissed by all recent workers.

(*b*) *Mineral Deficiency.*

(i) *Phosphorus.*—Although van Rensburg (1927) and Mathew (1929) believed that the administration of bonemeal acted as both a prevention and a cure for domsiekte their evidence is not convincing. De Kock (1928) showed that the

blood phosphorus of sheep suffering from domsiekte was normal. The fact that pregnancy disease appears in many countries where there is no evidence of a general aphosphorosis would appear to negative the suggestion that this disease is caused by a phosphorus deficiency. This factor, can, therefore, apparently be dismissed.

(ii) *Calcium.*—One of the earliest theories to gain prevalence was that the disease was closely associated with calcium metabolism. Dimmock (1930) assumed that the acidosis was associated with a decreased blood calcium. Peters and van Slyke (1931), however, are of the opinion that one of the early effects of an acidosis is to wash out the sodium, and to a lesser extent the calcium and magnesium, from the body. They consider that, if there is a decrease in the serum calcium in this disease, which appears doubtful from their studies, it is more likely the result rather than the cause of the diminished alkaline reserve. It is well known that a lowered blood calcium will not affect the buffer minerals.

Maguire (1932) mentions calcium deficiency as a possible cause and claims successful prophylaxis by the administration of a mixed mineral supplement, which was, however, given in crushed oats and wheat bran. The beneficial results can, therefore, not be attributed to the minerals only.

Platt (1931) was not able to produce the disease by feeding sheep on a calcium low ration and limiting their exercise. Sampson and Errington (1933) state that they found a normal calcium figure in a case of acetonaemia in a cow. If the analogy between the two diseases can be taken so far, this would also be an indication that calcium deficiency does not play a rôle in the causation of domsiekte.

Beyers (1933) has established the fact that in affected sheep the blood calcium deficiency can be dismissed.

On the evidence it can, therefore, be said that the question of a calcium deficiency can be dismissed.

(c) *Fractures, Tumours, etc., affecting the Brain.*

In a reference to nervous symptoms in sheep in general, Rushworth (1903), points out that these may be due to fractures or tumours affecting the brain. This is a matter of differential diagnosis in individual cases.

(d) *Pressure on the Ureter.*

Poten (1925) was of the opinion that the condition was due to pressure on the the ureter by the foetus. This may arise as a complication especially when the sheep has been down for some time, but the disease is certainly not a uraemia and affected sheep usually urinate freely.

(e) *Too High Protein Intake.*

Several references are made to " too rich diet " as a cause of the disease (Haworth, 1929, and Style, 1932), but it is doubtful whether the conclusion is justified. Harden (1936) was fairly successful in preventing convulsions in women by increasing the protein intake. Effkemann (1937) carried out an experiment in which five women, in the latter months of pregnancy, were given a diet containing 250 gms. of fat daily, while five other women received 200 gm. of protein. While tests showed an impairment of liver function in the former,

there was no evidence of liver injury in the latter group. It is believed that an increase in protein intake, above the usual level, may be beneficial in normal pregnancy. The authors have definitely shown that a protein supplement to a diet of dry hay tended to prevent domsiekte.* It would, therefore, appear that a diet too high in protein cannot be looked upon as a cause of the disease.

(f) Renal Insufficiency.

In the literature on eclampsia in the human, much stress is laid on malfunction of the kidneys. This does not appear to apply to our domestic animals. Oedema is not a characteristic of Domsiekte and affected sheep usually urinate freely, nor does the blood chemistry of a typical case indicate any urinary retention. It is true that there are fatty and nephritic changes present in the kidney after death, but this is generally considered to be sequel, not a cause, of the disease. (See under " pathological changes ".)

(g) Pregnancy Toxaemia.

The fact that the disease almost always appears in pregnant ewes has led to the theory that it may be due to toxins from the foetus. This idea would presumably presuppose some abnormality in the excretory system of either the foetus or the mother. Apart from the references to pre-existing kidney lesions in the human mother, already referred to, there is no evidence that this is the case. Further, the fact that cases have been reported in sheep after lambing (Maguire, 1932) seems to disprove this assertion. The frequently reported fact, that sheep usually recover after abortion or delivery, has probably been considered evidence in favour of the theory of toxins from the foetus, but, as will be seen later, there is another explanation for this. The fact that a complex, identical to Pregnancy Disease, has been produced in non-pregnant ewes at Onderstepoort (see Part II of this article) appears to dispose of the idea that the disease is caused by toxins from the foetus only.

Le Roux (1929) states that in eclampsia of the human the characteristic liver pathology involves a peripheral necrosis, that is, nearer to the portal than the central vein. He suggests that this indicates a toxic by-product carried by the portal and systemic circulation. Such a necrosis is not observed in domsiekte.

(h) Pregnancy.

If we discard the theory of toxic absorption from the foetus, we must try to decide what the rôle of pregnancy is. There is no doubt that the disease is very closely associated with the process of gestation. Stander and Cadden (1930) suggest that the depletion of carbohydrate in the body is due to the demand for glucose by the rapidly developing foetus, in the case of the ewe and human, and for milk production in the cow. It is evident that the condition generally occurs within a month of parturition, when foetal growth increases rapidly (Cloete, 1939). Ritzmann and Benedict (1931) showed that, during the last three months of pregnancy, a rise in basal metabolism occurred, amounting to about 18 per cent. per unit of surface area. Murlin (1910) found that the energy production increased with the number of pups carried by the bitch. If it is accepted that the rôle of pregnancy is that of drainage, it can readily be understood why the condition appears towards the end of gestation and especially when there are twin lambs present. The fact that non-pregnant sheep

* See Part II of this paper.

may also show the disease, under very prolonged semi-starvation, is also explained. It would appear, therefore, that the importance of pregnancy lies in the increased demands on the maternal system.

(*i*) *Lack of Exercise and Overfatness.*

The statement that pregnancy disease is partially due to lack of exercise and over-fatness, is frequently met with in the literature and appears to have been first made by Gilruth (1899). Baker (1920), Hudson (1928) and Belschner (1930) are among those who have also incriminated over condition as a predisposing factor. Even in the human, Burgham (1932) stated that toxaemia developed only with excessive previous gain in weight. It would appear that over-fat sheep may be considered as more susceptible to domsiekte, but that this factor is by no means essential for its production. This view is expressed by Traum (—), Leslie (1931) and Sampson *et al.* (1933).

The evidence with regard to lack of exercise is not convincing. The idea would appear to have arisen from the fact that the disease is not infrequently associated with supplementary feeding when exercise is limited. Beyers (1933) refers to the condition as "ophaalziekte" which literally translated would mean "fetching in disease". He states that it often occurs in Holland when the heavily pregnant ewes are brought in for supplementary feeding. It is difficult to fit this history into our present conception of the aetiology unless it is that owing to the strange conditions the sheep do not feed well. (See "change of environment".) Baker (1920) stated that the condition was due to a lack of exercise and overfeeding, and advocated, as preventive measures, making the sheep rustle for their feed during the last month of pregnancy, limiting the amount of dry feed and allowing grazing on green pasture. The reference to green pasture is probably the most significant. Similar suggestions are made by Dill (1932). As the present theory is that the main cause of the disease is a carbohydrate depletion of the body, it is very difficult to understand how matters can be improved by a further utilisation of available carbohydrates by unnecessary exertion. Probably lack of exercise has been incriminated because it often occurs in conjunction with overfatness and faulty feeding. In the Karroo areas of South Africa, where domsiekte is most troublesome, the sheep seldom suffer from lack of exercise.

(*j*) *The Age Factor.*

It has frequently been pointed out that older ewes are more susceptible (Faust, 1927; Marsh, 1928; and Dayus and Weighton, 1931). This is quite understandable. The condition is now regarded as purely one of metabolism and the lowered efficiency of the aged organ would naturally tend to predispose towards the disease.

(*k*) *Hormone Function.*

It is natural to assume that the hormones must play a big part in a metabolic disturbance such as domsiekte, but there is no direct evidence of any hormone imbalance. No lesions of endocrine organs have been described. The following reference to work on other species may, however, be of significance.

Maynard (1937) considered that the glycogenic function of the liver is under the control of certain hormones, notably epinephrine and insulin. The former is said to accelerate glycogenesis while the latter retards it. An imbalance of these hormones may lead to a rise or fall in blood sugar. These facts are well known in connection with diabetes.

Mirsky *et al.* (1937), in experiments on depancreatised dogs, came to the conclusion that glucose exerts a marked antiketogenic effect, in the absence of insulin, when administered in amounts adequate to cause glycogen retention in the liver.

Mackay and Barnes (1937), found that anterior pituitary extract had the property of producing ketosis and fatty deposition in the liver of fasting rats. Adrenalectomy not only abolishes this ketosis but prevents the accumulation of fat in the liver. Removal of the adrenal gland also reduces the amount of fat which is deposited in the liver during fasting.

In fourteen experiments on rats, Shapiro and Wertheimer (1937), found that a decrease of liver fat could be affected by the administration of an alcoholic extract of pancreas, but that extracts of spleen, brain and liver were without effect. Similarly Mackay (1937) concluded that an alcoholic extract of pancreas accelerated the disappearance of fat from the livers of fasting rats and reduced the fatty infiltration in rats of a low protein, fat-producing diet. Older females were said to be more susceptible to a fat deposition in the liver. According to Kaplan and Chaikoff (1937), the ingestion of pancreas exerts a definite control over the deposition of fat in the livers of de-pancreatised dogs.

(*l*) *Choline.*

In seeking an explanation for this liver de-fattening influence of pancreas, Aylward and Holt (1937), working with rats, failed to demonstrate the presence of a lipotropic factor in the pancreas, other than choline. The defatting influence of choline and the resultant increase in the ability of the liver to store glycogen was shown by Maclean *et al.* (1937). The work of Denel *et al.* (1937) confirms this and stresses the fact that choline decreases the ketonaemia of rats both on a high fat diet and when fasting. Channon *et al.* (1937) found that tri-ethyl choline has a similar action to, and not greatly less than, choline, in preventing fatty livers in rats.

This obvious relation of choline to fatty infiltration of the liver and ketonaemia, indicates that it may have a significant relation to domsiekte. So far we are not aware of any work that has been done in this connection.

(*m*) *Vitamins.*

As there is a marked disturbance in carbohydrate metabolism in domsiekte, the rôle played by vitamin B, must be considered. In this connection the work of Carlström *et. al.* (1939), is of great interest. They state:—" the disturbances in the organism arising in connection with vitamin B deficiency are now gradually considered to be due to a reduced capacity of the body cells to convert carbohydrates, conditioned by the fact that the oxidative breaking down of pyruvic acid—an intermediary product in the splitting of carbohydrate—cannot take place without the help of vitamin B, or possibly the latter's pyrophosphoric acid ester, cocarboxylase ". The authors treated convulsions in the blue fox, acetonaemia in cattle and neuroses, ataxia and fatty infiltration of the liver in the horse, successfully with " aneurine ". Steyn (1941) describes the successful treatment of acetonaemia in a cow with vitamin B_1. Williams and Spies (1938) state:— " it is generally accepted as an established fact that the supply of vitamin B_1 is rather precariously balanced, in so far as it is not formed within the organism (except in the case of ruminants), is not stored in any considerable quantity, its supply in the food is subject to great variations, and the resorption seems,

moreover, to be reduced in connection with different kinds of disturbances of the mucous membrane of the stomach and intestine.''. Cowgill *et al.* (1931), Cowgill (1934), and Benedict (1934) referred to various factors which may depress either the normal synthesis of thiamin in the ruminant, or the ability to use the vitamin. The need for vitamin B_1 increases with heightened metabolism and, therefore, would be much greater in the later stages of pregnancy. Although it would appear that vitamin B_1 is normally formed in the rumen, it would seem quite possible that either the synthesis or absorption might be interfered with in certain digestive disturbances. Atony of the rumen is usual in domsiekte and, as very little ingesta then passes from the rumen to the intestines, it would appear that the absorption of vitamin B_1 might be very limited under these circumstances. Writing on the prevention of eclampsia in the human, Anderson (1940) mentions that the diet should contain an adequate supply of vitamins B_1 and D. On the whole it would appear the question of vitamin deficiency has not been sufficiently considered in relation to domsiekte and that the possibility of an avitaminosis B_1 should not be summarily dismissed merely because we are dealing with a ruminant.

(n) Total or Semi-starvation.

Hopkirk (1934) reported the production of Pregnancy Toxaemia by the semi-starvation of fat, heavily pregnant ewes. Acetonuria and fatty changes in the liver were produced by Roderick *et al.* (1937) by reducing the diet of well-conditioned pregnant ewes and lambs. Fraser *et al.* (1938) produced what appears to be typical domsiekte by starving fat, aged ewes towards the end of pregnancy. They found an inverse ratio between the calorific value of the diet and the occurrence and severity of the Acetonaemia. Reduction of the dietary intake is the only means by which a condition closely resembling domsiekte has been produced experimentally and it would appear that a low intake is the basic cause of the condition.

In their publication of 1937, Roderick *et al.* point out that frequent references had then been made to the association of the disease with inferior feeding. Leslie (1933) stated that he invariably associated the disease with loss of weight, undernutrition and unbalanced and deficient diet. Two serious losses are reported following 24 hour train journeys. Dayus and Weighton (1931) state that the majority of cases occur in good-conditioned ewes that continued to gain in weight for the first three months of pregnancy but were subsequently unable to maintain their condition. A rapid decline in weight resulted in serious metabolic disturbances and subsequent ketosis.

(o) Change in Ration or Environment.

In Scotland Greig (1929) considered the predisposing factor to be a " sudden changing of grazing from poor to relatively rich pasture ". A significant reference is made to the fact that a pronounced loss of appetite occurs when the change is made.

Any sudden change in environment or handling may cause sheep to feed poorly, even though the food offered is of better quality than they have been accustomed to.

(p) Change in Climatic Condition.

It is significant that so many cases are reported after a climatic change. Dimmock *et. al.* (1928) observed that ewes frequently go down with the disease directly after a sudden change in the weather such as a cold spell or snowstorm.

It is well known that sheep graze badly in wet and inclement weather while cold would increase the energy requirements of the body. Snow might render the food inaccessible.

Clinical Symptoms.

There seems to be a general agreement on the clinical aspect of the disease. A clear description of the symptoms is given by Dimmock, Healy and Bullard (1928), in which the following points are mentioned. The ewe may lag behind the flock, and refuse to eat. Later nervousness, irritability, grinding of the teeth, walking in circles and standing with the head against objects, may be noticed. At first the ewe becomes partially and later completely blind. In the end convulsions or coma set in. Respirations are accelerated but the temperature remains normal. Constipation is more common than diarrhoea. Similar descriptions are given by Marsh (1928) and by Dayus and Weighton (1931).

Biochemical Changes.

A considerable amount of biochemical work has been reported, both on normal pregnant sheep and on sheep with pregnancy disease. For the sake of convenience these will be dealt with under three headings, viz., blood, liver and urine.

I. *The Blood.*

(*a*) *Acidosis*, or diminished plasma buffer value, is a constant feature of the disease and is a result of the hyperacetonaemia. This is particularly referred to in the works of Healy and Hull (1928), Roderick and Harshfield (1932), Dimmock *et al.* (1928) and Sampson and others (1933).

(*b*) *Blood Sugar.*—There are many reports of a decreased blood-sugar during the disease. (Roderick *et al.*, 1933; Sampson *et al.*, 1933; Fraser *et al.*, 1939.) There is no doubt that hypoglycaemia is a significant feature of the disease. Roderick and his co-workers, however, report an occasional hyperglycaemia and suggest that this is a sequel to the liver injury in that the glycogen storage capacity of that organ is interfered with. It is not quite clear, however, whether the hyperglycaemia persisted throughout the course of the disease or if not, at what stage it was noted. In our experiments we have not infrequently found a rise in blood-sugar following a period of hypoglycaemia and this rise in some cases exceeded the physiological limits so that a hyperglycaemia developed. The same phenomenon has been noted by other workers and it has been suggested that increase in blood-sugar is an expression of an increased protein catabolism during the formation of sugar from proteins. This would represent a physiological adaptation to an insufficient glucose supply.

(*c*) *Ketonaemia.*—Very numerous references are made to the hyperketonaemia associated with the disease, but no references could be traced to the differentiation of the ketone bodies, i.e. the proportions of acetone, aceto-acetic acid and hydroxybutyric acid.

(*d*) *Non-protein-nitrogen.*—Sampson, Gonzaga and Hayden (1933) found an increase in the non-protein-nitrogen and regard this " as evidence of oligouria culminating in fatal uraemia ". Roderick and Harshfield (1932), on the other hand, report that there is " little evidence of retention " and state that polyuria is a significant feature of the disease, being an attempt to flush out by dilution abnormal amounts of organic acids. Neither authors give the actual quantities

of urine passed so that the question cannot be said to have been settled. An increase in non-protein-nitrogen in pregnancy disease is, however, possible and even likely for the following reasons:—

(i) The nephrosis (see under pathological findings) which may interfere with kidney function.

(ii) Increased protein catabolism as compensatory for an insufficient carbohydrate intake.

(iii) The presence of metritis and retained afterbirth following abortion or parturition.

(*e*) *Other Blood Constituents.*—The following constituents do not appear to be significantly altered in the disease:—

(i) *Blood calcium.*—Healy and Hull (1928), Roderick and Harshfield and Hawn (1937), Beyers (1933).

(ii) *Blood phosphorus.*—No change was found in the inorganic and acid soluble phosphorus by the same authors as listed under blood calcium.

(iii) *Blood cholesterol* (Roderick *et al.*, 1933).

(iv) *Blood chlorides, uric acid and lactic acid* (Roderick and Harshfield, 1932).

(v) *Haemoglobin and bile pigments.* Beyers (1933) reports an increase in the haemoglobin content of the blood and also in the bile pigments, the latter, however, not giving rise to a clinical icterus.

II. *The Liver.*

Roderick, Harshfield and Marchant (1933) have investigated the chemical composition and functional activity of the maternal liver in cases of Pregnancy Disease with the following results:—

(*a*) The "crude" fat is enormously increased from a normal average of 28 per cent. to as high as 60 per cent. (See also Fraser *et al.*, 1939.) This is an indication that the increase in visible fat is a fatty infiltration rather than a fat phanerosis.

(*b*) The liver glycogen is markedly reduced. They suggest that this is partly due to the anorexia, partly to the deposition of fat in the liver interfering with glycogen storage and possibly to glycogenolysis of that which was previously present.

(*c*) The moisture content calculated on a percentage basis is decreased, but when taken on a fat and glycogen free basis, there is very little change.

(*d*) Dye Excretion Tests at first gave inconclusive results but subsequent reports show that tests with rose-bengal provided evidence of serious functional disturbance.

(*e*) There is no icterus, although, as stated above, Beyers (1933) reports the presence of bile pigments in the blood as characteristic, without, however, causing clinical icterus.

III. *The Urine.*

From a review of the available data the following can be stated to be the changes recorded:—

(*a*) Reaction is acid and reflects the acetonaemia and resultant alkali deficit—see Healy and Hull (1928), Roderick and Harshfield (1932).

(*b*) Acetonurea, often on a marked degree, appears to be a constant feature. See Sampson *et al.* (1933), Roderick and co-workers, Beyers (1933), Grieg (1929), Elder and Uren (1940) and others.

(*c*) Albuminurea is reported by many workers. (Beyers, 1933; Elder and Uren, 1940), and according to Roderick and Harshfield (1932) is a result of the nephrosis; casts were not seen.

(*d*) Urinary Ammonia. Sampson *et al.* (1933), Dimmoch *et al.* (1928) and Roderick and Harshfield (1932) report a marked increase.

The pathognomonic features of the urine in Pregnancy Disease are, therefore, acidity of reaction, acetonurea, increased ammonia and in some cases albuminuria.

Pathological Changes.

(*a*) *The Liver.*

An accumulation of fat in the liver is mentioned by practically all writers who deal with the pathological findings. M'Fadyean (1924) and de Kock (1928) describe the histology of the liver and both state that the fatty deposit is " usually peripheral " (i.e. in the periphery of the lobule) but the former shows that the interlobular distribution of the fat is not specific and may even vary in different portions of the same liver. The enormous increase in the fat content of the liver (Roderick *et al.*, 1932; Roderick *et al.*, 1933) goes to show that this increase in visible fat is an infiltration and not a degeneration. Necrosis of the hepatic cells as described in the case of eclampsia of the human does not appear to be present in pregnancy disease (Snook, 1939). A fatty infiltration cannot be looked upon as specific. As M'Fadyean (1924) states, " it is generally recognised that towards the end of pregnancy, even in normal conditions, there is a tendency towards fatty infiltration of the liver that approaches the pathological ". Snook (1939) states that he found a fatty infiltration of the livers of clinically normal ewes indistinguishable from that seen in comatose cases. Davel *et al.* (1937) state that in fasting rats, there is no direct relationship between the liver fat value and the ketonaemia. Hutyra and Marek (1922) speak of an " acute diffuse parenchymatous hepatitis " in connection with pregnancy disease, but this would appear to be a misnomer as inflammatory changes are not mentioned in the more recent literature.

Best (1934) points out that a high fat content of the liver is not always pathological and asks whether the very high fat content of the liver of hibernating animals plays any part in their decreased metabolic rate. He also states that conditions which exhaust the liver glycogen encourage the development of fatty changes in the liver cells.

Roderick *et al.* (1933) and Shaw (1933) both state that the excretory function of the liver in pregnancy disease is markedly affected as indicated by the rose bengal test.

(*b*) *The Kidneys.*

De Kock (1928) mentions that in some cases fatty changes are present in the kidney. The best description of the kidney lesions is that of Roderick *et al.* (1932), who describe nephrosis and fatty changes, but, this was considered to be the result rather than the cause of the disease. A significant article by Dibble and Hay (1940) records similar changes in the kidneys of rabbits following starvation.

(c) *The Alimentary Tract.*

Dayus and Weighton (1931) state that very little food is found in the stomach and intestine while Bruce (1919) mentioned that the reticulum and abomasum are empty and there is a constipation of the intestines.

Treatment.

In general the literature is not encouraging with regard to treatment. Hopkirk (1934) reports no beneficial results with any of the following, glucose, insulin, calcium carbonate (with or without glucose), formaldehyde, adrenalin or sodium bicarbonate.

(a) *Calcium.—Therapy.*

Leslie (1933) reports no response to calcium and McKenna (1931), also got no results from the injection of calcium gluconate. Bowes (1930), on the other hand claims that calcium gluconate gave good results in some cases.

(b) *Glucose.*

The presence of hypoglycaemia and acetonaemia immediately suggests the use of glucose in the treatment of domsiekte. Cutting (1931) made the following remarks with regard to the functions of glucose in the prevention of acidosis (*a*) " It supplies a readily available source of energy while at the same time sparing the fat catabolism and also preventing the production of ketosis by supplying anti-ketogenic bodies to neutralise the ketogenic bodies derived from the unavoidable fat catabolism ". (*b*) " It acts as a diuretic second only in efficiency to water itself and thereby tends to prevent the retention of acid waste-products." Mirsky *et al.* (1937) showed that, in depancreatised dogs, glucose exerts a marked antiketogenic effect, in the absence of insulin, when administered in amounts adequate to cause glycogen retention in the liver. Baker (1932) states " We have used it (calcium gluconate) in several hundred cases of pregnancy disease in ewes and even small doses effect a wonderful change for the better. If the animal shows eclamptic symptoms, such as grinding of the teeth or muscular tremors, and dextro-glucose—the main thing is to supply the needed amount—half enough will result in a temporary rally.". " Cameron and Goss (1940), however, state that the intravenous injections of glucose, even in the early stages was, valueless, although it reduced the acetonaemia.

The level of ketonaemia cannot in all cases be correlated with the severity of clinical symptoms (Fraser *et al.*, 1938). Davel *et al.* (1937) have shown that in fasting rats there is no direct relationship between the liver fat value and the ketonaemia.

It can be understood, therefore, that the administration of glucose alone will not be expected to cure all the symptoms of domsiekte, but its use is rational and strongly indicated.

(c) *Vitamins.*

The work of Carlström *et al.* (1939) on the rôle played by vitamin B_1 in certain diseases of animals and man in which acetonaemia and nervous symptoms appear, including acetonaemia of the cow, indicates that this vitamin might be of value in the treatment of domsiekte. There is no direct evidence either for or against its use, however.

(*d*) *Inflation.*

Bowes (1930) mentions inflation especially in post parturient " tremblings ".

Prevention.

Any prophylactic measure advocated is naturally a direct corollary of the authors' conception of the aetiology. As the latter aspect of the problem has already been discussed at length, it is not considered necessary to list all the preventive measures advocated.

The use of molasses, however, is so strongly advocated by some authors that it must be mentioned . Marsh (1928) reports that no cases were encountered in a flock where molasses was placed in the drinking water of pregnant ewes. Hull and Dimmock (1935) advocate the dosing of 4 ounces of molasses daily to pregnant ewes as a prevention.

Conclusion.

Although much of the literature is contradictory, certain definite conclusions can be drawn from its study. The outstanding points are as follows:—

Aetiology.—Many of the suggested causes such as mineral deficiency, toxic absorption from the uterus and lack of exercise, can be discarded. Age, overfatness and changes in the climatic or feeding conditions can be looked upon as predisposing or indirect causes. The disease is essentially a disturbance of metabolism, especially with regard to the carbohydrates, and this is usually manifested by a loss of body weight. Pregnancy is a powerful predisposing cause and acts through the increased drainage on the maternal system.

Biochemical Findings.—There is an acidosis, acetonaemia and hypoglycaemia together with an increase in the fat content of the liver.

Pathology.—A fatty infiltration of the liver appears to be constant, together with regressive changes in the kidneys.

Treatment.—No satisfactory method of treatment has yet been recorded.

Summary.

The available literature is reviewed and where possible conclusions are drawn.

References are listed which deal either directly or indirectly with the question of Pregnancy Disease of sheep.

LITERATURE CITED.

ANSELINO, K. J., and HOFFMAN, F. (1931). *Arch. f. Gynäk.*, 147: 652. cf. Relation between blood plasma proteins and toxemias of pregnancy. Dodge, Eva, F. and Frost, T. T. (1938). *Jour. Am. Med. Assoc.*, Vol. 3, p. 1898-1902.

ANDERSON, G. E. (1940). The treatment of pre-eclampsia. A rationale for dietary regulation in the pre-clynical stage. *Am. Jour. Obst. Gynecol.*, Vol. 40, pp. 517-525.

ALSTON, J. T. (1933). Palsy after calving. *Vet. Med.*, Vol. 28, No. 4, pp. 159-160.

ALLEN, F. M. (1923). Experimental studies in diabetes. *Series* Vol. 5, *Jour. Metab. Res.*, Vol. 4, pp. 189-254.

ALEXANDER, A. S. (1921). *Am. Sheep Breeder and Wool Grower.* Vol. 41, p. 566, cf. Pregnancy disease of sheep. Roderick, L. M., and Harshfield, G. S. (1932). *North Dakota Expt. Stn. Tech. Bull.*, 261.

AYLWARD, F. X., AND HOLT, L. E. (1937). The nature of the lipotropic agent in pancreas. *Jour. Biol. Chem.*, Vol. 121, pp. 61-69.

BAKER, E. T. (1920). Sheep diseases. *Am. Vet. Publishing Co., Chicago*, pp. 186-187.

BAKER, E. T. (1932). Calcium gluconate in veterinary practice. *Vet. Med.*, Vol. 27, pp. 142-144.

BEYERS, J. A. (1933). Acetonurie by Schapen. *Tydskrif voor Dieregeneeskunde*, Deel 60, bb 1081-1091.

BELSCHNER, H. G. (1930). *Agric. Gaz. N.S.W.*, Vol. 41, p. 613. cf. The Influence of diet upon ketonaemia in pregnant ewes. *Jour. of Physiol.*, Vol. 94, No. 3, pp. 346-357.

BELL, E. T. (1930). Textbook of pathology cf. Pregnancy diseases of sheep. Roderick, L. M., and Harshfield, G. S. (1932). *North Dakota Exp. Sta. Tech. Bull.*, 261.

BENEDICT, Fr. G. (1934). La metabolisme basal chez Phomme d'aprés les derniers recherches. *Annales de Med.*, Vol. 35.

BENEDICT, Fr. G., AND RITZMAN, E. G. (1927). *Carnegie Institution of Washington, Pub.* No. 377, cf. The pathogenesis of ketosis. Pregnancy disease of sheep. Roderick, L. M., Harshfield, G. S., and Hawn, M. C. (1937). *Jour. Am. Vet., Med. Assoc.*, Vol. 43, No. 1, pp. 41-50.

BEST, C. H. (1934). The rôle of the liver in the metabolism of carbohydrate and fat. *The Lancet*, Vol. 226, pp. 1155-1216.

BINGHAM, A. W. (1932). *Am. Jour. Obst. and Gynec.*, 23: 38 cf. Relation between blood plasma proteins and toxemias of pregnancy. Dodge, E. F., and Frost, T. T. (1938). *Jour. Am. Med. Assoc.*, Vol. 3, pp. 1898-1902.

BLATHERWICK, N. R. (1920). Neutrality regulations in cattle. *Jour Biol. Chem.*, Vol. 42, pp. 517-539.

BLOOR, W. R. (1925). Biochemistry of fats. *Chem. Rev.*, Vol. 2, pp. 243-300.

BODANSKY, M. (1923). *Am. Jour. of Physiol.*, Vol. 66, pp.375. cf. Further observations on the functional pathology of pregnancy disease of ewes. Roderick, L. M., Harshfield, G. S., and Merchant, W. R. (1933). *Cornell Veterinarian*, Vol. 23, pp. 348-353.

BOSWORTH, J. T. (1929). Some common ailments of ewes. *Vet. Rec.*, Vol. 9, No. 49, pp. 1071-1078.

BOWES, H. G. (1930). Sheep diseases. *The Vet. Rec.*, Vol. 10, No. 31, pp. 703-704.

BRENTANO, C. AND KEISER, D. V. (1937). Hunger als Ursache des Coma diabeticum. *Deutsch. Med. Wochenschr.*, T.63, z. 213-218.

BRUCE, C. A. (1919). Stercoremia of sheep. *Jour. Am. Vet. Med. Assoc.*, Vol. 55, N.S. Vol. 8, pp. 553-557.

CARPENTER, T. M. (1925). Prolonged fasting as affecting the composition of steer's urine. *Proc. Nat. Acad. Sci.*, Vol. 2, pp. 155-160.

CARLSTRÖM, B., MYBRÄCH, K., HOLMIN, N., AND LARSSON, A. (1939). Biochemical studies on B_1 avitaminoses in animals and man. *Acta Medica Scandinavica*, Vol. 102, Fasc. 3, pp. 175-213.

CAMERON, H. S., AND GOSS, H. (1940). Parturient paresis in ewes. *Jour. Am. Vet. Med. Assoc.*, Vol. 96, No. 755, pp. 165-169.

CAMERON, H. S. (1937). Sheep raising in California. *Vet. Med.*, Vol. 32, pp. 272-273.

CHANNON, H. J., PLATT, A. P., AND SMITH, J. A. B. (1937). *Biochem. Jour.*, Vol. 31, Part 2, pp. 1736-1742.

CAMERON, H. S., AND GOSS, H. (1940). Preparturient paresis in ewes. *Jour. Am. Vet. Med. Assoc.*, Vol. 96, pp. 165-169.

CARPENTIER, L. A. A. (1887). A practical treatise on obstetrics. Vol. 2, *Wm. Wood and* Co., p. 1887.

CHRISTALON, A. (1927-28). Quantitative Beshmingen der Acetonkörfer im Blute trächtiger und nichtträchtiger Kühe. *Arch. f. Tier.*, B. 57, t. 507-513.

COOKE, J. V., RODENBAUGH, F. H., AND WHIPPLE, G. H. (1916). Intestinal obstruction. *Jour. Exp. Med.*, Vol. 23, pp. 717-738.

COWGILL, G. R., ROSENBERG, H. A., AND ROGOFF, J. (1931). Studies in the physiology of vitamins. XVI. The effect of exercise on the time required for the development of the anorexia characteristic of lack of undifferentiated vitamin B_1. *Am. Jour. Phys.*, Vol. 98, pp. 589-594.

COWGILL, G. R. (1934). Vitamin B requirement of man. *Yale University Press, New* Haven, Chap. VIII.

CULLEN, G. E. (1917). Studies on acidosis. *Jour. Biol. Chem.*, Vol. 30, pp. 369-388.

CUTTING, R. A. (1931). Principles of preoperative and post-operative treatment (fifth instalment), disturbances of acid-base equilibrium: Acidosis and alkalosis. *Am. Jour. Surg. N.S.*, Vol. 12, p. 343.

DARROW, D. C., AND YANNET, H. (1935). The changes in the distribution of body water accompanying increase and decrease in extracellular electrolyte. *Jour. of Clin. Investigation*, Vol. 14, pp. 266-275.

DAYUS, C. V., AND WEIGHTON, C. (1931). Clinical observations on pregnancy toxaemia in ewes. *Vet. Rec.*, Vol. 11, pp. 255-257.

DE KOCK, G. (1928). A further note on domsiekte, or fatty infiltration of the liver in pregnant ewes. *South African Jour. of Sci.*, Vol. 25, pp. 274-277.

DE SNOO, K. (1937). The prevention of eclampsia. *Am. Jour. Obst. and Gynec.*, Vol. 34, pp. 911-939.

DEVEL, H. J. (JR.), MURRAY, S., HALLMAN, L. F., AND TYLER, D. B. (1937). Studies on ketosis 12. The effect of choline on the ketonuria of fasting rats following a high fat diet. *Jour. Biol. Chem.*, Vol. 120, pp. 277-288.

DEVEL, H. J. (JR.), HALLMAN, L. F., AND MURRAY, S., (1937). Studies on ketosis 11. The relation of fatty livers to fasting ketonuria in the rat. *Jour. Biol. Chem.*, Vol. 119, pp. 257-268.

DIBBLE, J. H., AND HAY, J. D. (1940). The nature of fatty change in the kidneys. *Jour. Path. and Bact.*, Vol. 51, No. 1, pp. 1-7.

DIECKMANN, W. J. (1935). Renal function in the toxemias of pregnancy. *Am. Jour. Obst. and Gynec.*, Vol. 29, p. 472.

DILL, R. (1932). Three pathological conditions affecting ewes. *Vet. Med.*, Vol. 27, pp. 26-29.

DIMMOCK, W. W., HEALY, D., AND BULLARD, J. (1928). Acidosis of pregnant ewes; so-called pregnancy disease of sheep. *Jour. Am. Vet. Med. Assoc., N.S.*, Vol. 25, pp. 511-516.

DIMMOCK, W. W., HEALY, D. J., AND HULL, F. E. (1928). Acidosis of pregnant ewes; so-called pregnancy disease of sheep. *Ky. Exp. Sta.*, Cir. 39, pp. 1-8.

DIMMOCK, W. W. (1930). Acidosis of pregnant ewes; so-called pregnancy disease of sheep. *Vet. Alumni Quarterly*, Ohio State Univ., Vol. 17, p. 149.

DODGE, EVA F., AND FROST, T. T. (1938). Relation between blood plasma proteins and Toxemias of pregnancy. *Jour. Am. Med. Assoc.*, Vol. 3, pp. 1898-1902.

DUNCAN, C. W., HOFFMAN, C. F., AND TOBIN, H. A. (1939). A chemical study of ketosis in a dairy herd. *Jour. Amer. Vet. Med. Assoc.*, Vol. 95, No. 753, pp. 690-700.

DYE, J. A., AND CHIDSEY, J. (1939). Ketone body—Total carbohydrate utilization ratios and their relation to the problem of ketosis. *Am. Jour. Physiol.*, Vol. 127, pp. 745-750.

EFFKEMANN, G. (1937). Experimentelle studie über den Einfluss einseitiger Nahrung auf die Leberfunktion in der Schwangerschaft. *Arch. Gynäkol.*, B. 163, T. 327-342.

ELDER, C., AND UREN, A. W. (1940). Pregnancy disease of sheep. *Mo. Expt. Sta.*, Bul. 412.

ENTENMAN, C., AND CHAIKOFF, I. L. (1941). Is choline the factor in the pancreas that prevents fatty livers in depancreatized dogs maintained with insulin? *The Jour. of Biol. Chem.*, Vol. 138, No. 2, pp. 477-485.

EUFINGER, H. (1928). Die Kolloidstruktur des plasmas während der Gravidität. *Klin. Wochenschr.*, B. 7, Nr. 11, T. 492-494.

FISH, P. A. (1929). The physiology of milk fever III. The blood phosphates and calcium. *Cornell Veterinarian*, Vol. 19, pp. 145-160.

FITZGIBBON, G. (1922). *Jour. Obst. and Gynec.*, Vol. 29, p. 402. cf. Relation between blood plasma proteins and toxemias of pregnancy. Dodge, E. F., and Frost, T. T. (1938). *Jour. Am. Med. Assoc.*, Vol. 3, pp. 1898-1902.

FAUST, H. L. (1927). A preparturient disease of sheep. *Vet. Alumni Quarterly, Ohio State Univ.*, Vol. 14, p. 110.

FRASER, A. H. H., GODDEN, W., SNOOK, L. C., AND THOMSON, W. (1938). The Influence of diet upon ketonaemia in pregnant ewes. *Jour. Physiol.*, Vol. 94, No. 3, pp. 346-357.

FRASER, A. H. H., GODDEN, W., SNOOK, L. C., AND THOMSON, W. (1939). Ketonaemia in pregnant ewes and its possible relation to pregnancy disease. *Jour. Physiol.*, Vol. 97, pp. 120-127.

FREY, F. F. (1918). Antepartum paralysis in sheep. *Am. Jour. Vet. Med.*, Vol. 13, n.s. Vol. 6, p. 283

GAIGER, S. H. (1928). *Rept. Dept. Vet. Path., Univ. of Liverpool.* cf. Nature of lambing sickness. Greig, J. R. (1929) *Vet. Rec.*, Vol. 9, pp. 509-511.

GAMBLE, J. L. (1937). Extracellular fluid. *Bull. John Hopkins Hosp.*, Vol. 61, pp. 151-173.

GILRUTH, J. A. (1899). *Sixth Ann. Rept. Dept. Agric. N.Z.*, cf. The Influence of diet upon ketonaemia in pregnant ewes. *Jour. Phys.*, Vol. 94, No. 3, pp. 346-357.

GILRUTH, J. A. (1909). *Div. Vet. Sci. N.Z. Dept. Agr. Bull.* 15. cf. Pregnancy diseases of sheep Roderick, L. M., and Harshfield, G. S. (1932). *North Dakota Exp. Sta. Tech. Bull.* 261.

GLOVER, G. H., NEWSON, I. E., ALKIRE, E. W. (1919). Investigations to determine cause of sheep diseases in Colorado. *Jour. Amer. Vet. Med. Assoc.*, Vol. 55, N.S. Vol. 8, pp. 5-22.

GREENE, H. S. N. (1938). Toxemia of pregnancy in the rabbit. II. *Studies Rocherf. Inst. Med. Res.*, Vol. 107, pp. 495-514.

GRIEG, J. R. (1929). Nature of lambing sickness. *Vet. Rec.*, Vol. 9, pp. 509-511.

HADLEY, F. B. (1918). Preparturient eclampsia of ewes. *Am. Jour. of Vet. Med.*, Vol. 13, N.S. Vol. 6, pp. 284.

HALDANE, J. B. S. (1928). Experimental and therapeutic alterations of human tissue alkalinity . *The Lancet*, Vol. 1, p. 537.

HARDEN, BOYD (1936). A study in pre-eclampsia and eclampsia. *University of Pittsburgh, Pittsburgh.*

HARDING, V. J. (1925). Metabolism in pregnancy. *Physiol. Rev.*, Vol.5, No. 3, pp. 279-302.

HASTINGS, A. B., AND MURRAY, H. A. (1921). Observations on parathyroidectomized dogs. *Jour. Biol. Chem.*, Vol. 46, pp. 233-255.

HAWARTH, J. A. (1929). *Calif. Woolgrower*, Vol. 5, p. 46, cf. Pregnancy diseases of sheep. Roderick, L. M., and Harshfield, G. S. (1932). *North Dakota Exp. Sta. Tech. Bull.* 261.

HAYES, W. F. (1931). Acetonaemia in Cattle. *North Am. Vet.*, Vol. 12, No. 3, p. 31.

HEALY, D. J., AND HULL, F. F. (1928). Diminished plasma buffer value in pregnancy disease of ewes. *Cornell Vet.*, Vol. 18, p. 73.

HENNING, M. W. (1932). Animal diseases in South Africa. Vol. 2, pp. 871-873.

HAYMAN, W. (1937). Metabolism studies in human beings on the age disposition to ketosis. *Jour. Nutrition*, Vol. 13, p. 10.

HOPKIRK, C. S. M. (1934). Pregnancy toxaemia of ewes *Aust. Vet. Jour.*, Vol. 10, pp. 59-64.

HUDSON, R. (1928). Acetonaemia and its association with the retention of uterine fluids. *Vet. Rec.*, Vol. 8, pp. 762-766.

HUDSON, R. (1931). Acetonaemia. *Vet. Rec.*, Vol. 11, No. 46, pp. 1149-1153.

HULL, F. E., AND NOLAN, A. F. (1940). Acetonaemia in swine. *Jour. Am. Vet. Med. Assoc.*, Vol. 97, No. 761, pp 162-164.

HULL, F. C., AND DIMMOCK, W. W. (1935). Pregnancy diseases of sheep. *Univ. of Ky. Cir.*, 274-, pp. 1-6.

HUTYRA, F. v., AND MAREK, J. (1922). Spez. Pathologie u. Therap. d. Haustiere, 6 Auf., Bd. 2, p. 414.

KAPLAN, A., AND CHARKOFF, I. L. (1937). The effect of choline on the lipid metabolism of blood and liver in the completely depancreatized dog maintained with insulin. *Jour. Biol. Chem.*, Vol. 120, pp. 647-657.

KENDALL, E. C. (1941). Glandular physiology and Theraphy. The function of the adrenal cortex. *Jour. Am. Med. Assoc.*, Vol. 116, No. 21, pp. 2394-2398.

LE ROUX, L. A. (1929). *Amer. Jour. Obst. & Gynec.*, Vol. 17, p. 90. cf. Pregnancy diseases of sheep. Roderick, L. M., and Harshfield, G. S. (1932). *North Dakota Expt. Sta. Tech.*, Bull 261.

LESLIE, A. (1931). Pregnancy disease in ewes. *Vet. Rec.*, Vol. 11, No. 46, pp. 1148-1149.

LESLIE, A. (1933). Pregnancy disease in ewes. *Aust. Vet. Jour.*, Vol. 9, pp. 9-14.

LEVINE, H., AND SMITH, A. H. (1927). Studies on ketosis in the rat. *Jour. Biol. Chem.*, Vol. 75, pp. 1-22.

LIEGEOIS (1933). Traite de Path. *Médicale des Animaux Domestiques*, p. 160, cf. Acetonurie by Schapen. Beyers, J. A. (1933). *Tydschrift voor Dierengeneeskunde*, Deel 60, bb. 1081-1091.

LUCKEY, D. F. (1918). Good care kills sheep. *Am. Jour. Vet. Med.*, Vol. 13, N.S. Vol. 5, pp. 248.

LYTTLE, W. H. (1932). *Fort Dodge Bio-Chem. Review.*, Vol. 2, p. 5. cf. Pregnancy disease of sheep. Roderick, L. M., and Harshfield, G. S. (1932). *North Dakota Exp. Sta. Tech.*, Bull. 261.

MACKAY, E. M. (1937). The influence of pancreas extract (" fat metabolizing hormone ") upon fat deposition in the liver on a low protein diet. *Amer. Jour. Physiol.*, Vol. 119, pp. 783-786.

MACKAY, E. M., AND BARNES, R. H. (1937). The effect of adrenalectomy on liver fat in fasting and after the administration of anterior pituitary extracts. *Am. Jour. Physiol.*, Vol. 118, pp. 525-527.

MACLEAN, D. L., RIDOUT, J. H., AND BEST, C. H. (1937). The effects of diets low in choline upon liver function, growth and distribution of fat in the white rat. *Jour. Expt. Path.*, Vol. 18, pp. 345-354.

MARSH, H. (1928). Some obscure diseases of sheep. *Jour. Am. Vet. Med. Assoc., N.S.*, Vol. 27, pp. 724-735.

MARSHAL, F R., AND POTTS, C. G. (1921). *U.S.D.A. Bull.* 996. cf. Acidosis of pregnant ewes. Dimmock, W. W., Healy, D., and Bullard, J. (1928). *Jour. Am. Vet. Med Assoc.*, N.S. Vol. 25, p. 511.

MATTHEW, A. (1929). Pregnancy toxemia in ewes. *The Vet. Rec.*, Vol. 9, p. 672.

MACQUIRE, L. C. (1932). Ovine ante- and post-partum paralysis. *The Vet. Jour.*, Vol. 88, pp. 148-149.

MAYNARD, L. A. (1937). Animal Nutrition. pp. 56-80.

M'FADYEAN, SIR JOHN (1924). Fatty infiltration of the liver as a cause of death in pregnant ewes. *Jour. Comp. Path. and Therap.*, Vol. 37, pp. 287-293.

McKENNA, W. R. (1931). Acidosis and pregnancy toxemia in ewes. *The Vet. Jour.*, Vol. 87, pp. 286-287.

McLINDEN, J. (1937). Sleepy sickness in sheep in New Zealand. *The Vet. Jour.*, Vol. 93, pp. 212-215.

McPHAIL, F. L. (1939). The toxemias of pregnancy. *Jour. Amer. Med. Assoc.*, Vol. 3, pp. 1894-1898.

MIRSKY, I. A., HEIMAN, J. D., AND BROK KAHN, R. H. (1937). The antiketogenic action of glucose in the absence of insulin. *Am. Jour. Phys.*, Vol. 118, pp. 290-296.

MURLIN, J. R. (1910). The metabolism of development. I. Energy metabolism in the pregnant dog. *Amer. Jour. Phys.*, Vol. 26, pp. 134-155.

NEWBURGH, L. H., AND LASHMET, F. H. (1933). The importance of dealing quantitatively with the water supply in disease. *Amer. Jour. Med. Sci.*, Vol. 186, pp. 461-471.

NEWSOME, I. E. (1918). *Am. Jour. Vet. Med.*, Vol. 13, N.S. Vol. 7, p. 353. cf. Some obscure diseases of sheep. Marsh, H. (1928). Ibid. Vol. 27, pp. 724-735.

OPIE AND ALFORD (1915). *Jour. Expt. Med.*, Vol. 21, No. 1. cf. Studies on the physiology of the liver. V. The hepatic factor in chloroform and phosphorus poisoning. *The Amer. Jour. of Phys.*, Vol. 65, No. 2, pp. 267-276.

PETERS, J. P., AND VAN SLYKE, D. D. (1931). Quantitative clinical chemistry. Vol. 1.

PLATT, K. B. (1931). Master's Thesis, Univ. of Minn., cf. Pregnancy diseases of sheep. Roderick, L. M., and Harshfield, G. S. (1932). *North Dakota Tech.* Bull. 261.

POTEN, W. (1925). *Monatschr. f. Geburtsh. u. Gynäk.*, 69-25. cf. Relation between blood plasma proteins and toxemias of pregnancy. *Jour. Am. Med. Assoc.*, Vol. 3, pp. 1898-1902.

PRIOR, R. (1926). *7th Biannual Rept. of Dept. of Agr. of Wash.*, p. 77. cf. Some obscure diseases of sheep. *Jour. Am. Vet. Med. Assoc.*, N.S. Vol. 27, pp. 724-735.

RITZMAN, E. G., AND BENEDICT, F. G. (1931). *Tech. Bull. No.* 45, *New. Hamp., Agr. Expt. Sta.*, cf. Ketonaemia in pregnant ewes and its possible relation to pregnancy disease. *Jour. Physiol.*, Vol. 97, pp. 120-127.

RODERICK, L. M., AND HARSHFIELD, G. S. (1932). Pregnancy disease of sheep. *Tech. Bull.* 261, *North Dakota Expt. Sta., Fargo.*

RODERICK, L. M., HARSHFIELD, G. S., AND MERCHANT, W. R. (1933). Further observations on the functional pathology of pregnancy disease of ewes. *Cornell Veterinarian*, Vol. 33, pp. 348-353.

RODERICK, L.M., HARSHFIELD, G. S., AND HAWN, M. C. (1937). The pathogenesis of ketosis. Pregnancy disease of sheep. *Jour. Amer. Vet. Med. Assoc.*, Vol. 43, No. 1, pp. 41-50.

ROSE, A. L. (1934). Pregnancy toxemia of ewes. *Aust. Vet. Jour.*, Vol. 10, pp. 111-117.

ROSENSTEIN, S. S. (1874). *Traité pratique des maladies des reins*, Paris, Adrein Delahaye.

RUSHWORTH, W. A. (1903). Sheep and their diseases. pp. 146-147.

SAMPSON, J., CONZAGA, A. C., AND HAYDEN, C.E. (1933). The ketones of the blood and urine of the cow and ewe in health and disease. *The Cornell Vet.*, Vol. 23, pp. 184-207.

SAMPSON, J., AND ERRINGTON, B. J. (1933). Acetonemia in a two-year-old Jersey heifer. *Cornell Vet.*, Vol. 23, pp. 223-227.

SAMPSON, J., AND HAYDEN, C. E. (1935). The acid-base balance in cows and ewes during and after pregnancy with special reference to milk fever and acetonemia. *Jour Amer. Vet. Med. Assoc.*, Vol. 39, pp. 13-23.

SHAPIRO, B., AND WERTHEIMER, E. (1937). Action of pancreatic extract on fatty liver. *Nature*, Vol. 140, p. 771.

SHAW, J. N. (1933). A liver function test in sheep. *Jour. Amer. Vet. Med. Assoc.*, Vol. 35, pp. 199-204.

SINGER, K., AND TAUBENHAUS, M. (1937). Zur Frage des Kohlehydratstoffwechselhormons. *Wien. Arch. im. Med.*, Vol. 31, pp. 59-66.

SNOOK, L. C. (1939). Fatty infiltration of the liver in pregnant ewes. *Jour. Phys.*, Vol. 97, pp. 238-249.

STANDER, H. J. (1929). The toxemias of pregnancy. cf. Pregnancy disease of sheep. Roderick, L. M., and Harshfield, G. S. (1932). *North Dakota Tech.*, Bull 261.

STANDER, H. J., AND CADDEN, J. F. (1930). Acetone bodies in normal pregnancy and in the toxemias of pregnancy. *John Hopkins Hosp.*, Bull. 47, pp. 382-390.

STINSON, O. (1928). Observations on twenty consecutive cases of the bovine disease known as post-parturient dyspepsia, second cleansing, low fever and more recently, Acetonuria, *The Vet. Red.*, Vol. 8, No. 41, pp. 880-881.

STEELE, J. H. (1890). Diseases of sheep. p. 213.

STEYN, H. P. (1941). *Jl. S.A.V.M.A.*, Vol. 12, No. 3, pp. 86-89.

STEWART, W. L. (1938). *4th Rept., Duke North., Mem., Fund.*, p. 25. cf. The influence of diet upon ketonaemia in pregnant ewes. *Jour. Physiol.*, Vol. 94, No. 3, pp. 346-357.

STRAUSS, M. B. (1935). *Amer. Jour. Med. Sci.*, 190-811. cf. Relation between blood plasma proteins and toxemias of pregnancy. *Jour. Amer. Med. Assoc.*, Vol. 3, pp. 1898-1902.

STRAUSS, M. B. (1937). *Amer. Jour. Med. Sci.*, Vol. 194, pp. 772-783. cf. Relation between blood plasma proteins and toxemias of pregnancy. *Jour. Amer. Med. Assoc.*, Vol. 3, pp. 1898-1902.

SJOMMELA, B. (1932). Nutritional and metabolic disorders in cattle. *Nutrition Abstracts and Rev.*, Vol. 6, pp. 621-632. (1922). *The Thirty-fifth Ann. Rept. of the Director Ky., Agr. Expt. Sta.*, p. 53.

TRAUM, J. (——). Preparturient paralysis of ewes. *Univ. of California*, Leaflet, College of Agric.

TRAUTMANN, A., UND KOCH, C. (1933). Das Verhalten der Alkali-reserve des Blutes während der Schwangerschaft, Geburt, Laktation und beim Neugeborenen Untersuchungenden ziegen. *Z. Züchtg. B. Tierzüchtgbial.*, Vol. 26, pp. 193-202.

TUCKER, H. F., AND ECKSTEIN, H. C. (1937). The effect of supplementing methionine and cystine on the production of fatty livers by diet. *Jour. Biol. Chem.*, Vol. 121, pp. 479-484.

VAN RENSBURG, S. (1927). Domsiekte in pregnant ewes. *S.A.V.M.A. Jour.*, Vol. 1, pp. 58-60.

VAN RENSBURG, S. (1931). Pregnancy disease in ewes. *Vet. Red.*, Vol. 11, No. 46, pp. 1147-1148.

W. H. W. (1939). Acetonemia in cows. *Vet. Med.*, Vol. 34, No. 11, p. 647.

WELLS, H. G. (1925). *Chemical Pathology*, 5th Ed., pp. 614-616.

WESTER, J. (1935). Orgaanziekten by de groote huisdieren. *Utrecht*, B. 585-599.

WILLIAMS, J. W. (1927). The toxemias of pregnancy and the treatment of eclampsia. *Jour. Amer. Med. Assoc.*, Vol. 88, pp. 449-454.

WILLIAMS, SPIES (1938). Vitamin B_1 (Thiamin) and its use in medicine. *The Macmillan Co.*, New York. cf. *Acta Medica Scandinavica*, Vol. 102, Fasc. 3, pp. 175-213.

WILLIAMSON, C. S., AND MANN, F. C. (1923). Studies on the physiology of the liver. V. The hepatic factor in chloroform and phosphorus poisoning. *The Amer. Jour. of Phys.*, Vol. 65, No. 2, pp. 267-276.

WIELOCH, J. (1925). *Arch. f. Gynäk.*, 123:337. cf. Relation between blood plasma proteins and toxemias of pregnancy. Dodge, E., and Frost, T. T. (1938). *Jour. Amer. Med.* Assoc., Vol. 3, pp. 1898-1902.

ZIMMERMANN, H. M., AND PETERS, J. P. (1937). Pathology of pregnancy toxemias. *Jour. of Clinical Investigation*, Vol. 16, pp. 397-420.