Care, A. D. & Gitelman, H. J. (1968). *J. Endocr.* **41**, xxi.
Care, A. D. & Keynes, W. M. (1964). *Proc. R. Soc. Med.* **57**, 867.
Care, A. D., Keynes, W. M. & Duncan, T. (1966). *J. Endocr.* **34**, 299.
Care, A. D., Sherwood, L. M., Potts, J. T. & Aurbach, G. D. (1966). *Nature, Lond.* **209**, 55.
Care, A. D., Vowles, L. E., Mann, S. O. & Ross, D. B. (1967). *J. agric. Sci., Camb.* **68**, 195.
Chase, L. R. & Aurbach, G. D. (1968*a*). In *Parathyroid Hormone and Thyrocalcitonin* (*Calcitonin*), p. 247. [R. V. Talmage & L. F. Belanger, editors.] Amsterdam: Excerpta Medica Foundation.
Chase, L. R. & Aurbach, G. D. (1968*b*). *Abstracts of Brief Communications, Third International Endocrine Congress*, p. 87. *International Congress Series* no. 157. Amsterdam: Excerpta Medica Foundation.
Cramer, C. F. (1963). *Endocrinology* **72**, 192.
Inskeep, E. K. & Kenny, A. D. (1968). *Endocrinology* **83**, 183.
Jowsey, J. & Simons, G. W. (1968). *Nature, Lond.* **217**, 1277.
Keynes, W. M. & Care, A. D. (1967). *Proc. R. Soc. Med.* **60**, 1136.
Mayer, G. P., Ramberg, C. F. & Kronfeld, D. S. (1967). *J. Nutr.* **92**, 253.
Mayer, G. O., Ramberg, C. F., Kronfeld, D. S., Buckle, R. M., Sherwood, L. M., Aurbach, G. D. & Potts, J. T. (1969). *Am. J. vet. Res.* (In the Press.)
Sherwood, L. M., Mayer, G. P., Ramberg, C. F., Kronfeld, D. S., Aurbach, G. D. & Potts, J. T. (1968). *Endocrinology* **83**, 1043.
Stott, G. H. (1968). *Fedn Proc. Fedn Am. Socs exp. Biol.* **27**, 156.
Vaes, G. (1968). In *Parathyroid Hormone and Thyrocalcitonin* (*Calcitonin*), p. 318. [R. V. Talmage and L. F. Belanger, editors.] Amsterdam: Excerpta Medica Foundation.

Chronic copper toxicity of ruminants

By J. R. Todd, *Ministry of Agriculture, Veterinary Research Laboratories, Stormont, Belfast, BT4 3SD*

There has been an active interest in the toxicology of copper since the middle of the 19th century and a review by Davenport (1953) covers the early work on the hazard to man and animals of both the acute and chronic forms. Review material specific to chronic copper poisoning in farm livestock has also been published by Broughton & Hardy (1934), Eden (1940), Todd (1962) and Bull (1964).

The first description of true chronic copper poisoning in farm animals would seem to be that of Mallory (1925) who produced the condition experimentally in sheep. Beijers (1932) described similar symptoms in sheep grazing orchards which had been sprayed with a copper fungicide, and 2 years later Broughton & Hardy (1934) published their detailed experimental investigations showing the dangers of excessive copper intakes to sheep. The similarity between the symptoms described in these reports and those of 'yellows' or 'toxaemic jaundice' in Australia was recognized (Bull, 1964) and the experiments of Albiston, Bull, Dick & Keast (1940) confirmed that this naturally-occurring condition was of similar origin. The importance of chronic copper poisoning as a nutritional hazard was, therefore, fully established.

More recently the danger has arisen under different circumstances in the British Isles, and it is now recognised that excessive accumulation of copper is one of the hazards when sheep are maintained indoors for prolonged periods.

Toxic syndrome

The clinical picture of chronic copper poisoning is characteristic and is quite

different from acute poisoning where one single large dose acts as a corrosive poison and causes enteritis, scouring, severe abdominal pain and perhaps death. Chronic copper poisoning on the other hand has two distinct phases:

(1) A period of passive accumulation of copper in the tissues. This period may vary from a few weeks to more than 1 year and during this time the animal exhibits no symptoms of toxicity.

(2) The toxic phase which is an acute illness referred to as the 'haemolytic crisis'. In some cases death may take place in a few hours, but more commonly the animal becomes dull, refusing to eat, but has an excessive thirst. Examination of the mucous membranes reveals jaundice as the predominant symptom. The eye is usually sunken and the veins show the chocolate colour of methaemoglobin. Haemoglobinuria is also a prominent feature. The illness progresses rapidly and usually ends in death in from 2 to 4 days.

British breeds of sheep rarely survive the haemolytic crisis, but Merinos may survive two or three crises before succumbing (Marston, 1950). The survival rate among calves is variable; in our experience of cases occurring on farms, few survive, but in the outbreak reported by Shand & Lewis (1957) there were only two deaths, although twenty of the animals in a group of twenty-one underwent an haemolytic episode.

The post-mortem appearance of the carcass is that of generalized icterus. The cut surface of the liver usually shows severe jaundice, although where death is sudden it may be muddy-brown. The appearance of the kidney is probably the most characteristic feature, particularly in sheep, in that it is completely gorged with haemoglobin breakdown products. The capsule has a black metallic sheen, and on section both medulla and cortex are found to be black. The spleen is greatly enlarged with the parenchyma a deep brown to black colour. Altogether the picture is typical of an acute haemolytic episode.

Species susceptibility

Most of our information on the susceptibility of different species comes from accidental or unwitting overdosage. Ruminants appear to be more susceptible than monogastric animals, of which only pigs present a problem under practical farm conditions.

Sheep are the most susceptible species and can be affected at any age, most reported cases being in mature animals (Ogilvie, 1954; Clegg, 1956; Pearson, 1956; Pryor, 1959; Bracewell, 1958; Senior, 1959; Gracey & Todd, 1960; Reitz, 1936; Kowalczyk, Pope & Sorensen, 1962). On the other hand, cattle seem to become less susceptible to chronic copper poisoning as they mature. Young calves are almost as susceptible as sheep, and outbreaks, due to excessive copper intakes, do occur on farms (O'Moore, 1956; Shand & Lewis, 1957). Older calves are more tolerant, but cases have occurred in yearling animals under exceptional circumstances (Todd & Gracey, 1959; Kidder, 1949). Todd & Gribben (1965) reported a probable case of chronic copper poisoning in a Jersey cow, but adult cattle seem to tolerate high copper intakes for extended periods. Cunningham (1946) fed 5 g copper sulphate

daily to a cow for 9 months without ill effects, and Chapman, Nelson, Kidder, Sippel & Kidder (1962) found no evidence of toxicity in steers given orally up to 8 g copper sulphate in a gelatin capsule daily for 12 months and then up to 12 g daily for a further 4 months. However, the latter workers also reported that two out of three steers given 12 g copper sulphate daily as a drench died in 2 months, which would seem to indicate a remarkable difference in toxicity between the two methods of administration.

From the point of view of a nutritional disorder, however, chronic copper poisoning in ruminants can be considered as being almost entirely confined to sheep.

Clinical biochemistry and pathology

Under the conditions which lead to chronic copper poisoning there is an accumulation of copper in the animal body. This accumulation is almost entirely located in the liver, there being virtually no change in the concentration in any of the other tissues (Table 1).

Table 1. *Copper content of sheep tissue (ppm, wet-matter basis)*

Tissue	Normal sheep*	Sheep on high-Cu diet†	Cu-poisoned sheep†
Liver	12	295 ±72	432 ±89
Kidney	4·8	5·4±2·3	60 ±42
Spleen	5·0	2·7±1·8	18·5± 7·7
Heart	5·0	4·6±1·1	8·4± 4·4
Lung	4·8	3·0±0·8	9·8± 4·6
Muscle	2·1	2·4±0·5	2·5± 1·0
Brain	—	3·8±0·6	4·6± 1·7

*Eden (1940).

†Todd & Thompson, unpublished observations, mean and standard errors.

In normal animals the liver copper rarely exceeds 50 ppm in the fresh tissue, whereas with excessive copper storage the levels may exceed 1000 ppm. None of the other tissues contain more than a few ppm of copper, even though the liver concentration may be extremely high. These findings contrast with Wilson's disease in man where elevated copper levels are also found in other tissues, e.g. brain. The last column in Table 1 shows that when animals have undergone the haemolytic crisis there is a marked elevation of copper in the kidney and to a lesser extent in the spleen. Slight elevations occur in other tissues and are probably caused by the increased levels of copper in the blood.

During the period of accumulation of copper the blood copper levels remain within the normal range, but when liver stores are high then any stress may precipitate the catastrophic release of copper into the blood stream. The blood copper concentration may rise to three to twenty times normal and is probably the direct cause of the haemolysis which takes place some 24–48 h later. The haemolysis is very rapid and the haemoglobin level may fall to one-quarter or less of its original level within 2–3 days (Todd & Thompson, 1963). A similar haemolysis can be produced in sheep by repeated intravenous injections of small amounts of copper over

2–4 days (Todd & Thompson, 1964). In both types of haemolytic episode minimum haemoglobin values in animals which recovered have been about 3%.

Other biochemical changes take place at this time and are qualitatively similar in both sheep and calves (Todd, Gracey & Thompson, 1962; Todd & Thompson, 1963, 1965). Methaemoglobin may increase to some 2–4% (35% of the total haemoglobin) during the 1st and 2nd days of the haemolytic crisis and then falls again rapidly. Glutathione (non-protein thiols) concentration falls markedly at the commencement of the haemolytic crisis to levels of less than 10% of the pre-crisis levels (Table 2).

Table 2. *Blood glutathione content in chronic copper poisoning (mg/100 ml whole blood)*

Normal sheep	24·6–45·3
Poisoned sheep:	
Before haemolytic crisis	27·7–50·1
After haemolytic crisis	0·6–3·1

There is a wide variation in the blood glutathione levels in individual sheep and results indicate that haemolysis begins when the glutathione level falls to about half its initial concentration.

These changes in glutathione and methaemoglobin are analogous to the haemolytic episodes produced in certain human subjects by drugs of the primaquin type, and individuals who react in this way have been shown to have erythrocytes deficient in the enzyme glucose-6-phosphate dehydrogenase (G-6-PD). The relative activities in different species are listed in Table 3, and it can be seen that the activities in drug-sensitive humans are very much lower than normal and that sheep erythrocytes have activities much lower than those of other domestic animals though not quite as low as in drug-sensitive human beings.

Table 3. *Relative glucose-6-phosphate dehydrogenase activities of the erythrocytes in different species**

Man:	
Normal	10·35
Drug-sensitive	0·55
Sheep	1·23
Cow	7·3
Pig	11·1
Horse	16·5

*Salvidio, Pannacciulli & Tizianello (1963).

At the onset of the haemolytic crisis there are also very marked increases in the activities of serum enzymes, lactic dehydrogenase (LD), glutamic-oxalacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT), and both LD and GOT show increases some 6–8 weeks before the onset of the haemolytic crisis (Todd & Thompson, 1963; Van Adrichem, 1965). Ross (1964) has used serum GOT levels in forecasting the possibility of clinical cases of chronic copper poisoning occurring in housed sheep.

These increases suggest that there is widespread destruction of liver tissue taking place at the time of the haemolytic crisis, and central necrosis of liver lobules has been described by several workers as the main lesion in animals which have died of chronic copper poisoning (Clegg, 1956; Pearson, 1956; Sutter, Rawson, McKeown & Haskell, 1958). In calves slaughtered after high copper intake but before clinical symptoms appeared, Shand & Lewis (1957) found similar lesions but much less severe than in calves which had died of the disease.

Barden (1962), using histological methods, confirmed the redistribution of copper at the time of the haemolytic crisis. Before the crisis the copper was mainly located in the liver parenchyma cells with very little in the Kupffer cells, whereas after the crisis the copper could also be found in the Kupffer cells. Engorgement of the uriniferous tubules with broken-down erythrocytes and haemoglobin derivatives is a constant finding (Marston, 1950; Pierson & Aanes, 1958) and necrosis of the tubules has also been found (Clegg, 1956; Pearson, 1956).

The haemolytic crisis is also accompanied by qualitative and quantitative changes in the blood cells (Chamberlain, 1933; Todd & Ross, 1966 (unpublished observations)). Red cell numbers decrease to one-quarter or less of the pre-crisis level and nucleolated red cells and cells which show basophilic stipling appear. There is also a three- to five-fold increase in white cells, the increase being mainly in the neutrophil fraction.

Conditions of occurrence

Overdosage with copper compounds can lead to chronic copper poisoning, but of more particular interest from the nutritional standpoint are the conditions under which the disease occurs but where copper intakes are apparently within the normal range. These conditions are confined to sheep, and have apparently not been recorded in cattle.

The metabolism of copper represents a very complex situation affected not only by the intake of copper itself, but also by other factors in the diet including molybdenum, sulphate and perhaps calcium, zinc, iron and other factors as yet ill-defined. The copper, molybdenum, sulphate interrelationships are probably the most important from the point of view of ruminant nutrition. The antagonism between copper and molybdenum was first recognized in the 'teart' areas in Somerset by Ferguson, Lewis & Watson (1938, 1943) and Ferguson (1943). Subsequently Dick & Bull (1945) in Australia showed experimentally that the storage of copper in the livers of sheep and cattle could be significantly reduced by increasing the dietary intake of the molybdenum. Later Dick (1954) showed that adequate intakes of sulphate were also necessary to allow the molybdenum to exert its limiting effect on copper storage. These interrelationships are important in the aetiology of chronic copper poisoning.

Toxaemic jaundice in Australia. From 1926 onwards deaths occurred in sheep grazing pastures in New South Wales and Victoria. The disease was referred to as 'yellows' and was subsequently recognized as being a form of chronic copper poisoning. Further studies showed that there were two main types:

(a) Phytogenous chronic copper poisoning which occurred in restricted areas

only, but could result in losses of up to 20% of the animals at risk in any given year. This type occurred particularly when favourable rainfall encouraged the early and rapid growth of subterranean clover (*Trifolium subterraneum* L.). Under these circumstances the herbage was found to contain negligible amounts of molybdenum (0·1–0·2 ppm of the dry matter) and normal to high amounts of copper (up to 20 ppm of the dry matter) (Bull, Albiston, Edgar & Dick, 1956). Very low intakes of molybdenum, resulting in a high ratio of copper:molybdenum, may lead to the rapid increase in liver copper, and the occurrence of phytogenous chronic copper poisoning can, therefore, be directly explained by the mineral composition of the herbage.

(b) *Hepatogenous chronic copper poisoning.* In other areas where toxaemic jaundice occurred it was found that certain weeds growing in the pastures contained hepatotoxic alkaloids. If eaten in sufficient quantity these weeds could cause death, but if sublethal amounts were consumed then the alkaloids caused both biochemical and morphological changes in the liver cells which greatly enhanced their powers of accumulating copper and thus predisposed the animals to chronic copper poisoning. The most important of the species involved is the heliotrope plant (*Heliotropium europaeum*), but others such as the ragworts (Senecio sp.) also have similar effects. The primary lesion in this instance is considered to be the liver damage caused by the toxic weeds.

Jaundice in housed sheep. It has become apparent in recent years that when sheep are kept indoors for extended periods, chronic copper poisoning is one of the possible hazards. Bracewell (1958) reported that 24 out of 720 ewes housed for periods of up to 16 months, died of haemolytic jaundice. For the first 5 months a mineral supplement contributing 43 ppm copper to the dry matter of the ration had been incorporated, but at this point the first cases of poisoning occurred and the supplement was withheld thereafter. In spite of this, further cases occurred for a further 11 months. Senior (1959) reported a similar case in sheep where no extra copper was included in the ration. With the increasing numbers of sheep either over-wintered or fattened indoors cases of chronic copper poisoning have become more prevalent, and not all of these are associated with excessive intakes of copper. We have investigated several of these and, in one case involving ewes housed for about 2 months during the winter, the overall copper content of the ration was about 30 ppm in the dry matter, and in another outbreak in lambs maintained indoors from birth to 5 months of age, samples of the hay and concentrates fed were found to contain 6 ppm and 11 ppm copper in the dry matter respectively.

In most outbreaks only a small proportion of the flock dies, probably no more than 1–2%, and Hemingway & MacPherson (1967) have pointed out that, under normal feeding systems, with no supplementary copper added to the rations of lambs fattened indoors for a period of 16–20 weeks, the danger of chronic copper poisoning occurring is not great. There is a great variability between individual animals in their ability to accumulate copper. Table 4 shows the distribution of the copper contents of the livers of thirty sheep which had been maintained indoors for a period of 10 months. One animal died of chronic copper poisoning after 6 months indoors,

but no further deaths occurred, and it can be seen that of the thirty samples twenty contained less than 300 ppm in the wet tissue and only one contained more than 500 ppm.

Table 4. *Individual variability in copper accumulation in the liver of sheep maintained indoors for* 10 *months* (*one death after* 6 *months*)

Liver Cu distribution (ppm wet matter)	No of animals
100–199	3
200–299	17
300–399	6
400–499	3
>500	1

This would tend to support the view that only a small proportion of the animals is in danger under these circumstances, although any set-back or stress could precipitate the toxic syndrome. Also, in special circumstances such as when rams are kept indoors when not in use, and when pedigree stock are being maintained indoors and prepared for exhibition at agricultural shows, losses have in some instances been very much higher.

Either environmental or dietary factors could be involved in the apparent increased susceptibility of housed sheep to chronic copper poisoning. Information on the effects of environmental factors on metabolism is scanty, but Poole (1967) found no differences in the liver copper contents of lambs fed the same ration for approximately 12 weeks under three environmental regimes, namely (a) penned outdoors; (b) penned indoors in a well-ventilated house; and (c) penned indoors in a thermostatically controlled unit. These findings would tend to rule out environmental factors as playing a dominant role in copper metabolism, although further work would be required before a final assessment could be made.

Under dietary factors which can contribute towards chronic copper toxicity the inadvertent inclusion of extra copper must be taken into consideration. This can occur in a variety of ways, e.g. (a) mineral supplements may contain copper; (b) anthelmintics are often supplemented with trace elements, particularly cobalt and copper; and (c) pelleting of the ration—the use of a bronze die in the pelleting process has been known to increase the copper content of the ration by some 10 ppm.

As indicated above, however, cases of chronic copper poisoning occur where excessive copper intakes cannot be demonstrated. Other factors in the ration have, therefore, been investigated. The evidence on the effect of protein concentration on copper storage seems to be equivocal. In growing pigs Wallace, McCall, Bass & Combs (1960) found that the toxicity of 750 ppm of copper decreased as the protein level in the ration was increased. Also McCall & Davis (1961), working with rats, found that when the diet contained 25% of protein a diet containing 1000 ppm of supplementary copper produced no significant increase in liver copper concentration, whereas there was a highly significant increase in liver copper storage when

the diet contained only 10% of protein. On the other hand, MacPherson & Hemingway (1965) found that at low copper intakes, increasing the crude protein content of the ration of sheep had no effect on the concentration of copper in the livers. At high copper intakes (1 g copper sulphate per animal per day) the ration high in crude protein did apparently have an effect and decreased the incidence of chronic copper poisoning in the animals.

Further information on the effect of protein intake on liver copper stores in sheep is presented in Table 5 (Robinson, Forbes & Todd, unpublished observations). As the crude protein content of the diet increased, the stores of copper in the livers decreased and there was a highly significant correlation between liver copper content and crude protein intake for individual animals. The crude protein concentration in the different diets in this experiment was altered by substituting soya-bean meal for barley, and Table 5 shows that, as well as being a source of protein, the soya-bean was also a source of molybdenum. The molybdenum contents of the rations, therefore, increased with the crude protein content and this in itself could have affected the metabolism and retention of copper. In the experiment of MacPherson & Hemingway (1965) the protein concentration of the ration was altered by adding a small amount of blood meal, which was a poor source of molybdenum.

Table 5. *Effect of the crude protein and molybdenum contents of the diet on the copper content of the liver of sheep*

(Ten sheep/treatment; 15-week feeding period)

Dietary content		Liver Cu content (ppm wet matter)	
Crude protein (% dry matter)	Mo (ppm dry matter)	Mean	Range
8·7	0·4	197	101–256
15·1	2·9	149	68–271
21·3	3·9	85	51–106
24·7	5·5	73	48–99
Group slaughtered before experiment		107	82–144

In pigs O'Donovan, Spillane & O'Grady (1966) found that, on diets containing 250 ppm of supplemental copper, the average liver copper content was almost 1800 ppm in the dry matter when the protein source was dried skim milk, but only 800–900 ppm when the protein source was white-fish meal or soya-bean meal. The effect of protein concentration on liver copper may, therefore, be confounded with other factors in the protein source.

Mills (1964) has reviewed the influence of the type of dietary protein on trace element metabolism and, although the protein content of the ration *per se* may have an effect on copper metabolism, the parts played by other known interfering factors, such as molybdenum and sulphate, will have to be taken into account before a final assessment can be made.

Copper accumulation and live-weight gain

It is pertinent to consider whether excessive accumulation of copper in the liver may interfere with live-weight gain. The increases in serum enzyme activities commencing 6–8 weeks before clinical symptoms appear would indicate increasing liver damage from about this time onwards, and could possibly result in lack of thrift. Practical experience, however, indicates that this is not the case. Copper-poisoned animals are not necessarily emaciated, and in fact most animals affected are found to be in good bodily condition.

Also, the animals represented by the liver copper distribution values presented in Table 4 were weighed regularly throughout the experimental period and there was no difference in live-weight gain between those with the highest liver copper stores and those with the lowest. Also the animal which died of chronic copper poisoning in this experiment gained at the same rate until clinical symptoms appeared 3 days before death.

REFERENCES

Albiston, H. E., Bull, L. B., Dick, A. T. & Keast, J. C. (1940). *Aust. vet. J.* **16**, 233.
Barden, P. J. (1962). Copper Metabolism in Farm Animals. PhD Thesis, University of Edinburgh.
Beijers, J. A. (1932). *Tijdschr. Diergeneesk.* **59**, 1317.
Bracewell, C. D. (1958). *Vet. Rec.* **70**, 342.
Broughton, I. B. & Hardy, W. T. (1934). *Bull. Tex. agric. Exp. Stn* no. 499.
Bull, L. B. (1964). *The Victorian Veterinary Proceedings* July 1964, p. 17.
Bull, L. B., Albiston, H. E., Edgar, G. & Dick, A. T. (1956). *Aust. vet. J.* **32**, 229.
Chamberlain, W. E. (1933). *Aust. vet. J.* **9**, 2.
Chapman, H. L. Jr, Nelson, S. L., Kidder, R. W., Sippel, W. L. & Kidder, C. W. (1962). *J. Anim. Sci.* **21**, 960.
Clegg, F. G. (1956) *Vet. Rec.* **68**, 332.
Cunningham, I. J. (1946). *N.Z. Jl Sci. Techol.* **27A**, 372.
Davenport, S. J. (1953). *Inf. Circ. U.S. Bur. Mines* no. 7666.
Dick, A. T. (1954). *Aust. J. agric. Res.* **5**, 511.
Dick, A. T. & Bull, L. B. (1945). *Aust. vet. J.* **21**, 70.
Eden, A. (1940). *J. comp. Path.* **53**, 90.
Ferguson, W. S. (1943). *J. agric. Sci., Camb.* **33**, 116.
Ferguson, W. S., Lewis, A. H. & Watson, S. J. (1938). *Nature, Lond.* **141**, 553.
Ferguson, W. S., Lewis, A. H. & Watson, S. J. (1943). *J. agric. Sci., Camb.* **33**, 44.
Gracey, J. F. & Todd, J. R. (1960). *Br. vet. J.* **116**, 405.
Hemingway, R. G. & MacPherson, A. (1967). *Vet. Rec.* **81**, 695.
Kidder, R. W. (1949). *J. Anim. Sci.* **8**, 623.
Kowalczyk, T., Pope, A. L. & Sorensen, D. K. (1962). *J. Am. vet. med. Ass.* **141**, 362.
McCall, J. T. & Davis, G. K. (1961). *J. Nutr.* **74**, 45.
MacPherson, A. & Hemingway, R. G. (1965). *J. Sci. Fd. Agric.* **16**, 220.
Mallory, F. B. (1925). *Am. J. Path.* **1**, 117.
Marston, H. R. (1950). In *Copper Metabolism*, pp. 272, 313. [W. D. McElroy and B. Glass, editors.] Baltimore, Md: John Hopkins Press.
Mills, C. F. (1964). *Proc. Nutr. Soc.* **23**, 38.
O'Donovan, P. B., Spillane, T. A. & O'Grady, J. F. (1966). *Anim. Prod.* **8**, 333.
Ogilvie, D. D. (1954). *Vet. Rec.* **66**, 279.
O'Moore, L. B. (1956). *Irish vet. J.* **10**, 225.
Pearson, J. K. L. (1956). *Vet. Rec.* **68**, 766.
Pierson, R. E. & Aanes, W. A. (1958). *J. Am. vet. med. Ass.* **133**, 307.
Poole, D. B. R. (1967). *Res. Rep. An Foras Talúntais* p. 172.
Pryor, W. J. (1959). *Aust. vet. J.* **35**, 366.
Reitz, J. H. (1936). *Bull. W. Va agric. Exp. Stn* no. 271.
Ross, D. B. (1964). *Vet. Rec.* **76**, 875.
Salvidio, E., Pannacciulli, I. & Tizianello, A. (1963). *Nature, Lond.* **200**, 372.

Senior, V. E. (1959). *Can. J. comp. Med.* **23**, 229.
Shand, A. & Lewis, G. (1957). *Vet. Rec.* **69**, 618.
Sutter, M. D., Rawson, D. C., McKeown, J. A. & Haskell, A. R. (1958). *Am. J. vet. Res.* **119**, 890.
Todd, J. R. (1962). *Vet. Bull., Weybridge* **32**, 573.
Todd, J. R. & Gracey, J. F. (1959). *Vet. Rec.* **71**, 145.
Todd, J. R., Gracey, J. F. & Thompson, R. H. (1962). *Br. vet. J.* **118**, 482.
Todd, J. R. & Gribben, H. J. (1965). *Vet. Rec.* **77**, 498.
Todd, J. R. & Thompson, R. H. (1963). *Br. vet. J.* **119**, 161.
Todd, J. R. & Thompson, R. H. (1964). *J. comp. Path.* **74**, 542.
Todd, J. R. & Thompson, R. H. (1965). *Br. vet. J.* **121**, 90.
Van Adrichem, P. W. M. (1965). *Tijdschr. Diergeneesk.* **90**, 1371.
Wallace H. D., McCall, J. T., Bass, B. & Combs, G. E. (1960). *J. Anim. Sci.* **19**, 1153.

Urinary calculi in ruminants

By A. C. FIELD, *Moredun Research Institute, Edinburgh*

Urolithiasis is not at present an important problem for the livestock industry in the United Kingdom, but the probable introduction of more intensive systems of management may change this position. The rapid fattening of male animals with high-energy diets predisposes to formation of phosphatic calculi and obstructive urolithiasis in the feed lot system of the USA and it is a form of this type of management which is most likely to be introduced to this country. For this reason, this review will be limited to the problem of phosphatic calculus formation, although other calculi, especially siliceous forms cause economic loss in extensive areas of the world.

Much of the information on urolithiasis in ruminants comes from empirical attempts at reducing the high incidence of calculi associated with the feeding of certain important animal feeding-stuffs in USA. There are few comprehensive experiments designed solely to study the aetiology of calculus formation and data from studies in humans have been used, principally in the section on the theories of calculus formation, despite the frequent species differences in the composition of calculi, in urine pH and in diets.

Theories of calculus formation

A satisfactory hypothesis for the aetiology of calculus formation must explain the initiation or nucleation of calculi, their subsequent growth and why they lodge in the kidney or bladder instead of being passed out in the urine. Current hypotheses fall broadly into three categories.

Matrix theory. The urinary macromolecules, collectively known as urinary colloids, have been incriminated in urolithiasis as they are invariable components of the moeity of calculi (Boyce, Garvey & Norfleet, 1954; Boyce & Swanson, 1955). In the matrix theory, calculus formation is viewed as a process similar to calcification of cartilage, bone and teeth. Here a precedent matrix provides a specialized medium in which the dissolved calcium, magnesium, phosphate and other ions combine and crystallize to eventually mineralize the matrix. Unfortunately, urinary protein excretion cannot be correlated with the incidence of urinary calculi in ruminants, because