IMPLICATION OF CALCINOGENIC PLANTS IN ANIMAL PRODUCTION

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INTRODUCTION

Many factors have been implicated in the low productivity of different classes of livestock in many areas of the tropics and sub-tropics. These have been categorized under nutrition, management and environmental factors. Nutrition of the animal has been considered of primary importance where the factors of management and environment have been reasonably well controlled. Nutrition of the large and small ruminant stock in many developing countries have been almost entirely based or unimproved grassland tracts and browse, in which several weed species abound. Incidence of sudden death in the flock, reproductive failure and general unthriftiness have been blamed on specific nutrient deficiencies or inadequate intake of nutrients required for efficient production. Evidences accumulating from elsewhere (Collier, 1927; Carrillo and Worker, 1967; Worker and Carrillo, 1967; Döbereiner et al., 1971; Kirksen et al. 1972; Krook et al., 1975a, b) point to the involvement of wild plant, weeds in some of the pathological conditions which adversely affect productive and reproductive performance in the livestock. The significance

of such plants in the low productivity of tropical livestock under present managemen practices has not been assessed as is often completely ignored in the discussion of animal productivity in this region. This paper reviews relevant work in the area of calcinogenic plants with a view ot highlighting their implication for animal productio under range conditions.

HISTORY OF CALCINOGENIC PLANTS

"Enteque seco" (wasting of unknown origin), is a chronic wasting disease of grazing animals which has been recognized for many years in the lowland areas of the province of Buenos Aires in Argentina. It was described in 1898 by Lignieres who thought it might result from chronic pasteurellosis. Subsequent observations failed to confirm the suggestion of an infectious nature of this entity which is responsible for death or slaughter of 300,000 cattle annually and unknown number of sheep (Worker and Carrillo, 1967).

Collier (1927) suggested that the prolonged ingestion of the shrub, Solanum glaucum Dun. was the cause of the disease.

Carrillo and Worker (1967) and Worker and Carillo (1967) published experimental evidences that Solanum malacoxylon Sendtner (syn. S. glaucophyllum) is th cause of the disease. Feeding small amounts of dried leaves and aqueous extract of the shrub caused a significant hypercalcemia and hyperphosphatemia which was presumed to be responsible for the principal pathological changes of the disease.

In Brazil, Pardi and Santos (1947) observed that 5.24% of 2,172 cattle slaughtered in the pantanal region of Mato Grosso showed pulmonary ossification and calcification of the blood vessels and 29.2% had gross renal lesions.

Dobereiner et al. (1971) studied the naturally occurring disease, "espichamento" or "espichacao", in the same region and reproduced the condition in bovines by oral administration of dried leaves of S. malacoxylon.

Arnold and Fincham (1950) and Arnold (1954) described a chronic progressive disease of livestock in Jamaica known as the "Red earth disease" or "Manchester Wasting Disease".

Arnold and Fincham (1950) and Arnold (1969) suggested that the disease was caused by a vitamin D-like principle which exacerbated the existing imbalance for calcium, magnesium and phosphorus in the pasture.

"Naalehu disease", a disease similar to "enteque seco" and Manchester Wasting Disease" (Arnold and Bras, 1956) occurs in Hawaii (Hendershot 1942; Lynd et al. 1965; Willers et al. 1956; Lynd, 1969). Lynd (1969) suggested that the disease may be caused by a diet low in phosphorus and magnesium but rich in calcium and potassium.

Solanum sodomaeum has been mentioned in connection with "Naalehu disease" (Ross and Furumoto, 1971) but the results of their investigations have not been conclusive.

Onderscheka et al. (1967), Libiseller and Gunhold (1969), Kohler and Libiseller (1970) described a calcinotic disease of cattle, "Weidekrankeit", in the Alpine region of Austria. Although Onderscheka et al. (1967) attributed the pathogenesis of the disease to chronic magnesium deficiency, Kohler and Libiseller (1970) could not find any evidence of mineral deficiency.

An "enzootic calcinosis" of cattle was described in 1970 (Dirksen et al. 1970) in the Bavarian Alps in Germany. The disease has been reproduced in sheep by feeding hay from the affected pastures (Dirksen et al. 1971). Further work in rabbits (Dirksen et al. 1974) showed that pastures rich in Trisetum flavescens, contain the calcinosis factor.

Krook et al (1975) described a chronic debilitating disease in Florida horses and cattle due to ingestion of leaves of the shrub, Cestrum diurnum, (day-blooming jessamine, wild jasmin, king of the day).

Gill et al. (1976) described enzootic calcinosis in sheep in Mattewara, India which they thought might be due to complex mineral imbalance, although the possibility of a plant poisoning was not ruled out. After a chemical analysis of soil, water and forage from the affected area, Singh et al. (1976) concluded that the existence of calcium phosphorus, potassium and magnesium imbalances in feeds and forages of the affected farm possibly contributed to the causation of soft tissue calcinosis.

Calcinogenic Plants in Animal Production.

THE PHYSIOLOGICAL BASIS OF THE CALCINOGENIC PLANTS' ACTION

Trisetum flavescens, the causative agent of enzootic calcinosis, belongs to the Graminaceae family. The active factor has not yet been identified.

Both Solanum malacoxylon and Cestrum diurnum belong to the Solanaceae family and have been shown to contain factors similar to 1d25$(OH)_2$ D_3 (Wasserman and Corradino, 1974; Wasserman et al. 1976) the active metabolite of vitamin D_3 (Lawson et al, 1971; Norman et al, 1971). The 1 25 $(OH)_2$ D_3 - like activity of S. malacoxylon and C. diurnum was assessed by determining their effectiveness in chicks fed a high strontium diet. Such a regimen depresses calcium absorption and inhibits the synthesis of the duodenal vitamin D dependent calcium-binding protein (CaBP) (Corradino et al. 1971), an effect shown to be due to inhibition of conversion of 25 (OH) D_3 to 1 25$(OH)_2$ D_3 by the 1 hydroxylase enzyme of the kidney (Omdahl and De Luca, 1972).

Using the organ-culture chick duodenum, Corradino and Wasserman (1974) demonstrated that S. malacoxylon stimulated the duodenal uptake and the mucosal-to-serosal transport of ^{45}Ca, indicating that the activity of the factor does not depend on preliminary metabolism by some other tissue and that, indeed it resembles 1, 25$(OH)_2$ $-D_3$ in terms of bipotency.

Wasserman et al. (1975, 1976) reported that C. diurnum powder at 1.5 or 3% of the diet reversed the inhibitory effect of high strontium diet in young chicks

with regards to duodenal absorption of ^{47}Ca, the synthesis of the duodenal vitamin D dependent calcium-binding protein and duodenal concentration of cyclic adenosine - 3'5' - monophosphate (c AMP). The plant also significantly increased plasma calcium levels as compared to the group receiving stable strontium plus vitamin D_3 alone.

Walling et al. (1975) further demonstrated that C. diurnum extract is capable of stimulating intestinal calcium transport in cholecalciferol-deficient nephrectomized rats as measured by an in vitro method. Although both S. malacoxylon and C. diurnum contain substances similar to 1 25 $(OH)_2$ D_3, neither factor is identical to 1 25$(OH)_2$ D_3. Both factors exert their initial actions which decline rapidly in activity (Mautalen, 1972; Corradino and Wasserman, 1974; Wasserman et al. 1976). The S. malacoxylon factor is soluble in water but not in fat, and very soluble in methanol chloroform mixture (2:1) (Wasserman et al. 1975, 1976). The soluble in water and that soluble in the methanol : chloroform mixture are both capable of reversing the inhibitory effect of stable strontium diet but, however, the methanol : chloroform soluble material is about six times as active as the aqueous extract (Wasserman et al, 1976).

The bioassay of the cholecalciferol-like activity of C. diurnum indicated it to contain approximately 30,000 - 35,000 I.U. cholecalciferol equivalents per kg. dried leaf powder (Wasserman et al. 1976), while a similar assay of S. malacoxylon

indicated it contained about 330,000 I.U. cholecalciferol equivalent/kg, of dried leaf (Wasserman et al., 1975).

An understanding of the physiological basis of C. diurnum and S. malacoxylon toxicoses derives directly from current knowledge of vitamin D. metabolism. Normally the amount of 1, $25(OH)_2$ D_3 produced by the kidney is feed-back regulated, thereby controlling the rate of calcium absorption form the digestive system (Omdahl and DeLuca, 1973). Since C. diurnum and S. malacoxylon apparently contain factors that function like 1 $25(OH)_2$ D_3 the primary controlling point in vitamin D metabolism is by-passed and more calcium is absorbed than can be physiologically accomodated and thus, hypercalcemia occurs (Krook et al., 1975a, b).

The chemical structure of these calcinogenic factors are not available. However, recent information on the nature of one of the Solanum malacoxylon factors suggests that it is a cholecalciferol-like steroid, having a 5,7 - unsaturated ring structure, the triene system in a trans orientation, a hydroxyl in the 3-position and contains carbohydrate which might account for the water solubility of the Solanum malacoxylon factor (Peterlik and Wasserman, 1975). Wasserman et al., (1976), also noted that it would not be surprising if the Cestrum diurnum and Solanum malacoxylon factors were similar chemical entities since the biological properties are similar and that the fact that Cestrum diurnum factor had less carbohydrate would

account for the differences in the polarity of these molecules.

BLOOD CHEMISTRY

Calcium and Phosphorus

Arnold and Fincham (1950) and Arnold (1954) reported that the blood calcium is high, blood phosphorus low in "Manchester Wasting Disease". Carrillo and Worker, (1967); Worker and Carrillo (1967) and Dobereiner et al. (1971) reported that the dried leaves or aqueous extracts of Solanum malacoxylon are capable of causing a rise in the serum levels of calcium and phosphorus in cattle. Camberos and Davis (1969) used isotope studies to investigate the effects of S. malacoxylon on sheep and concluded that there was an increased resorption and retention of dietary calcium and phosphorus.

Camberos et al. (1970) reported hypercalcemia, occasional hyperphosphatemia and increase in calcium and phosphorus product in guinea-pigs fed either air-dried leaves or aqueous extract of S. malacoxylon.

Marcilesse et al. (1971), in a study of acute experimental "enteque seco" in rabbits, noted that oral or subcutaneous administration of aqueous extract of S. malacoxylon produced an increase of the phosphate and calcium product in plasma, irrespective of the difference in dietary condition. The increase in serum phosphate levels was found to be linearly related to the log of the administered dose of S. malacoxylon. The plasma calcium levels increased 24 hours after a single oral dose of

aqueous extract of S. malacoxylon but failed to do so if the extract was given subcutaneously. When "high" doses were administered daily, plasma calcium decreased to basal values after initial response.

Sansom et al. (1971) suggested that the toxic effect of S. malacoxylon is medicated by a large increased calcium absorption from the gut.

Mautalen (1971) reported that administration of aqueous extract of S. malacoxylon to rabbits produced hyperphosphatemia and a transient rise in serum calcium.

Campos et al. (1973) fed a diet "practically free of calcium" to vitamin D-deficient rats and seven days later, injected an extract of S. malacoxylon subcutaneously. Serum calcium concentrations became elevated at 24 hours and maximized at 48 hours. There was also an early transient increase in serum phosphate levels at 6 hours. Campos et al (1973) further noted that S. malacoxylon factor was effective in parathyroidectomized animals. However, contrary to the findings of Mautalen et al. (1971) and Campos et al. (1973), Uribe et al. (1974) and Basudde and Humphreys (1975) were unable to demonstrate an increase in serum calcium in rats and rabbits respectively after an administration of an aqueous extract of S. malacoxylon. A rapid hyperphosphatemia eas observed in the rabbit (Basudde and Humphreys, 1975). In "Weidekrankheit", Onderscheka (1967); Libiseller and Gunhold (1969); Kohler and Libiseller (1970) reported elevated plasma calcium and phosphorus levels in the affected cattle.

In enzootic calcinosis of cattle, Dirksen et al, (1970) noted that the serum is high but seldom above upper physiological limit and that the serum phosphorus is also periodically elevated.

In Cestrum diurnum poisoning, Krook et al. (1975a, b) reported that plasma calcium was elevated to moderate or severe degree in horses and cattle but later decreased toward low normal values in the cattle. The feeding of 3% dried leaves of C. diurnum to normal and hyperparathyroid pigs induced a rapid and persistent rise in plasma calcium value. While hyperphosphatemia occurred in the normal pigs, there was an initial transient hyperphosphatemia with subsequent and terminal hypophosphatemia in the hyperparathyroid pigs (Kasali, 1976).

Magnesium

Onderscheka (1967) postulated that "Weiderkrankheit" was due to chronic magnesium deficiency although Libiseller and Gunhold (1969) and Kohler and Libiseller (1970) could not substantiate this finding.

Arnold (1969) reported that the lesions of "Manchester Wasting Disease" could be reproduced experimentally if both calcium and vitamin D were in oversupply and especially when a state of magnesium deficiency also existed.

Dirksen et al. (1970) reported, normal serum magnesium level for cattle affected with "enzootic calcinosis".

In mineral metabolic studies; Camberos et al. (1970b) reported that in guinea pigs, fed an extract of S. malacoxylon, there was an increased absorption of calcium,

phosphorus and magnesium but a lower retention of magnesium than in the controls. On the other hand, Campos et al. (1973) reported that plasma magnesium value was unaffected in guinea pigs fed an extract of S. malacoxylon.

Basudde and Humphreys (1975) reported that although an administration of aqueous extract of S. malacoxylon to rabbits did not cause any significant change in plasma magnesium, the urinary magnesium was markedly increased.

Alkaline Phosphatase

There are very few reports in the literature concerning the activity of this enzyme in diseases due to ingestion of calcinogenic plants.

Marcilesse et al. (1971) and Basudde and Humphreys (1975) reported a significant decrease in serum alkaline phosphatase values of rabbits after oral administration of aqueous extract of Solanum malacoxylon.

In a study of effect of S. malacoxylon in young cattle, Dobereiner et al. (1976) reported that the levels of the enzyme tended to decrease during periods of administration of the plant.

Kasali (1976) reported that the administration of 3% dried leaf of Cestrum diurnum to normal and hyperparathyroid pigs caused significant hypophosphatasemia.

CLINICAL SIGNS AND SYMPTOMS

The clinical signs in these related disease entities include weight loss, apaty,

kyphosis, protracted kneeling, unwillingness to walk, loss of tendon contours, bradycardia and increased abdominal respiration (Arnold and Fincham 1950; Arnold and Bras, 1956; Lynd et al. 1965; Carrillo and Worker, 1967; Worker and Carrillo, 1967 ; Dammrich et al. 1970; Hanichen et al. 1970; Dobereiner et al. 1971; Dirksen et al., 1970, 1973, 1974; Krook et al, 1975a, b; Kasali et al. 1976. Induration of the abdominal aorta detected on rectal examination as well as infertility have also been reported in enzootic calcinosis in Germany (Dirksen et.al., 1970).

PATHOLOGY

(a) Soft Tissue Calcinosis

The tissues preferentially mineralized in the calcinotic conditions are the elastic tissue, the kidneys, cardiovascular system, the lungs, stomach and tendons (Collier, 1927; Arnold and Fincham, 1950; Arnold and Bras, 1956; Lynd et al. 1965; Carrillo and Worker, 1967; Worker and Carrillo, 1967; Camberos et al., 1970; Dammrich et al., 1970; Hanichen et al., 1970; Dirksen et al., 1970, 1973, 1974; Dobereiner et al. 1971; Marcilesse et al., 1971; Krook et al., 1975a, b; Done et al., 1976; Gill et al., 1976; Kasali, 1976). Dystrophic calcinosis of the ovaries has also been described (Dirksen et al., 1971).

There is atrophy of the chief cells of the parathyroid glands in S. malacoxylon (Carrillo, 1976) and C. diurnum toxicoses (Krook et al., 1975a, b; Kasali, 1976).

Electron microscopical examination of the parafollicular ("C") cells of the thyroids in S. malacoxylon and C. diurnum toxicoses revealed increased physiological activity of these cells which are responsible for producing the hormone, thyrocalcitonin (Carrillo, 1973; Krook et al., 1975a, b).

(b) Skeletal Changes

Arthrosis of the joints has been reported in "Manchester Wasting Disease" (Arnold and Bras, 1956), "Naalehu" disease (Lynd et al., 1965), enzootic calcinosis in cattle in Germany (Dirksen et al., 1970) and enzootic calcinosis of sheep in India (Gill et al., 1976).

Although there are many reports in the literature describing the osseous changes in these related calcinotic diseases, the interpretations of the histologic changes are contradictory. This poses some unanswered questions as to the clinico-pathologic interpretations of these related disease entities.

Dammrich et al., (1970) described the histological lesion in bones of cattle affected by enzootic calcinosis as osteomyelosclerosis which he attributed to increased bone formation and not to retarded resorption.

Carrillo (1973) who studied the skeletal manifestations of S. malacoxylon poisoning by fluorochrome labelled sections and conventional histologic methods described osteopetrosis, thickened cortical bone with numerous cementing lines,

and a thick coating of osteoid in relation to an active row of osteoblasts. He also attributed the osteopetrosis to enhanced apposition of bone.

Krook et al., (1975a, b) described the radiographic and histologic skeletal lesions in horses and cattle poisoned with Cestrum diurnum. Radiographic and histologic studies revealed diffuse osteopetrosis of epiphysis and the metaphysis with minimal marrow spaces between the thick and confluent trabeculae. Osteopetrosis was accompanied by a complete cessation of osteocytic osteolysis and chondrolysis resulting in abnormal retention of chondroid core. The inhibiting effects of C. diurnum factors on the resorbing osteocytes resulted with prolonged chronicity of the disease, in the death of the osteocytes especially in the areas of oldest bone with disintegration of their territory. They, therefore, concluded that osteopetrosis was due to arrested osteocytic osteolysis and chondrolysis and rejected the postulate that osteopetrosis was due to excessive formation of bone.

In a detailed study of C. diurnum toxicosis in normal and hyperparathyroid pigs, Kasali (1976) reported that C. diurnum caused a decreased ash per unit volume and cortical indices of the long bones. Radiographic and microradiographic studies of the humeri showed osteopetrosis of the epiphyses and metaphyses. Histologically, osteoptrosis was shown to be caused by arrested osteocytic osteolysis and chrondrolysis due to direct toxic action of C. diurnum factor on the resorbing ostocytes. Hypoparathyroidism established histologically and hypercalcitonism based on

morphological evidences contributed to the arrested bone resorption. Further degenerative changes in the resorbing osteocytes culminated in osteonecrosis and in osteopenia. Kasali (1976) further demonstrated that osteopenia in C. diurnum toxicosis was due to two different factors. The first was resulting osteoclasia in response to the necrotic bone tissue. The second factor, evidenced by fluorochrome labeling was due to atrophy of the osteo blasts, inhibition of bone flow mechanism, and hence bone remodelling.

CONCLUSION

The implication of calcinogenic plants in infertility, death and slaughter of considerable number of animals annually in the affected areas poses a serious threat to livestock production in terms of economic loss. However, the calcinogenic plants could have therapeutic value in metabolic diseases of animals. Milk fever is a complex metabolic disease characterized by hypocalcemia and hypophosphatemia near paturition and initiation of lactation in dairy cattle. The disease is fatal unless calcium salts are injected. It may well be that this condition will in future be treated or prevented by including powdered calcinogenic plants in diet since they offer a readily available source of 1 $25(OH)_2 D_3$. Also, an inclusion of such an additive in diets of laying hens that have been in lay for some months

might improve the absorption of available dietary calcium and thus help preserve egg shell quality. This would be especially useful in the heavy-laying strains.

Since every dry-powdered preparation is likely to be of different potency, the role of the biochemist is essential in elucidating knowledge of their activity so that standardization could be effected.

The prospect of being able to add crude powdered preparation to the diet of farm animals is an attractive one to those involved in animal production.

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