University of Tennessee, Knoxville
TRACE: Tennessee Research and Creative Exchange

Masters Theses | Graduate School

8-1978

The effect of supplemental iodine on vitamin A in rats and on thyroxine and vitamin A in parturient dairy cows and their calves

Patricia Kate White

Follow this and additional works at: https://trace.tennessee.edu/utk_gradthes

Recommended Citation

White, Patricia Kate, "The effect of supplemental iodine on vitamin A in rats and on thyroxine and vitamin A in parturient dairy cows and their calves. " Master's Thesis, University of Tennessee, 1978.
https://trace.tennessee.edu/utk_gradthes/7871

This Thesis is brought to you for free and open access by the Graduate School at TRACE: Tennessee Research and Creative Exchange. It has been accepted for inclusion in Masters Theses by an authorized administrator of TRACE: Tennessee Research and Creative Exchange. For more information, please contact trace@utk.edu.

To the Graduate Council:

I am submitting herewith a thesis written by Patricia Kate White entitled "The effect of supplemental iodine on vitamin A in rats and on thyroxine and vitamin A in parturient dairy cows and their calves." I have examined the final electronic copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Animal Science.

Eric W. Swanson, Major Professor

We have read this thesis and recommend its acceptance:

M. C. Bell, J. K. Miller, J. W. Oliver

Accepted for the Council:
Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

To the Graduate Council:

I am submitting herewith a thesis written by Patricia Kate White entitled "The Effect of Supplemental Iodine on Vitamin A in Rats and on Thyroxine and Vitamin A in Parturient Dairy Cows and Their Calves." I recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Animal Science.

Eric W. Swanson

Eric W. Swanson, Major Professor

We have read this thesis
and recommend its acceptance:

M. C. Bell

J. K. Miller

J. W. Oliver

Accepted for the Council:

Vice Chancellor
Graduate Studies and Research

Ag-VetMed

Thesis
78
.W536
cop. 2

THE EFFECT OF SUPPLEMENTAL IODINE ON VITAMIN A IN RATS AND ON THYROXINE AND VITAMIN A IN PARTURIENT DAIRY COWS AND THEIR CALVES

A Thesis

Presented for the

Master of Science

Degree

The University of Tennessee, Knoxville

Patricia Kate White

August 1978

1364925

CRANFIELD

ACKNOWLEDGMENTS

The author is truly grateful to Dr. Eric W. Swanson, for the guidance and help he unselfishly gave to aid her in the pursuance of her graduate studies. The cooperation and suggestions of committee members, Dr. M. C. Bell, Dr. J. K. Miller, and Dr. J. W. Oliver, were also much valued. Additional thanks goes to Richard E. Fish for his faithful assistance and support.

Special recognition is given to the workers at the University of Tennessee Dairy Farm in Knoxville who assisted in the care and treatment of the animals involved in this research project.

The author is also thankful for the financial assistance given to her by the Ralston Purina Company in the form of a research fellowship.

To family and friends goes the most sincere appreciation possible for the patience they showed and moral support they gave.

ABSTRACT

Parturient Holstein cows were administered daily doses of supplemental iodine as EDDI at 1.25, 2.50, and 5.0 mg. I/kg. of body weight and compared with contemporary controls in order to determine the effects iodine supplementation might have on vitamin A and thyroxine levels in the cow and her calf. Iodine was given from early stages of gestation until the cows were about 120 days into the following lactation. Blood samples were taken from the jugular vein of control and iodine-supplemented cows approximately 30 days prior to, on day of, and 30 days following calving. Plasma samples from calves were taken on day of calving. All plasma was analyzed for vitamin A, thyroxine, and total iodine content. Results of iodine administration on plasma vitamin A or thyroxine concentration of cattle gave no differences between diet groups, while plasma iodine increased with increased iodine administration. The high levels of iodine had no noticeable effects on plasma vitamin A levels in the calves. Higher thyroxine levels were found in calves from control cows, as they were almost twice the levels of the group supplemented with the highest level of iodine.

Stage of gestation was found to affect vitamin A, thyroxine, and iodine levels in the cow. Plasma vitamin A and thyroxine values dropped to minimums on day of calving and then increased to almost normal (the value obtained 30 days prior to calving) by 30 days after calving. The plasma iodine level rose to a high on day of calving and then declined to a value close to the pre-calving level in the days following.

Rats on a low vitamin A diet were supplemented with 0 and 250, 500, or 1000 ppm of iodine for 9 weeks and then killed. Heavier livers

were found in the high iodine group than in controls. Differences in the concentration of liver vitamin A or plasma vitamin A due to the iodine feedings were not statistically significant. Differences in liver vitamin A per gram of tissue approached significance with the control group storing slightly less than the iodine groups. Rat plasma iodine, as in the cow, increased with the increasing levels of iodine fed.

It was concluded from these studies that the feeding of excess iodine does not significantly affect vitamin A concentration in the plasmas or livers of rats or in the plasma of cows and their neonatal calves. Also iodine supplementation does not affect plasma thyroxine concentration in mature cattle. Iodine supplementation did significantly lower plasma thyroxine in calves, but it was not much lower than average thyroxine values reported in the literature for the normal calf.

The study also confirmed the trends in plasma vitamin A, thyroxine, and iodine levels observed by other researchers during the periparturient period of bovine.

TABLE OF CONTENTS

CRANESE CREST

LIST OF TABLES

CHAPTER I

INTRODUCTION

Iodine is necessary in the diet in trace amounts, 0.25 ppm in feed dry matter is adequate in non-goitrogenic diets for growing or non-lactating cows and 0.50 ppm in lactating cows (N.R.C., 1978), for the production of thyroid hormones. However, it has also been given orally for its pharmacological properties, especially in the treatment of chronic respiratory diseases and fungal infections (Newton *et al.*, 1974), for the protection from foot rot and actinomycosis (Herrick, 1972), and also as an external application for sanitation of udders and teats. In view of the small dietary requirement and the medicinal uses for iodine, it is possible that in some cases animals may consume or absorb from skin many times their daily requirement. Feeding levels of iodine in excess of those needed for the normal functioning of the body has been associated with symptoms such as goiter (Baker and Lindsey, 1968; Correa and Welsh, 1960), eye lesions (Arrington *et al.*, 1965; Newton and Clawson, 1974) and eye irritations (Herrick, 1972), excess nasal mucus and coughing (Newton *et al.*, 1974; McCauley, Johnson, and Alhadji, 1972), increased lacrimation, salivation, loss of appetite, and dry skin (Herrick, 1972), lowered conception rates, calves born extremely weak or stillborn, fetal resorption (McCauley, Johnson, and Alhadji, 1972), weak calves born with excess fluid in their tissues (Fish and Swanson, unpublished data), and increased incidence of abortion in cattle (Hillman, Bolenbaugh, and Conveg, 1976). At excessively high iodine intakes a reduction in feed intake and growth rate in the bovine was also observed (Fish and Swanson, unpublished data; Newton *et al.*, 1974).

Vitamin A deficiency has been shown to manifest symptoms similar to those mentioned above for high levels of iodine. A stratified keratinizing of epithelial tissue can occur which causes degeneration of the mucosa of the respiratory tract, mouth, salivary glands, eyes, tear glands, and intestinal tract (N.R.C., 1978). The affected animal becomes more susceptible to infection resulting in the occurrence of respiratory problems which are also observed with high iodine feeding. In later stages, changes in the eyes occur such as lacrimation, keratitis, corneal softening, xerophthalmia, corneal clouding, and sometimes permanent blinding from infection. These corneal problems are similar to those described by Newton and Clawson (1974) in pigs receiving 800 to 1600 ppm of iodine in their diets. The lesions in these pigs caused opacity of the cornea and hyperplasia of the corneal epithelium. Warkany (1945) observed eye lesions in calves from vitamin A deficient dams. Unpublished data from feeding dry cows excessive iodine at the University of Tennessee indicates some occurrence of eye opacity.

Madsen and Earle (1947) found that a prolonged vitamin A deficiency in cattle may result in edema as characterized by swelling of the legs, shoulders and brisket, abdomen, hind quarters, and elsewhere. Moore, Huffman, and Duncan (1935) also observed edema in vitamin A deficient animals, pointing to a possible electrolyte disturbance. Electrolyte aberrations might also be the cause of the tissue fluid found in the previously mentioned bovine neonates from dams receiving high iodine levels.

The lack of vitamin A in the pregnant cow's diet may cause a shortened gestation period, a high incidence of retained placenta, and birth of dead, incoordinated or blind calves (N.R.C., 1978). Blindness

due to vitamin A deficiency may be permanent due to an optic nerve constriction. Spielman *et al.* (1946), Warkany (1945), and Swanson *et al.* (1968) reported stillborn, blind, or weak calves and Guilbert and Hart (1934) observed premature or dead calves, along with diarrhea in newborns and opthalmia in young growing animals. Takahashi *et al.* (1975) discovered that severely vitamin A deficient female rats failed to conceive while mildly deficient females usually aborted or resorbed the fetuses in later gestation. Thompson (1969) also found fetal resorption in severely vitamin A deficient animals. Many of these observations are similar to those made of animals receiving high iodine diets.

Steers studied by Guilbert and Hart (1934) showed signs of avitaminosis A such as mucus discharge from the nose, tears from the eyes, loss of appetite, and skin roughness, all of which are also associated with iodine toxicity. Similar signs also found in vitamin A deficient rats included lack of growth, respiratory difficulties, and matted hair (Zile, Bunge, and DeLuca, 1977).

Iodine or thyroxine and vitamin A in plasma are all associated with the same types of plasma proteins. Vitamin A complexes with retinol-binding protein and prealbumin in the human and rat (Kanai, Raz, and Goodman, 1968; Ismadi and Olson, 1975; Muto and Goodman, 1972). This prealbumin which interacts with retinol-binding protein (TBP) appears to be identical to the "thyroxine-binding" prealbumin in human plasma (Kanai, Raz, and Goodman, 1968) so that, in addition to its binding site for RBP, the human prealbumin molecule contains an independent binding site with a high affinity for thyroxine (Muto and Goodman, 1972). L-thyroxine also

has two other transport proteins in the human which are thyroxine binding globulin (TBG) and albumin (Raz and Goodman, 1969). Another possible relationship between vitamin A and thyroxine is indicated by similar changes in their concentrations following alterations in levels of their carrier proteins. Total protein concentration in the blood has been observed to decline a few weeks prior to calving followed by a slight rise after calving (Rowlands *et al.*, 1975). Likewise, both vitamin A and thyroxine concentrations in the blood have been reported to decrease in the first day postpartum, and return to normal during the second and third week postpartum, respectively (Stöckl, Schuh, and Schmid, 1975).

To further associate vitamin A and iodine, a relationship has been found between vitamin A and thyroid function. Vitamin A deficiency has been linked with thyroid hypertrophy in female white rats and atrophy in males by Coplan and Sampson (1935) while Lipsett and Winzler (1947) observed heavier thyroid glands in deficient animals of either sex. Lipset and Winzler (1947) found iodine uptake per milligram of thyroid tissue to be appreciably lower in vitamin A deficient animal with a decreased rate of thyroxine formation resulting. A normal functioning thyroid gland is required for an animal to convert carotene to vitamin A and store it in the liver (Johnson and Baumann, 1947). Further evidence implying that the rate of conversion of carotene to vitamin A by the cow and goat depends on the thyroid status of the animal was presented by Chanda *et al.* (1951). It has also been reported that carotene as well as vitamin A lowers the basal metabolic rate in rats receiving exogenous thyroxine and that

carotene prevents weight loss in rats injected with thyroxine (Wohl and Feldman, 1939).

Though the thyroid is necessary for carotene conversion to vitamin A, it had been observed that thyroxine administration can induce a vitamin A deficiency (Glover, 1973). In explanation, Wohl and Feldman (1939) reported that the excess thyroxine may destroy and deplete the vitamin A reserves of the body. Both protein-bound iodine and thyroid weight have been shown to be reduced at the highest level of vitamin A supplementation (Anderson, Hubbert, and Roubicek, 1964) which could indicate a competition for plasma protein binding between iodine and vitamin A.

Since thyroid function is related to vitamin A in the body, and the level of protein-bound iodine in plasma is considered an indicator of thyroid function, the fact that some of the manifestations of a vitamin A deficiency are similar to those occurring when excess levels of iodine are fed might indicate that feeding high iodine levels may affect the vitamin A status of the bovine or rat. The present study examines this possibility along with possible effects of iodine on thyroxine level in the bovine.

CHAPTER II

LITERATURE REVIEW

Vitamin A is an essential nutrient for all vertebrates and can be ingested by the animal as carotene, vitamin A alcohol, or vitamin A ester (Moore, 1957). Iodine is another nutrient which is necessary in the diet in small amounts for thyroid hormone production, and is often given in larger amounts for its pharmacological properties (Newton *et al.*, 1974). A relationship between these two nutrients is of interest in that some of the manifestations of a vitamin A deficiency resemble symptoms seen with iodism and/or hypothyroidism (Wohl and Feldman, 1939), the two are carried by similar plasma proteins, and vitamin A and thyroxine appear to be antagonists.

Vitamin A Transport and Storage

In order to better understand where vitamin A might be affected or lack of it might cause an effect when high levels of iodine are fed to animals, the main features in the transfer of vitamin A and carotene from the diet to the blood and liver are reviewed in Figure 1 (Moore, 1957). The vitamin A (retinol) ingested is esterified (Figure 1). This is the main form in the wall of the small intestine of rats, calves, chickens, and sheep irrespective of the form of vitamin A fed (Ganguly, 1960). These retinyl esters are then incorporated into the chylomicrons of lymph and transported from the intestine via intestinal lymphatics (Goodman, 1969). According to Ganguly (1969), esterification may prevent retinol from diffusing out of the cell and may protect retinol against the attack

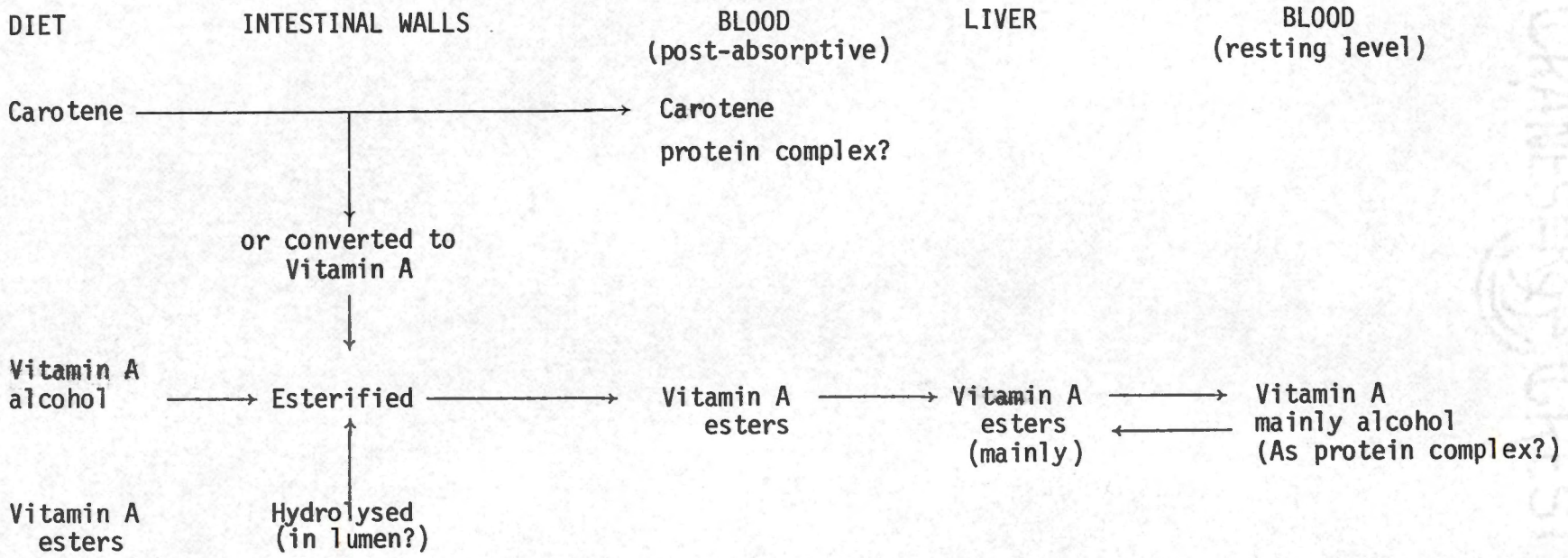

Figure 1. Main Features in the Transfer of Vitamin A and Carotene from the Diet to the Blood and Liver.

Source: Moore, 1957.

of the enzymes like retinol dehydrogenase of the intestinal mucosa. After entering the vascular compartments, newly formed retinyl esters are taken up mainly by the liver where they undergo turnover and are stored (Goodman, 1969). Baumann, Riising, and Steenbock (1934) found rats and Ascarelli (1969) in chickens, that 95 percent of vitamin A storage was in the liver. Small amounts were detected in kidneys and lungs, but the brain, blood, muscle, and digestive organs gave negative results in studies by Baumann, Riising, and Steenbock (1934). They found no vitamin A in non-hepatic tissues unless the liver also contained it (Smith and Goodman, 1971). The tissues of rats showing deficiency symptoms contained no vitamin A, nor could vitamin A be detected in non-hepatic tissue of rats which were fed a low vitamin A diet until their livers ceased to give a positive test for vitamin A. Moore (1931) also found that while the amount of vitamin A carried in the blood was influenced little by increasing the liver reserve, the liver still played an important role in the regulation of the concentration of the vitamin throughout the body. He added that when the liver reserve is reduced, a point is reached when the customary level of vitamin A in the blood can no longer be maintained. The liver's role in the regulation of the vitamin in the body was further substantiated by Smith and Goodman (1971) in human studies which showed the plasma vitamin A levels to decrease markedly in patients with liver disease.

While the ester of vitamin A is the predominant form stored in the liver the free alcohol has been suggested to be the probable normal physiologically active form of the vitamin (Ganguly, 1960). The organism maintains the vitamin A alcohol content of its tissues from the stores of the liver ester and just one lipoprotein probably transports vitamin A

ester from intestines and deposits it in the liver, another lipoprotein readily carries it from the liver to different tissues as free alcohol for metabolic needs, according to Ganguly (1960) and Smith and Goodman (1971).

Iodine Transport and Storage

A summary of the transfer of iodine from diet to target tissues begins with the ingested iodine being converted to iodide in the gastro-intestinal tract and absorbed into the blood from which it is actively transported into the thyroid gland. Here the iodide (I^-) is reconverted into iodine (I°) which combines with tyrosine. Two molecules of diidoniated tyrosine combine to form thyroxine (T_4) which is, as is triiodothyronine (T_3), bound to a protein (thyroglobulin) as a means of storage in the thyroid's follicula lumen. This protein is split off when T_4 or T_3 are released from the follicular cell into the blood. Most of the thyroxine and T_3 become bound to certain plasma proteins and then circulate in equilibrium with a small amount of their free forms which are really the effective hormones.

Functions of Vitamin A and Iodine

Vitamin A and iodine have been shown necessary for several body functions with a deficiency of vitamin A (not a common occurrence in herbivorous animals) showing symptoms similar to those shown by excess iodine in the diet.

Vitamin A regulates the stability of certain types of biological membranes (Roels *et al.*, 1969). According to Seward, Mitchell, and Hove (1969), the vitamin may be an integral structural component of cellular

and subcellular membranes with a shift in its relative concentration in the membranes being sufficient to cause changes in permeability and stability. This was demonstrated in erythrocytes from vitamin A deficient rats by Roels *et al.* (1969). The erythrocytes were markedly swollen and distorted compared to controls which led to the conclusion that retinol regulates the stability of the rat erythrocyte membrane and normalizes its shape. Its importance in certain biological membranes may be one reason a prolonged vitamin A deficiency may lead to anasarca (Madsen and Earle, 1947).

Vitamin A also plays a role in mucopolysaccharide formation in the rat (Carroll, 1969). In excess, vitamin A leads to an increase in mucous type epithelium while in deficiency it leads to an increase in connective type tissue. In agreement, DeLuca and Wolf (1969) explain in another way that in the absence of vitamin A, the protein synthesizing machinery of the cell is directed to produce keratin while in its presence the production of glycoprotein which is the principal constituent of mucus is stimulated. An opposite effect is seen with iodism in that there is excess mucus secretion of the respiratory tract. In fact, the stimulation of mucus secretions is the basis for the use of iodides and iodates as expectorants (Newton *et al.*, 1974).

The main use of iodine appears to be for thyroid hormone production. It is necessary in small amounts (0.25-0.50 ppm of the diet according to the N.R.C. (1978)), but since iodine compounds are commonly used to treat or prevent diseases such as foot rot, bovine respiratory disease complex, mastitis, actinomycotic infections, and other chronic infectious processes (McCauley, Johnson, and Alhadji, 1972), it seems possible that the animals

may consume many times their daily requirements (Newton *et al.*, 1974). With this in mind, a discussion of the effects of excess iodine (Nagataki (1974) defines excess iodine as an amount greater than that necessary for the formation of normal quantities of thyroid hormone) in the diet and their similarity to the effects of a vitamin A deficiency in an animal will follow.

Effects of Excessive Iodine and Deficient Vitamin A

Deficiency of vitamin A can lead to epithelial keratinization which is seen as degeneration of the mucosa of the respiratory tract, mouth, salivary glands, eyes, tear glands, intestinal tract, urethra, kidneys, and vagina. This makes these structures highly susceptible to infection, colds, pneumonia, and in later stages, changes in the eye such as lacrimation (Guilbert and Hart, 1934), keratitis, softening of the cornea, xerophthalmia, cloudiness of the cornea, and sometimes permanent blindness from infection occurs (N.R.C., 1978). Mead and Regan (1931) reported external eye lesions associated with vitamin A deficiency in calves as did Warkany (1945) in calves from vitamin A deficient dams. Blindness has been reported in calves born to dams on vitamin A deficient diets (Spielman *et al.*, 1946; Warkany, 1945; Olson, 1969) while Guilbert and Hart (1934) observed ophthalmia in young growing animals. Total blindness which occurs can be caused by degenerative changes of the optic nerve (Guilbert and Hart, 1935). Night blindness has also been seen in vitamin A deficient animals (Guilbert and Hart, 1935; Zile, Bunge, and DeLuca, 1977). These and additional eye anomalies have been reported in rats (Morriss, 1976; Moore, 1957; Zile, Bunge, and DeLuca, 1977), pigs (Palludan, 1976; Kalter and Warkany, 1959; Hale, 1933), and various other animal species Moore, 1957).

An excess of iodine in the diet, as did a deficiency of vitamin A, caused lacrimation and irritated eyes in the bovine (Herrick, 1972) and eye lesions in rats and pigs (Arrington *et al.*, 1965; Newton and Clawson, 1974). Newton and Clawson (1974) observed an opacity of the cornea and hyperplasia of the corneal epithelium in pigs receiving 800 and 1600 ppm of iodine in their diets. These pigs also developed encrustation around the eyes. Unpublished data from the University of Tennessee indicates the occurrence of eye opacity in calves born after dry cows received excessive iodine.

Vitamin A deficiency is characterized by mucus discharge from the nose (Guilbert and Hart, 1934) and other respiratory difficulties (Zile, Bunge, and DeLuca, 1977). Profuse nasal discharge and coughing were also observed in calves fed either 100 or 200 ppm of iodine, sometimes at lower levels, in their diets (Newton *et al.*, 1974). The same symptoms along with excessive lacrimal secretion were observed in feedlot steers being fed ethylenediamine dihydriodide (EDDI) as a foot rot preventive (McCauley, Johnson, Alhadji, 1972). Herrick (1972) also reported nasal discharge and increased salivation as iodism symptoms which disappeared after withdrawal of iodides.

Madsen and Earle (1947) found that prolonged vitamin A deficiency in cattle may result in edema as characterized by swelling of the legs, shoulders and brisket, on the abdomen, in the hindquarters and elsewhere. Moore, Huffman, and Duncan (1935) also observed edema in vitamin A deficient animals. Perhaps the edema found associated with iodine and vitamin A can be attributed to a common cause such as an electrolyte imbalance or possibly an accumulation of acidic mucopolysaccharides in

the interstices of tissues as is seen in hypothyroidism (Oliver and Neher, 1971). This latter condition may alter the microcirculation by hindering the diffusibility of materials between capillaries and cells which would further contribute to fluid retention in tissue interstices according to Oliver and Neher (1971).

Other vitamin A deficiency symptoms include diarrhea (Guilbert and Hart, 1934; Warkany, 1945; Madsen and Earle, 1947), appetite loss and lack of growth (Olson, 1969), skin roughness, matted hair (Zile, Bunge, and DeLuca, 1977; Guilbert and Hart, 1934), disturbances of the central nervous system in rats and cattle (Zile, Bunge, DeLuca, 1977; Madsen and Earle, 1947), and various reproduction related problems. Herrick (1972) reported loss of appetite and dry skin in cattle as iodism signs. The effects of elevated dietary iodine intake on the calf include a depressed gain and lowered feed intake (Newton *et al.*, 1974), the magnitude being significant in one study for diets containing 50, 100 or 200 ppm of added iodine. Fish and Swanson (unpublished data) also observed a reduction in feed intake and growth rate in the bovine consuming excessively high amounts of iodine (200-300 ppm). Moore (1957) gave some of the common effects of avitaminosis A in chickens to be loss of appetite, cessation of growth, and lowered egg production which could eventually cease. Those eggs laid by vitamin A deficient chickens could usually be hatched. When chickens were fed excess iodine, a similar lowered growth (Mayberry and Hockert, 1968), a drop in egg production, and decreased percentage of hatchability were found (Arrington *et al.*, 1967).

Zile, Bunge, and DeLuca (1977) suggested from their studies with rats that the tissue of vitamin A deprived animals may have an impaired

ability to withstand various exogenous stresses. They found bacterial infection of the upper respiratory tract of animals to be a common complication associated with vitamin A deficiency. Olson (1969) also reported an increased susceptibility to infection. McCauley, Johnson, and Alhadji (1972) observed four field cases with cattle in which feeding of organic iodide also interfered with the animal's ability to cope with an infectious or non-infectious insult under situations of extra stress such as transport, inclement weather, high milk production, or parturition. McCauley, Linn, and Goodrich (1973) observed cattle stressed by shipment and in various stages of bovine respiratory disease complex (BRDC) being given large amounts of EDDI each day. Their observations indicated an increase in damage normally expected from this disease complex possibly due to the high iodide ration under these conditions. Soon after iodide was added to the ration, anorexia, excess salivation, hyperthermia, coughing, and almost complete nonresponse to therapy for BRDC was seen. High mortality and high incidence of unthriftiness in survivors was also reported. The effects of EDDI in cattle unstressed by BRDC were hyperthermia, excess salivation, coughing, and lethargy; these signs disappeared after removal of EDDI.

It has been found in some species such as the rat (Nagataki, 1974; Correa and Welsh, 1960), human (Wolff, 1969), and horse (Baker and Lindsey, 1968) that iodide can inhibit thyroid hormone synthesis when it is ingested in large amounts. Excessive iodine intake may result in goiter if inhibition is prolonged, but it has not been reported as a naturally occurring disease in a mammal other than man (Baker and Lindsey, 1968). Most animals are resistant to the goitrogenic effect of iodides

(Mayberry and Hockert, 1968). The thyroid sensitivity to excess iodine differs with species and within species.

Despite the variable intake of iodine by the human, the normal thyroid seems to produce a constant amount of thyroid hormone. The incidence of hypothyroidism or iodide goiter is quite low though it can occur among people exposed to iodine excess, and hyperthyroidism induced by excess iodine is rare. A similar response was shown in rats (Nagataki, 1974). Mayberry and Hockert (1968) did report an inhibition of thyroxine synthesis in humans with high serum iodide levels. The problem in iodide goiter is the inability to obtain a normal escape mechanism from the Wolff-Chaikoff effect which Wolff (1969) described as the effect occurring when the quantity of organic iodine formed as a function of iodide concentration supplied increased to a maximum and then decreased sharply with an additional increase in iodide concentration. Wolff (1969) observed a second major effect of excess iodide which is to inhibit release of organic iodine from the thyroid if the parenchyma is stimulated. This action of iodide is generally attributed to the inhibition of thyroglobulin proteolysis though supporting evidence is meager. Galton and Pitt-Rivers (1959) also found that rats given high iodine doses for 7 weeks showed inhibited organic binding of iodine for the first 3 or 4 days following which the binding was resumed in spite of continued treatment though a slight decrease was noted in the following weeks.

A chronic iodide load in the mouse was also observed to inhibit the release of iodocompounds from the thyroid gland. Baker and Lindsey (1968) attributed this as others have to a possible decrease in thyroidal protease activity.

Ammerman (1964) also found that large doses of iodine inhibit temporarily organic binding of iodine by the thyroid in rats. Following this inhibition, adequate amounts of thyroid hormone are produced in spite of continued high level feeding of iodine. Correa and Welsh (1960) failed to get myxedema or inhibition of organic binding of iodine by the thyroid gland in rats fed excessive iodide for 9 months, but the rats did develop a goiter apparently due to excessive colloid accumulation rather than cellular proliferation.

Drew, Barber, and Williams (1975) observed in a herd of barren mares receiving excess dietary iodine one mare with an enlarged thyroid, increased body fat, and lack of estrus. The mare recovered from symptoms when treated with thyroid extract.

Horvat *et al.* (1959) have tried to implicate a vitamin A and carotene deficiency as being an etiological factor in the development of endemic goiter in their work with people of the island of Krk. Remington, Harris, and Smith (1942) in their studies found no reason to believe that vitamin A deficiency is an etiological factor in the development of simple goiter.

More similarities between excess iodine and avitaminosis A effects are seen when reproductive and neonate problems are examined. Takahashi *et al.* (1975) discovered that severely vitamin A deficient rats failed to conceive while mildly deficient females conceived, but usually aborted or resorbed fetuses in later gestation. Under these conditions, malformed fetuses and pups were produced. Thompson (1969) also found fetal resorption in severely vitamin A deficient animals. Takahashi *et al.* (1975) observed smaller livers and kidneys in neonates from a group of

rats on a low level of vitamin A. They suggested that the vitamin A deficiency may mainly affect the development and functioning of the placenta with secondary effects on the fetus. Perhaps retinol-binding protein delivers retinol to specific transport sites in the placenta or across the placenta and then to specific sites in the fetus. This is a point where excessive iodine in the diet could contribute to avitaminosis A in the fetus by possibly occupying these sites making them unavailable to retinol.

Since little or no vitamin A is stored in the fetus, problems can arise. A sufficiency of the vitamin must pass the placental barrier to provide for normal fetal development, therefore a lack of vitamin A or its precursor, carotene, in a pregnant cow's diet may result in a still-born, blind, or weak calf. Permanent blindness in neonates can be caused by a stenosis of the optic foramen (N.R.C., 1978). Perhaps in some way this can be related to the fact that the thyroid hormones are essential to normal fetal skeletal maturation (Fisher and Dussault, 1974). Excess iodine may inhibit both thyroid hormones and vitamin A resulting in the skeletal stenosis. Others have also reported premature, dead, or weak calves being born to deficient animals (Guilbert and Hart, 1934; Warkany, 1945; Swanson *et al.*, 1968). Swanson and coworkers (1968) found a vitamin A level of 5 micrograms per 100 ml. of plasma and 1.0 microgram per gram of liver a short time before parturition in vitamin A deficient cows having dead or weak calves. Cattle with plasma carotene levels of 25 micrograms and vitamin A levels of 16 micrograms per 100 ml. usually show no signs of a vitamin A deficiency, however, higher levels are needed for normal reproduction (Warkany, 1945). Warkany (1945) found that heifers with plasma carotene levels from 30 to 60 micrograms and vitamin A levels from

10 to 20 micrograms per 100 ml. had dead, weak, or blind calves. Calves from heifers with carotene levels of 78, 96, and 143 micrograms and vitamin A levels of 22 and 24 micrograms per 100 ml. were of good quality. Davis and Madsen (1941) and Eaton *et al.* (1970) agreed that these levels were accompanied by normal calves.

Other reproduction related symptoms of vitamin A deficiency include shortened gestation periods and high incidence of retained placenta (N.R.C., 1978).

Many problems have also been associated with an excess iodine intake, some of which are much like those associated with vitamin A deficiency. Ammerman *et al.* (1964) reported a failure of lactation in rats fed high levels of inorganic iodine. Mortality of newborns increased as iodine intakes increased and approached 100 percent at 2500 ppm of iodine in the dam's diet. A prolonged gestation period was also observed. The mechanism by which high levels of dietary iodine may inhibit lactation is unknown, however one suggestion is that it may be related in someway to thyroid activity (Ammerman *et al.*, 1964).

In rabbits a significant number of deaths of newborns from mothers fed 250 ppm and more of iodine was found, but the mammary glands contained a normal quantity of milk (Arrington, *et al.*, 1965). The same researchers found no effect due to feeding 1500 to 2500 ppm of iodine as potassium iodide to pigs for 30 days prior to farrowing. They concluded as others have that there is a difference between species in response or intolerance to the toxic effects of excess iodine.

In chickens fed levels of iodine up to 5000 ppm, egg fertility was unaffected, but high embryonic death, low hatchability, and delayed

hatching were observed (Arrington *et al.*, 1967). The percentage hatchability decreased with increased levels of iodine. Weak chicks were obtained from the iodine-fed hens and the thyroid weights of chicks from hens fed 2500 ppm were three times larger than controls.

Excessive iodine intakes by cattle have also been associated with lowered conception rates, fetal resorption, and birth of dead or extremely weak calves. (McCauley, Johnson, and Alhadji, 1972). Hillman, Bolenbaugh, and Convey (1976) reported an increased incidence of abortion in cattle.

Some mammals actively transport iodide across the placenta making fetal blood iodine 2 to 2.5 times greater than maternal blood iodine (Baker and Lindsey, 1968). Baker and Lindsey (1968) observed a possible result of this when as much as 50 mg. of iodide per day were consumed by pregnant mares. Congenital goiter resulted in some foals. Wolff (1969) observed iodine goiter in human neonates due to placental transfer of iodides from mothers being treated with iodides. This transfer is meant to assure adequate iodide for the fetus under normal circumstances, but it functions adversely when maternal iodide intake is excessive (Baker and Lindsey, 1968). Dam's milk is also an important source of excess iodide and this has been substantiated in the mare by a continued elevation of fetal plasma inorganic iodide for several weeks after birth (Baker and Lindsey, 1968). A similar result occurs with vitamin A and this will be discussed with the results of the present study.

From their observations of pregnant mares receiving excessive levels of iodine, in their diets, Drew, Barber, and Williams (1975) reported the birth of one full-term filly foal, unable to stand unaided, with an

enlarged goiter. Another foal which had an enlarged hyperplastic thyroid weighing 92 grams compared with the normal 15 grams died soon after birth. A third also showed an enlarged thyroid and limb weakness. A fourth foal, 2 weeks premature, also had an enlarged thyroid (50 grams) and limb abnormalities. An explanation given by Baker and Lindsey (1968) was that a reduction of plasma thyroid hormone concentration below a critical level triggers the accelerated release of thyrotropin from the anterior pituitary. If the thyroid cannot release the hormone sufficiently to release the hormone sufficiently to raise plasma thyroxine levels, the pituitary continues to discharge thyrotropine and thyroid mass increases in response to sustained thyroid-stimulating hormone (TSH) stimulation.

Studies of placental transport of thyrotropin in man and experimental animals (rat) indicate that congenital thyroid enlargement results from stimulation by fetal rather than maternal TSH (Baker and Lindsey, 1968). Baker and Lindsey (1968) showed that the goitrous foals in their study had elevated plasma TSH levels at birth and two of their dams also had increased plasma levels. They inferred that these animals had reduced plasma thyroid hormone concentrations. Several postulations as to why this occurs have been discussed, one being that the excess iodide prevents release of hormones from the thyroid gland. In the horse, unlike the rat, but closely resembling man, mouse, and chicken, inhibition of thyroid synthesis appears to continue as long as excessive iodide is ingested. In the rat, the thyroid gland is inhibited transiently by excessive iodide. Newton *et al.* (1974) found that addition of 25, 50, 100, and 200 ppm to the diet of calves tended to produce heavier thyroid glands on a body weight basis.

Transport Proteins associated with Vitamin A and Iodine or Thyroxine

The same types of plasma proteins are found to be associated with vitamin A and iodine or thyroxine.

Vitamin A circulates in the plasma as retinol, its alcohol form (Kanai, Raz, and Goodman, 1968; Peterson, 1971; Parrish, Wise, and Hughes, 1948; Ismadi and Olson, 1975). It has been suggested that this retinol is apparently associated with a transport protein which in man differs from serum albumin (Peterson, 1971; Ismadi and Olson, 1975; Kanai, Raz, and Goodman, 1968). Erwin, Varnell, and Page (1959) found vitamin A and carotene in the bovine to be principally associated with an albumin. Retinol-binding protein (RBP) was found to be the specific protein to which the retinol is bound. The concentration of retinol in the blood appears largely dependent on the synthesis of its carrier, RBP, by the liver (Moore *et al.*, 1972). RBP is very important in the fetus for it delivers retinol to specific transport sites in the placenta or even across the placenta and delivers retinol directly to specific sites on the fetus. Without it development suffers (Takahashi *et al.*, 1975).

The interaction of retinol with RBP was found to be of considerable physiological importance in the rat (Muto and Goodman, 1972) and undoubtedly the same holds true for other species. This interaction solubilizes the water insoluble retinol molecule and protects the unstable retinol molecule against chemical degradation.

This retinol-RBP complex forms in the liver (Ismadi and Olson, 1975). Retinol-binding protein appears to have a single binding site for one molecule of retinol in the human and rat (Muto and Goodman, 1972; Kanai, Raz, and Goodman, 1968) and the interaction between the two is

highly specific (Kanai, Raz, and Goodman, 1968). This complex (retinol-RBP) after being released into the plasma is finally associated with another protein which is involved in transporting vitamin A in fasting plasma (Ismadi and Olson, 1975). Little free RBP is found circulating in the plasma according to Ismadi and Olson (1975). This is either partially degraded by the kidney and excreted in the urine or is completely degraded. They observed the RBP-complex to be relatively stable in plasma.

The second retinol-transport protein with which the RBP complexes is called prealbumin in the rat and human (Kani, Raz, and Goodman, 1968; Ismadi and Olson, 1975; Muto and Goodman, 1972). Since no prealbumin has been observed in cattle (Tanabe, Ishii, and Tamaki, 1969; Blumberg and Robbins, 1960) another protein fraction present (albumin or globulin) probably is utilized. Prealbumin is synthesized in the liver (Ismadi and Olson, 1975).

This protein-protein interaction protects the retinol-binding protein molecule by preventing glomerular filtration of the relatively small RBP molecule and hence its loss in the urine. It is also possible that the RBP-prealbumin complex may further stabilize and protect the retinol molecule (Kanai, Raz, and Goodman, 1968).

The capacity of prealbumin to form a complex in the human with RBP seems limited so that when the relative amount of RBP in the mixture was progressively increased, the prealbumin apparently became saturated with RBP (Kanai, Raz, and Goodman, 1968). Some say one molecule of prealbumin can interact with one molecule of RBP to form a stable complex (Kanai, Raz, and Goodman, 1968) while VanJaarsveld *et al.* (1973) observed four binding sites for RBP on the prealbumin molecule.

Raz, Shiratori, and Goodman (1970) found that the addition of only two atoms of iodine per molecule of RBP significantly reduced its affinity for prealbumin; further iodination produced progressive reductions in the affinity of RBP for prealbumin. The iodination of RBP up to the level of 4.3 atoms of iodine per molecule did not appear to interfere with the interaction of retinol with RBP since no loss of retinol occurred from the RBP preparation iodinated to this extent.

The prealbumin which interacts with RBP appears to be identical to the "thyroxine-binding" prealbumin in human plasma (Kanai, Raz, and Goodman, 1968) so that in addition to its binding site for RBP, the human prealbumin molecule contains an independent binding site with a high affinity for thyroxine (Muto and Goodman, 1972), which under normal conditions is the main form of iodine in the blood (Woeber and Ingbar, 1974). Normally, probably 30 percent or more of plasma prealbumin molecules circulate in complex with RBP and less than 1 percent of total plasma prealbumin circulates in complex with thyroxine (Raz and Goodman, 1969). The interaction of prealbumin with RBP was independent of its interaction with thyroxine (Raz and Goodman, 1969; vanJaarsveld *et al.*, 1973), therefore, Raz and Goodman (1969) found the binding capacity and affinity of prealbumin for thyroxine to be similar both in the presence and absence of RBP. These findings indicated that the formation of the prealbumin-retinol-binding protein complex did not interfere with the ability of prealbumin to interact with thyroxine. Also, the addition of enough thyroxine to saturate prealbumin did not impair the ability of prealbumin to interact with RBP. Prealbumin could simultaneously interact with one molecule of thyroxine and one of RBP. Raz and Goodman (1969) concluded

that it appeared that the protein-protein interaction between prealbumin and RBP involved a site on the prealbumin molecule separate and different from the site involved in the prealbumin-thyroxine interaction.

Prealbumin which is estimated to contain a single binding site for thyroxine, is one of three proteins responsible for the plasma transport of L-thyroxine (Raz and Goodman, 1969). Under normal conditions, most of plasma thyroxine circulates bound to thyroxine-binding globulin. Estimates reported by Raz and Goodman (1969) of the proportion of endogenous thyroxine normally bound to prealbumin varied, with recent estimates being in the range of 30 percent or 15 percent. Albumin is the third transport protein.

Thyroxine exists in both a bound and unbound free state in the serum and the concentration of free thyroxine circulating unbound to serum proteins has been suggested to be more closely related to thyroidal status than is the concentration of total thyroxine (Robbins and Rall, 1960; Burke and Eastman, 1974).

Since findings suggest that both RBP and prealbumin are synthesized in and secreted by the liver, it does not seem unusual that their production rates are comparably disturbed in the presence of liver disease (Smith and Goodman, 1971) or other physiological changes which might occur. In a vitamin A deficiency, low albumin levels were found, but total globulins increased (Cama *et al.*, 1957; Madsen and Earle, 1947). In hyperthyroidism, albumin and prealbumin levels were low while in hypothyroidism little change occurred in their concentrations (Cama *et al.*, 1957; Madsen and Earle, 1947), but a large increase in alpha-globulins occurred (Cama *et al.*, 1957).

The thyroxine-binding capacity of prealbumin or level of prealbumin was reported by Smith and Goodman (1971) to decrease during pregnancy, pre- and postpartum, with malignant diseases, post-surgery, and in the presence of fever and of a number of acute and chronic illnesses. In certain renal diseases plasma RBP and vitamin A levels were found elevated and in some cases the affinity of RBP for prealbumin was found to be less than normal. Smith and Goodman (1971) also observed that the plasma RBP circulating was less saturated with retinol than normal in renal disease. All of these possible effectors of the transport proteins of vitamin A and thyroxine help to further relate vitamin A deficiency with iodine excess as they affect the body.

Vitamin A and the Thyroid Gland

Studies of vitamin A and the thyroid gland have shown an obvious relationship between the two. Since iodine is the main constituent of the thyroid hormone, thyroxine (thyroxine is 65 percent iodine in the human according to Brody (1974)), then feeding excess iodine might directly or indirectly affect vitamin A status in the body by influencing thyroid activity.

In rats, heavy vitamin A medication, though it allowed normal growth, was found to depress basal metabolism and reduce the weight of thyroid glands (Sadhu and Brody, 1947). Anderson, Hubbert, and Roubicek (1964) also observed reduced thyroid weight with high vitamin A supplementation. Sadhu and Brody (1947) suggested that when vitamin A is fed in excess, its double bond takes up iodine from the thyroxine making thyroxine ineffective and thereby reducing the metabolic rate. The iodinated vitamin A may then depress the secretion of the anterior

pituitary thyrotrophic hormone as thyroxine does and thus, diminish thyroid size. Anderson, Hubbert, and Roubicek (1964) supported the theory that vitamin A influences thyroid activity by acting on the hypophysis to modify the release of thyrotrophic hormone.

A vitamin A deficiency has been found to cause enlarged thyroids in female rats (Coplan and Sampson, 1935). Enlarged thyroids have also been observed in horses fed high levels of iodine (Drew, Barber, and Williams, 1975). Perhaps these enlargements are due to related mechanisms. Lipsett and Winzler (1947) found iodine uptake per milligram of thyroid tissue to be appreciably lower in vitamin A deficient rats. They also observed a significantly lower rate of thyroxine formation in vitamin A-free rats. They concluded that iodine metabolism is abnormal in the vitamin A-deficient rat.

Johnson and Baumann (1947) found a functioning thyroid gland to be necessary for an animal to convert carotene to vitamin A and store it in the liver. Chanda *et al.* (1951) also presented evidence implying that the rate of conversion of carotene to vitamin A by the cow and goat depended on the thyroid status of the animal. Kunde (1926) observed xerophthalmia in thyroidectomized rabbits that had been fed a diet adequate in carotene to meet the vitamin A requirement of a normal rabbit.

An early observation of the milk from goats which had been thyroidectomized showed that the normally pure white milk became yellow due to carotene. Again, this shows that in the absence of the thyroid less carotene was converted to vitamin A (Smith and Perman, 1940).

The administration of desiccated thyroid tissue to rats was reported to greatly increase the amount of vitamin A stored in the body when carotene was fed (Johnson and Baumann, 1947; Serif and Brevik, 1960). This increase in storage in spite of a possibly increased requirement for the vitamin led Johnson and Baumann (1947) to also conclude that more vitamin A was formed from carotene in the thyroid's presence than its absence and that perhaps this was due to better absorption of carotene or by an effect on the enzyme responsible for the conversion of carotene to vitamin A. They along with Serif and Brevik (1960) and Cama *et al.* (1957) found little vitamin A produced from beta-carotene and stored in the hypothyroid rat, but the amount in the hyperthyroid rat may be twice that produced by the normal rat. The changes that frequently occur in the gastrointestinal mucosa during hypothyroidism may hinder proper vitamin A absorption (Wohl and Feldman, (1939) thereby explaining the lower vitamin A values. These differences in liver vitamin A levels may be due only to differences in the extent of utilization of the liver reserves by the different groups rather than to the conversion of a precusor to vitamin A (Bamji and Sundaresan, 1961). Remington, Harris, and Smith (1942) observed that a markedly prolonged time was required to deplete rats of vitamin A when they were thyroidectomized. This period was shortened when intact animals were injected with thyroxine. Moore (1957) and Logaras and Drummond (1938) did not necessarily support these results. Moore (1957) reported enlarged livers in rats treated with thyroid and concluded that thyroxine may increase storage of vitamin A. Logaras and Drummond (1938) did not observe an increased utilization or decreased vitamin A storage in rats due to thyroxine.

Brody (1974), Johnson and Baumann (1947), and Smith and Perman (1940) reported increased vitamin A requirements in hyperthyroid animals. Brody (1974) observed a tendency toward liver damage with hyperthyroidism which would interfere with vitamin A storage. Since thyroxine can bind with carotene colloidally, it could act to retard the formation of vitamin A from carotene (Smith and Perman, 1940). Excess thyroxine may also destroy or deplete vitamin A reserves of the body. (Wohl and Feldman, 1939; Glover, 1973).

Chanda *et al.* (1951) reported from their results that the vitamin A forming step is not entirely under the control of thyroid hormone and that some vitamin A formation occurs even in its complete absence. They also suggested that the form of thyroid hormone effective in conversion of beta-carotene to vitamin A is triiodothyronine rather than thyroxine which they found to have no metabolic activity with respect to beta-carotene conversion.

Other thyroid-vitamin A relationships reported include the partial counteracting of an increased basal metabolic rate by vitamin A or carotene administration in thyroxine injected rats and the improvement of hyperthyroid patients treated with vitamin A rich diets (Wohl and Feldman, 1939). Smith and Perman (1940) found basal oxygen consumption in cats to increase less when thyroxine plus carotene was given rather than when thyroxine alone was administered. Brody (1974) observed a drop or stop in body weight loss due to thyroid administration when sufficient vitamin A was given. A drop in efficiency of carotene conversion in calves subjected to the stress of high ambient temperatures compared with those in a cooler environment was reported in a paper by Anderson, Hubbert, and Roubicek (1964). This was thought to be the result of lowered thyroid

activity at the higher temperatures. Both protein-bound iodine and thyroid weight were found to be reduced at very high levels of vitamin A supplementation (Anderson, Hubbert, and Roubicek, 1964) indicating a possible competition for plasma protein binding between iodine and vitamin A.

Poor dark adaptation, which is considered a conclusive sign of vitamin A deficiency has also been observed in hypothyroid patients (Smith and Perman, 1940). The same result was found in hyperthyroidism, but here the deficiency was due to the destruction of vitamin A in the body rather than failure to manufacture vitamin A.

CRANES CREST

CHAPTER III

METHODS AND MATERIALS

I. RAT EXPERIMENTS

A study was done with white rats to determine the effect of feeding high levels of iodine as EDDI on the storage of vitamin A in the liver.

Animals

Forty Sprague-Dawley female rats approximately 2 months of age and weighing an average of 142 grams each were randomly grouped in individual cages into 4 treatments of 10 rats each.

Treatment

All rats were fed a low vitamin A diet *ad libitum*. The composition of the diet was as follows:

Ingredient	*Percent of diet*
Ground yellow corn	52.94
Casein	11.76
Skim milk powder	14.71
Soybean oil meal	8.82
Brewer's yeast	2.94
Irradiated yeast	0.02
Salt mix	4.00
Fat and oil	1.71
Dextrose	3.10
Total	100.00

Enough EDDI was added to give 250 (2.66 grams EDDI/8.5 kg. feed), 500 (5.31 g./8.5 kg.), and 1000 (10.31 g./8.25 kg.) ppm of iodine in 3 of the rations while the control diet was not supplemented with iodine. Rations were fed 9 weeks during which rats were weighed weekly and their food consumption recorded. At the termination of the experiment, the rats were anesthetized with ether and decapitated in order to get a total bleeding. Blood samples had to be pooled within treatment groups in order to have enough plasma for analyses. Blood was collected in heparinized tubes and plasma was frozen until needed. The livers were also taken from each rat and frozen.

Analyses

Plasma vitamin A was determined according to Kimble (1939) using either 3 or 4 ml. of plasma, depending on the amount available. The liver vitamin A was determined by the procedure of Bunnell *et al.* (1954) using a single extraction with Skelly solve-B. Liver samples of approximately 2 grams were saponified and extracted, and 0.5 ml. aliquots of the petroleum ether extract were used for the Carr-Price reaction.

Plasma iodine was determined by the method of Brown, Reingold, and Samson (1953) for determining protein-bound iodine by dry ashing. Adaptations of this procedure included omitting the two water rinsing steps. The plasma sample was added after the supernatant from zinc hydroxide was discarded. The quantity of plasma used was reduced for samples high in iodine. The control samples were analyzed with 1 ml. of plasma and 5 ml. of supernatant were used for reduction of the ceric ammonium sulfate by arsenious acid and iodine. The 250 ppm and 500 ppm plasmas were analyzed using 0.1 of plasma and 2 and 1 ml. of supernatant, respectively . Plasma of the 1000 ppm group was analyzed

with 0.05 ml. plasma from which 1 ml. of supernatant was taken for the color reaction.

Analysis of variance and mean separation by "least significant difference" were performed on the data (Steel and Torrie, 1960).

II. BOVINE EXPERIMENTS

This study concerned the second phase of an experiment involving the administration of various levels of supplemental iodine as EDDI (ethylenediamine dihydriodide) to cattle.

Animals

The study began January 1976 with the supplementing of 1.25, 2.5, 5.0, and 7.5 mg. I per kg of body weight to 4 groups with 6 lactating Holstein cows each of similar age among groups. After approximately 12 weeks the cows were regrouped by stage of gestation into groups given 5.0 and 7.5 mg. I per kg. of body weight. In about 4 weeks, 20 of these cows were allocated again into 3 groups supplemented with 1.25, 2.5, and 5.0 mg. I per kg. of body weight daily and 6 cows of comparable ages and gestation stages were designated as controls.

Treatment

Two groups of 7 cows each in mid-gestation were given 2.5 (100 ppm of the diet) and 5.0 (200 ppm) mg. I/kg. body weight, and a group of 6 cows in which pregnancy had not been diagnosed definitely was given 1.25 (50 ppm) mg. I/kg. body weight. For this study only 6 cows in the 5 mg. group, 5 in the 2.5 mg. group, and 4 in the 1.25 mg. group were available for plasma analyses in the periparturient period. A group of 6 controls of similar age and stage of gestation which received no iodine supplement was used for the iodine analysis. An additional 22 control cows which

calved during the same period were also used for the vitamin A analysis. Iodine supplementation ended when the cows were about 120 days into lactation. The cows were on limited grass pasture in season and were often fed green chopped summer annual grasses and mixed hay. The supplemental iodine was given as EDDI mixed with dextrose at a 1:4 ratio. First, it was mixed with the pelleted feed, but as lactation advanced and feed allowances decreased it was given daily in capsules. Doses were weighed into large gelatin capsules for each cow and the capsule was given by balling gun once daily at about 1300 hours. Average doses for the 3 groups were 0.711, 1.495, and 3.172 grams of iodine per cow daily for the 1.25, 2.5 and 5.0 mg. groups, respectively. These levels had been given through the previous lactation, the dry period, and into the early part of the present lactation. Adjustments were made for body weight changes after calving so that the average iodine doses by groups were 0.741, 1.582, and 3.222 grams per cow daily. The control cows received the same diet as the others. The concentrate they received contained 0.5 percent trace mineralized salt, which contained 0.007 percent iodine. From the average total iodine concentrations of 131 mg. per liter of plasma, and 108 mg. per liter of milk for 2 months, the iodine intake of control cows was estimated at about 5 mg. per cow daily. This basal amount was also consumed by cows supplemented with iodine.

Blood samples from the jugular vein were taken in heparinized tubes as close to 30 and 7 days prior to calving as possible, on the day of calving, and 10 and 30 days after calving. The 22 extra control cows were sampled at varied times before calving (averaging 25 days prior

to parturition), on the day of calving, and approximately 30 days after calving. Whenever possible, blood samples by jugular vein puncture were taken from the calves on day of birth, and 10 and 30 days after birth. Blood was centrifuged and the plasma frozen until needed for analyses.

Analyses

Plasma from the iodine supplemented cows and the 22 extra controls was analyzed for plasma vitamin A levels according to Kimble (1939) on approximately 30 days prior to, day of, and 30 days after calving. Plasma vitamin A was also determined on day of calving for calves when samples were available. Due to plasma scarcity, only 2.5 or 3.0 ml. of plasma were used for the cows and 3 or 4 ml. for the calves. Thyroxine levels were also determined in plasma from all cows and calves at the same time intervals as were done for vitamin A. Chopra's (1972) method for determining thyroxine in unextracted serum by radioimmunoassy was used with several changes. The actual procedure used for thyroxine analysis is as follows:

Reagents

Stock $T_4{}^{125}I$ (Amersham Corporation)

Thyroxine antiserum-rabbit (Endocrine Sciences)

Normal rabbit serum (Pentex Rabbit Serum--Miles Labs, Inc.)

ANS (8-Anilino-1-naphthalene-sulfonic acid ammonium salt) (Eastman Kodak Co.)

Sheep anti-rabbit gamma-globulins--precipitating antibody (Antibodies Inc.)

L-Thyroxine-free acid (Sigma Chemical Co.)--for standard curve

Sodium diethylbarbiturate (Fisher Scientific Co.)--15.6 g./liter deionized water

T_4-free plasma--obtained from thyroidectomized calf at the University of Tennessee

Radioimmunoassay Procedure

1. Dilute plasma--1:3--in 2 percent normal rabbit serum (NRS) (add 100 µl. plasma to 300 µl. buffer-NRS)
2. Add 100 µl. of diluted plasma to duplicate tubes
3. Add 100 µl. of T_4-free plasma (1:3 dilution) to all total, NSB (non-specific binding), 0, and standard curve tubes (tubes 1-22)
4. Add
   a. 100 µl. standard curve solution (No. 11-22)--Duplicates of 5, 10, 20, 40, 60, and 80 ng. T4/ml. NRS.

or b. 100 µl. Buffer-NRS to sample and 0 tubes (No. 8-10 and 23+)

or c. 200 µl. Buffer-NRS to total and NSB tubes (1-7)

5. Add 200 µl. isotope (ANS-^{125}I-T_4-Buffer) solution to all tubes
6. Add 100 µl. antibody solution to all tubes *except* total and NSB tubes (No. 1-7)
7. Mix gently with Vortex mixer
8. Incubate all tubes 1 hour at 37° C, then place in ice water bath (4° C) for 15 minutes
9. Add 100 µl. of second antibody solution to all *except* total tubes (No. 1-3)
10. Mix
11. Incubate for 20 hours at 4° C
12. Centrifuge sample and standards at 4° C for 25 minutes at 3000 RPM

13. Draw off supernatant with suction, *except* for total tubes
14. Cover total tubes then place all reaction tubes in counting vials
15. Count in gamma counter 2-5 minutes, to ensure minimum of 2000 counts for sample tubes

The results were analyzed according to the "logit-log" method of Rodbard (1974) with the weighted linear regression being used. The taped program for interpreting the gamma counter results with a Model HP-9815A desk calculator was obtained from Hewlett-Packard Calculator Products Division.

Total plasma iodine was determined for the cows on samples taken 30 days prior to calving, day of calving, and 30 days after calving and for calves from these cows on day of calving when available, by the method used in the preceeding rat experiment.

Analysis of variance and mean separation were performed on all data (Steel and Torrie, 1960).

CHAPTER IV

RESULTS AND DISCUSSION

Experiments with Growing Rats

At the end of the 9-week experimental period no significant difference was found among groups in average body weights of the rats, indicating that the iodine in the feed had no apparent affect on weight gain (Table 1). The average daily feed consumption was also very close among all groups, averaging approximately 11 grams of feed per day per rat (Table 1). Iodine supplementation did not affect ration consumption

Vitamin A. Average liver weights for the group fed 1000 ppm of iodine in their diet were significantly higher ($P < .05$) than the other three groups (Table 1). This increased liver size was apparently caused by the higher level of feed iodine. Enlarged livers have been associated with treatment of the rat with thyroid extract. However, according to Nagataki (1974) excess iodide does not affect the release of thryoid hormone in intact untreated rats. Galton and Pitt-Rivers (1959) found that organic binding of iodine though lower than normal at first, returned to normal several days after the feeding of high doses of iodine began. Therefore the increase in liver size is probably not due to an alteration in thyroidal activity due to excess iodine. Perhaps the excess iodine has some effect on the liver itself causing it to increase in size.

Differences in vitamin A per gram of liver among the four groups approached sifnificance ($P < .05$), but a logical trend was not evident (Table 1). The control group had the lowest concentration of vitamin A in livers, followed by the 1000 ppm and 500 ppm groups. The 250 ppm group had

Table 1. Effect of Iodine Supplementation on Maintenance of Liver Vitamin A in Rats Fed a Vitamin A Deficient Diet for 9 Weeks

Item	Iodine in Feed			
	0	250 PPM	500 PPM	1000 PPM
No. of animals	10	10	10	10
Body weight at start, g	141.2	148.0	139.3	140.1
Body weight at end, g.	212.4	216.7	209.4	212.4
9-week weight gain, g	71.2	68.7	70.1	72.3
Daily Feed Consumption, g.	11.4	11.4	11.3	11.6
Liver weight, g.	4.3	4.4	4.5	5.0[a]
Total liver vitamin A, µg.	153.2[a]	183.4	178.6	187.6
Liver vitamin A, µg./g.	36.4	43.6	40.5	37.5
Plasma vitamin A, µg/100ml.	15.9	17.1	17.6	15.4
Total plasma iodine, µg/L[b]	111.0	2942.0	3913.0	6259.0

[a]Value significantly different from other values in the same line not bearing the same superscript (liver weights $P < .05$; total liver vitamin A $P < .01$)

[b]All values in same line differ significantly ($P < .001$).

the highest vitamin A per gram of liver tissue. The data suggest that iodine feeding slightly increased vitamin A storage in the liver of the rat. The larger livers noted with high iodine feeding may account for some of the increased vitamin A stored in the livers of the iodine groups.

The total vitamin A was significantly lower in livers of the control group compared with the other three. This is a result of the combination of smaller livers and slightly less vitamin A per gram of liver in the controls than in the iodine-fed rats.

Plasma vitamin A followed a similar trend as concentration of liver vitamin A, but it was not statistically different between diet treatment groups (Table 1).

The average vitamin A content of the livers of all the rats on experiment was 39.5 micrograms or 131.67 I.U. of vitamin A per gram of liver. Muto *et al.* (1972) reported moderate liver vitamin A storage for a rat to be 15 to 20 micrograms per gram of liver, but Moore (1957) reported normal values of 250 I.U. of vitamin A per gram of liver for the rat. According to Moore's standard, rats in this study were lower in vitamin A than the typical rat, which is what was expected since they were on a relatively low vitamin A diet. The vitamin A values of plasma for all rats averaged 16.5 micrograms or 55 I.U. per 100 ml. of plasma which is again below Moore's (1957) normal plasma vitamin A value of 80 I.U. per 100 ml. of plasma. Normally plasma vitamin A remains stable unless there is a large deficiency of liver vitamin A. A deficiency was not apparent in this study. Baumann, Riising, and Steenbock (1934) never found vitamin A in non-hepatic tissues of an animal unless the liver also contained vitamin A. Therefore, though they had been on a low vitamin A diet for 9 weeks, these rats were not yet seriously deficient in vitamin A.

Iodine. Plasma iodine levels of the rats increased significantly ($P < .005$) with increasing amounts of iodine fed (Table 1). This was a good

indication that the rats were consuming the iodine they were calculated to receive in their diets. The rate of increase in plasma iodine with increases in dietary iodine was not strictly linear.

Experiments with Pregnant Cows

Vitamin A. A statistical analysis of the plasma vitamin A of the cows (Table 2) in this study indicated a significant difference ($P < .005$) due to the period the plasma samples were taken (before, on day of, or after calving), but no significant difference appeared due to the level of iodine administered. Therefore, even the largest amount of supplemental iodine (200 ppm or 5 mg. I/kg. of body weight) had no influence on the vitamin A in the plasma. The plasma vitamin A values were more than adequate for the normal functioning of the animals in all diet groups. The liver vitamin A would better indicate the animal's vitamin A status, but cow liver samples were not obtained.

For plasma vitamin A, the data indicated a downward trend from 30 days prior to parturition which may have, attaining a low on day of calving. It then rose after calving to a level not significantly different from the level recorded at 30 days prior to calving. This trend which occurred in all groups seems to be normal. Sutton *et al.* (1945) reported that all cows in their study when considered as a group decreased in blood plasma vitamin A by 52 percent from the 3 week prepartum level, with the lowest point at the third day postpartum. Stöckl, Schuh, and Schmid (1975) studying primiparous cows during the puerperalphase, found that both vitamin A and beta-carotene decreased in the first day postpartum, and then returned to normal in the second and third week, respectively, after parturition. A drop in the total protein concentration

Table 2. Effect of Iodine Supplementation on Plasma Vitamin A in Cows

Treatment[a]	No.	Time Relation to Parturition		
		Prepartum	Parturient[b]	Postpartum
		← µg/100 ml →		
Controls (-I)	28	50.6	31.5	44.8
Iodine Suppl.				
50 PPM	4	47.2	28.3	43.1
100 PPM	5	41.9	38.8	45.1
200 PPM	6	54.0	40.4	43.3
All cows	43	49.7	33.3	44.5

[a] Differences among treatments not statistically significant.

[b] Values significantly different from other values in the same line ($P < .005$).

in the blood (including albumin and globulin) has been observed in the weeks prior to calving (Rowlands *et al.*, 1975). Since plasma vitamin A is transported by certain proteins in the albumins and globulins, their decline can lead to the drop in the plasma vitamin A seen before parturition. The fall in these proteins has been shown to be partly caused by decreased liver synthesis. Rowlands *et al.* (1975) observed an increase in both of these proteins after calving, just as plasma vitamin A increases. Braun (1945) also found a significantly sharp drop of plasma vitamin A level starting about 2 weeks before parturition or abortion, reaching its lowest level a few days after calving and then rising to the former level. He found that certain pathological conditions affected vitamin A level similarly including acute infections, localized abscesses,

or gangrenous mastitis. These effects could explain some of the variability or occasional unusual vitamin A values for the cows in this study. Braun (1945) observed the sharp drop in vitamin A level before symptoms were manifest and the restoration to normal levels only when infection subsided. Since large doses of vitamin A did not prevent these sudden decreases, disturbance in conversion of carotene to vitamin A was ruled out as the sole cause of low blood levels.

It is quite likely that mammary secretion of colostrum, which is rich in globulin and albumin, also removes much carotene and vitamin A from circulating blood after calving since vitamin A-binding proteins are in these blood proteins. A sharp decline in the blood plasma level of carotene and vitamin A has been associated with a rapid filling of the udder (Sutton *et al.*, 1945). Sutton and Soldner (1943) discovered that the blood plasma vitamin A and carotene values of 18 dairy cows during their winter feeding period were maintained at normal levels of approximately 16 micrograms and 400 micrograms per 100 ml. of plasma, respectively, until about 1 week prior to parturition. At the time the mammary gland began to fill there was a precipitous drop in plasma vitamin A. The average levels of carotene and vitamin A within 3 days of parturition were 235 micrograms and 8.2 micrograms per 100 ml, respectively. Plasma samples from within 1 to 3 days post-freshening averaged 220 micrograms carotene and 7.5 micrograms vitamin A per 100 ml. A gradual rise was then observed, but vitamin A and carotene levels did not return to normal by 4 weeks following calving.

Another possible reason for the fall in vitamin A near calving and for reproductive failures associated with vitamin A deficiency is the

sparing effect of progesterone and the antagonistic effect of estrogen on vitamin A (Hayes, 1969). The physiological fall in the progesterone level during late pregnancy could increase the requirement and utilization of vitamin A and account for lowered plasma vitamin A levels associated with that period of gestation.

Thyroxine. The plasma thyroxine (Table 3) was found to be significantly different ($P < .005$) for the sample periods in about the same manner as vitamin A. No significant difference due to iodine supplementation was found. Convey *et al.* (1977) reported no alteration of plasma thyroxine concentration in cattle supplemented with iodine. The plasma thyroxine (T_4) values for these cattle fell within the range of 3.6 to 8.9 micrograms per 100 ml. of plasma observed by Reap, Cass, and Hightower (1978). Plasma thyroxine followed the same path as plasma vitamin A, as it fell to a low at calving. Plasma thyroxine increased postpartum, but by 30 days it was usually lower than the value shown 30 days prior to calving. All of the period means (pre-, day of, and post-calving) were significantly different from each other. This drop in plasma thyroxine concentration around calving could be due to several things. Unlike vitamin A, no evidence had been shown of loss of thyroxine in the milk or colostrum (Reineke and Turner, 1944; Lewis and Ralston, 1953) and little, it any, loss occurs through the placenta (Nathanielsz, 1970; Carr *et al.*, 1959; Miller *et al.*, 1967; Fisher and Dussault, 1974). The decrease in plasma albumin and globulin at parturition may in some way affect the total plasma thyroxine level, as nearly all of the plasma thyroxine is bound to protein.

Table 3. Effect of Iodine Supplementation on Plasma Thyroxine in Cows

Treatment[a]	No.	Time Relation of Parturition[b]		
		Prepartum	Parturient	Postpartum
		← ng/ml →		
Controls (-I)	28	67.0	33.0	53.5
Iodine Suppl.				
50 PPM	4	68.0	39.7	44.1
100 PPM	5	53.6	30.6	45.7
200 PPM	6	52.7	24.1	56.4
All cows	43	63.5	32.1	52.1

[a]Differences among treatments not statistically significant.

[b]All period means significantly different ($P < .005$).

An unlikely explanation, though possible in control cows, is that since the fetal system loses iodine only through placental diffusion, not fecal or urinary excretion, it may act as a trap for maternal iodine (Gorbman *et al.*, 1952). Over a period of time the fetal system might deplete the dam's iodine and exert a goitrogenic effect on the maternal thyroid. In extreme conditions this could cause a decrease in the dam's thyroxine until the fetus is born, thereby ridding the dam of such a goitrogenic effect. Another possibility is that an increase in thyroxine turnover rate could occur on day of calving resulting in a lower plasma T_4 value.

Gorbman *et al.* (1952) found a reduction in the function of the thyroid of late gestation cows when they injected radioiodine tracer into

two near-term cows. They observed adult thyroids not only from these cows, but from an injected ox, to be slow in synthesizing thyroxine when compared with fetuses.

As with vitamin A, sex steroids also influence thyroxine status. These steriods in pharmacological doses produce pronounced effects on thyroxine-binding globulin (TBG) and thyroxine-binding prealbumin (TBPA). Estrogens produce increased binding capacity of TBG and possible decreased capacity of TBPA, along with increased serum protein-bound iodine (Oppenheimer, 1968) most of which is considered thyroxine. This explains the increased binding capacity of TBG and increased plasma iodine levels in pregnant females and newborn infants. This is a likely reason for the prepartum plasma thyroxine level usually being higher than on the day of calving and postpartum levels. The estrogen level in the animal increases during gestation and then drops at calving. This drop could result in a decreased serum protein-bound iodine level due to a decreased TBG binding capacity.

Iodine. Total plasma iodine levels (Table 4) for the cows indicated a significant effect due to supplemental iodine ($P < .005$). A definite upward move in plasma iodine followed an increase in iodine administered orally. Wolff (1969), Newton *et al.* (1974), Newton and Clawson (1974), and Baker and Lindsey (1968) also reported increased serum iodine values with increased iodine in the diet. This increased plasma iodine did not show any obvious effects on the vitamin A status of the animals (Table 2). Nasal discharge was noted in most of the animals in the 200 ppm group and in one cow in the 100 ppm group. It was attributed to iodism rather than vitamin A deficiency. No outward signs of altered thyroid size in the cows were observed. Apparently, the cows were able to excrete much

Table 4 Effect of Iodine Supplementation on Plasma Iodine in Cows

Treatment[a]	No.	Time Relation to Parturition		
		Prepartum	Parturient[b]	Postpartum
		← µg/L →		
Controls ($^{-}$I)	6	161	146	109
Iodine Suppl.				
50 PPM	4	2,966	4,135	3,150
100 PPM	5	4,997	6,149	3,633
200 PPM	6	11,173	18,493	11,321
Total	21			

[a]All treatment means significantly different ($P < .005$).

[b]Values significantly different from other values in the same line ($P < 0.1$)

of the excess iodine through their feces, urine, milk, and probably the placenta, since very high plasma iodine values were found in their calves.

The difference in plasma iodine between the periods the samples were taken was significant at the 10 percent level and closely approached significance at the 5 percent level of probability. The trend was one showing an increase in plasma iodine from the 30-day perpartum sampling to day of calving sampling and then a decline from day of calving to the postpartum sampling. Plasma iodine levels for the pre- and postpartum periods were not significantly different from each other. One explanation for an increased plasma iodine at parturition is that the cows received a constant daily iodine dose by capsule which along with lowered feed and water intakes at calving (causing decreased iodine excretion), could result in higher iodine retention. The drop in plasma iodine after calving

can be attributed mainly to loss of iodine in the milk. Iodine, as well as vitamin A, is associated with proteins which are lost in the colostrum (Lewis and Ralston, 1953; Baker and Lindsey, 1968).

The average for the control cows showed a plasma iodine decline from the first blood sampling to the last, but since much variation was seen among these animals, this trend probably lacks credibility. Several of the controls showed the trend reported for the other groups. I would, therefore tend to consider it the normal whether iodine was fed or not.

Experiments with Neonatal Calves

Vitamin A. The plasma vitamin A of the neonatal calves (Table 5) was not significantly different among the four diet groups (0, 50, 100, 200 ppm of iodine) of the dams. The average level was 8.5 micrograms per 100 ml. of plasma which was only approximately 25 percent of their dam's level. The plasma vitamin A level of the calf depends on several factors. Researchers tend to agree that the vitamin A reserves in the liver and plasma of the fetus at birth are low (Guilbert and Hart, 1934; Spielman *et al.*, 1946; Baumann, Riising, and Steenbock, 1934; Baetz and Hubbert, 1974; Moore, 1971; Dann, 1932; Ismadi and Olson, 1975). Since a lack of vitamin A or its precursor, carotene, in the pregnant cow's diet may result in a dead, blind, or weak calf, it has been concluded that a sufficiency of this vitamin must cross the placental barrier to provide for normal fetal development (Spielman *et al.*, 1946).

The amount of vitamin A passed from dam to fetus depends, among other things, on diet of the dam (Braun and Carle, 1943; Spielman *et al.*, 1946; Baker *et al.*, 1953; Baumann, Riising, and Steenbock, 1934; Fountain

Table 5. Effect of Iodine Supplementation on Dams on Plasma Vitamin A Thyroxine, and Iodine in Calves on Day of Calving

Treatment	No.	Plasma Vitamin A[a]	No.	Plasma Thyroxine	No.	Total Plasma Iodine[d]
		(µg/100 ml.)		(ng/ml)		(µg/L)
Controls (-I)	6	7.4	6	210.7[b]	4	426
Iodine Suppl.						
50 PPM	3	7.4	3	171.6[bc]	3	14,135
100 PPM	5	10.5	5	102.4[c]	5	18,959
200 PPM	7	8.4	7	109.2[c]	7	36,252
All calves	21	8.5	21	145.5	19	

[a]Differences among treatments not statistically significant.

[b]Treatment means significantly different from other values in same column with different superscripts ($P < .01$).

[c]All treatment means significantly different ($P < .005$).

et al., 1948). Supplementation of dairy cattle rations with high levels of vitamin A during the last 30 days of gestation increased plasma levels and liver stores of vitamin A in newborn calves (Baker *et al.*, 1953).

Baker *et al.* (1953) found vitamin A in the liver and plasma of the bovine fetus to be influenced by liver stores of the cow at parturition. Even so, the reserves in calves at birth are low even if their dams have abundant stores (Guilbert and Hart, 1934). Baetz and Hubbert (1974) reported that the bovine liver does not begin to store significant amounts of vitamin A until after birth. The small vitamin A store of the rat fetus is contained chiefly in the liver (Dann, 1932). This is also true with other species.

The vitamin A content in human fetal plasma was found to be about 50 percent of its mother's (Ismadi and Olson, 1975), which is somewhat higher than seen in this study with calves. Ismadi and Olson (1975) found that over 90 percent of the vitamin A in human fetal blood is bound to retinol-binding protein in the form of a complex with prealbumin. Since newly synthesized retinol-binding protein is released only in the presence of an adequate amount of retinol in the liver, the low vitamin A stores in fetuses near term and in newborn infants may limit the outflow of retinol-binding protein (Ismadi and Olson, 1975). This would explain the low plasma vitamin A in the fetus. A similar process undoubtedly occurs in the bovine.

The concensus appears to be that larger amounts of vitamin A are transferred to the calf during lactation (Moore, 1971; Dann, 1932) rather than in gestation, and that plasma and liver vitamin A of the nursing calf are closely associated with carotene and vitamin A intake of the dam during lactation (Baker *et al.*, 1953; Baumann, Riising, and Steenbock, 1934). Colostrum, which is rich in vitamin A, is well absorbed by offspring so that it helps build a store in the liver (Morton, 1960). Moore and Berry (1944) confirmed this effect with Holstein calves. At birth their plasma vitamin A averaged 3.3 micrograms per 100 ml. of plasma. After consuming colostrum the plasma vitamin A increased four to five times averaging 15.6 micrograms per 100 ml. The calves in this study had average plasma vitamin A values close enough to these calves to be considered sufficient in vitamin A. At time of sampling, it is assumed that all calves had had time to consume some colostrum.

Thyroxine. Plasma thyroxine was found statistically different ($P < .01$) between calves of control cows and the 100 and 200 ppm iodine groups, but not between the controls and 50 ppm group or the 50 ppm and the two higher groups (Table 5). Apparently, the higher the iodine intake, the less thyroxine was bound in plasma. This could also be due to the Wolff-Chaikoff effect in which high iodide inhibits thyroid hormone production (Wolff and Chaikoff, 1948).

The plasma thyroxine value for calves of the control group (210.7 ng/ml) was quite high compared with the calf plasma thyroxine value of 140 micrograms per liter observed immediately after birth by Kahl, Wrenn, and Bitman (1977). Nathanielsz (1969) reported thyroxine values Jersey calves of 128 to 116 micrograms per liter from birth to 24 hours of age. The 100 ppm and 200 ppm diet groups were just slightly below these values, indicating a possible depressing influence of high iodine supplementation on thyroxine. Plasma thyroxine in the calf is much higher than its dam's on the first day of life and then declines gradually (Nathanielsz and Thomas, 1973; Kahl, Wrenn, and Bitman, 1977).

Fisher and Dussault (1974) attributed a rise in fetal serum thyroxine as partially due to an increase in serum TBG concentration which in turn is due to an increase in placental estrogen secretion during the latter half of pregnancy. The total thyroxine secretion increases during the latter half of pregnancy in response to fetal thyroxine stimulating hormone (TSH). The fetal pituitary-thyroid system functions independently of maternal control. They again stressed that fetal thyroid hormone secretion exceeds maternal secretion on a body weight basis. At birth the calves in this project had plasma thyroxine values two to four times greater

than their dams. Gorbman *et al.* (1952) reported the fetal thyroid could accumulate more than twice as much iodide as the maternal gland. They also demonstrated a greater rate of thyroxine formation in the fetus compared with its mother, as did Aschbacher *et al.* (1966).

This large disparity in apparent thyroidal function between the fetus and mother is thought to be due to a difference in thyrotropic hormone concentration in the fetal and maternal circulations (Gorbman *et al.*, 1952). No matter what the cause, the fetal thyroid still shows more active thyroxine production than the adult. In the bovine fetus, Koneff *et al.* (1949) observed concentration and storage of organic iodine in the fetal thyroid while the gland was still devoid of its characteristic architecture and prior to any histological manifestation of its specific function. Thyroxine-like iodine was detected in the thyroid gland of a 60-day bovine fetus. The livers of the fetuses contained almost no iodine, just as they lacked vitamin A. Thereafter, the amounts of thyroxine-like and total iodine in the gland increased steadily. Apparently, with increasing age, the fetal thyroid acquires an increased capacity for iodine storage (Wolff, Chaikoff, and Nichols, 1949).

Iodine. The plasma iodine levels of the calves (Table 5) increased significantly as the iodine intake of the dam increased ($P < .005$). This is understandable since iodine can be transmitted through the placenta and through the milk to the fetus or neonate. Plasma iodine values for calves were also found to be from two to five times greater than the dam's even in the control calves. This is due to the active transport of iodide across the placenta to the fetus where it is not only concentrated

in the blood, but is also found in other fetal fluids, thyroids, stomach, and other sites (Miller *et al.*, 1967). Miller *et al.* (1967) also mentioned the occurrence of considerable fetal ingestion of iodine-containing amniotic fluid during late preganancy. The iodine reaching the fetal stomach in this way would be absorbed from the intestinal tract, as in the adult. After birth there is a high rate of fecal and urinary iodine excretion, two pathways of excretion the fetus does not have before birth.

Some abnormalities were seen in certain calves born of dams in the higher iodine supplemented groups which could have been interpreted as vitamin A deficiency. Since the dams and neonates appeared to have normal levels of plasma vitamin A, then the mechanism causing symptoms attributed to iodism, did not affect vitamin A stores. The group with the highest level of supplementation (200 ppm) had several calvings from 2 to 13 days prior to the expected date. Tissue edema along with darkened kidneys, both possibly due to excessive iodine, was noted in one of the calves which was born dead. A slight goiter which later disappeared was observed in one calf, the mother of which had shown excessive nasal discharge and also retained placenta. Both signs have been attributed to iodism. A rather large thyroid (29 grams) was also reported in a female calf that died of causes related to dystocia. Cows in the 100 ppm diet group had one premature calving (19 days early) of a small but normal calf which later died of pneumonia. The calf had tissue edema and liver congestion, but whether these can be associated with iodine toxicity is questionable. Another calf, born dead, had an enlarged thyroid (26 grams), darkened kidneys, blood filling the body cavity, edematous tissues and organs,

mottled liver, cloudy eyes, and abnormally large adrenal glands. Newton *et al.* (1974) found heavier adrenal glands in calves fed high iodine diets and suggested it might be due to stress caused by the excessive iodine. Many of the other aforementioned abnormalities have also been listed as symptoms of iodism. No unusual signs were noted in calves from the low iodine or control groups. Plasma samples from the dead calves were included in the chemical and statistical analyses of the samples from normal calves. The plasma thyroxine values were obviously lower for these calves, but their plasma iodine and vitamin A did not appear abnormal. Including the data from calves dead at birth did not change the results of the statistical analyses.

CRANES CREST

CHAPTER V

SUMMARY

No significant effect on vitamin A levels of plasma or liver was found due to supplementation of the basal diet of rats with various excessive amounts of iodine. High levels of iodine in the diet (250 to 1000 ppm) produced an increase in concentration of vitamin A per gram of liver tissue which approached significance. This result could indicate a small increase in total liver vitamin A storage or a decrease in the mobilization of vitamin A from the liver due to feeding iodine. The highest level of iodine feeding resulted in significantly larger livers than control or lower iodine diets.

Iodine supplementation had no apparent effect on plasma vitamin A in cows or calves. The vitamin A and thyroxine levels in the cow's plasma were seen to drop around calving and then increase after calving in all treatment groups.

The plasma thyroxine levels in the calves on the day of birth were affected by their dam's diet although the dam's thyroxine levels were not influenced by the iodine supplementation. Calves from control cows had the highest plasma thyroxine values, and those from 100 and 200 ppm groups were the lowest. There was an indication that excessive plasma iodine in calves interfered with thyroxine binding in plasma.

Plasma iodine levels were found to be significantly different among iodine supplemented groups in both cows and calves. The higher the iodine supplementation the higher the plasma iodine, but the increase was not strictly linear. A trend was also seen in all iodine-supplemented cows of a higher plasma iodine level on day of calving. This trend was not

evident in controls due to wide variation in plasma iodine values among cows and sampling periods.

The calves showed lower plasma vitamin A values (25 percent as much) and much higher thyroxine (3 to 6 fold) and iodine (2 to 3 fold) concentrations than their dams when plasma samples of both taken on day of calving were compared.

Thus, this research indicates an increase in liver size and possible increase in liver vitamin A concentration in rats due to the feeding of large quantities of iodine, however, no effect on plasma vitamin A was observed. Supplementing the bovine with high levels of iodine (up to 200 ppm of the diet) was found to have no influence on plasma vitamin A concentration in the cow or its fetus. Although this iodine supplementation did not affect the plasma thyroxine concentration of the cow, it did tend to decrease thyroxine production in the fetus.

LITERATURE CITED

CRANES CREST

LITERATURE CITED

Ammerman, C. B., L. R. Arrington, A. C. Warnick, J. L. Edwards, R. L. Shirley, and G. K. Davis. 1964. Reproduction and lactation in rats fed excessive iodine. J. Nutr. 84:107.

Ammerman, C. B. and S. M. Miller. 1972. Biological availability of minor mineral ions: a review. J. Anim. Sci. 35:681.

Anderson, T. A., F. Hubbert, Jr., and C. B. Roubicek. 1964. Effect of thyroxine, thiouracil and ambient temperature on the utilization of vitamin A by vitamin A-deficient rats. J. Nutr. 82:457.

Arrington, L. R., R. A. Santa Cruz, R. H. Harms, and H. R. Wilson. 1967 Effects of excess dietary iodine upon pullets and laying hens. J. Nutr. 92:325.

Arrington, L. R. R. N. Taylor, Jr., C. B. Ammerman, and R. L. Shirley. 1965. Effects of excess dietary iodine upon rabbits, hamsters, rats, and swine. J. Nutr. 87:394.

Ascarelli, I. 1969. Absorption and transport of vitamin A in chicks. Am. J. of Clin. Nutr. 22:913.

Aschbacher, P. W., R. G. Cragle, E. W. Swanson, and J. K. Miller. 1966. Metabolism of oral iodide and 3, 5-diiodosalicylic acid in the pregnant cow. J. Dairy Sci. 49:1042.

Baetz, A. L. and W. T. Hubbert. 1974. Vitamin A in the bovine fetus. Am. J. Vet. Res. 35:1189.

Baker, H. J. and J. R. Lindsey. 1968. Equine goiter due to excess dietary iodide. J. Amer. Vet. Med. Assoc. 153:1618.

Baker, F.H., R. MacVicar, L. S. Pope, and C. K. Whitehair. 1953. Placental and mammary transfer of vitamin A and carotene by beef cows. Soc. for Exp. Biol. and Med. Proceed. 83:571.

Bamji, M. and P. Sundaresan. 1961. Effect of thyroid activity on the absorption, storage and utilization of orally administered vitamin A aldehyde (retinal) in rats. J. Nutr. 74:39.

Baumann, C. A., B. M. Riising, and H. Steenbock. 1934. Fat-soluble vitamins: XLII. The absorption and storage of vitamin A in the rat. J. of Biol. Chem. 107:705.

Blumberg, B. S. and J. Robbins. 1960. Thyroxine-serum protein complexes. Single dimension gel and paper electrophoresis studies. Endocrinol. 67:368.

Braun, W. 1945. Studies on the carotenoid and vitamin A levels in cattle. J. of Nutr. 29:61.

Braun, W. and B. N. Carle. 1943. The effect of diet on the vitamin A content of the bovine fetal liver. J. or Nutr. 26:549.

Brody, S. 1974. Bioenergetics and growth. Hafner Press, New York.

Brown, H., A. M. Reingold, and M. Samson. 1953. The determination of protein-bound iodine by dry ashing. J. Clin. Endocrinol. and Metab. 13:444.

Bunnell, R. H., J. E. Rousseau, Jr., H. D. Eaton, and G. Beall. 1954. Estimation of vitamin A and carotenoids in calf liver. J. Dairy Sci. 37:1473.

Burke, C. W. and C. J. Eastman. 1974. Thyroid hormones. Br. Med. Bull. 30:93.

Cama, H. R., N. C. Pillai, P. R. Sundaresan, and C. Venkateshan. 1957. The effect of thyroid activity on the conversion of carotene and retinene to vitamin A and on serum proteins. J. Nutr. 63:571.

Carr, E. A., W. H. Beierwaltes, G. Raman, V. N. Dodson, J. Tanton, J. S. Betts, and R. A. Stambaugh. 1959. The effect of maternal thyroid function on fetal thyroid function and development. J. of Clin. Endocrinol. and Metab. 19:1.

Carroll, J. 1969. Phenolsulfotransferase in the developing rat. Amer. J. Clin. Nutr. 22:978.

Chanda, R., H. M. Clapham, M. L. McNaught, and E. C. Owen. 1951. The digestibility of carotene by the cow and the goat as affected by thyroxine and thiouracil. Biochem. J. 50:95.

Chopra, I. J. 1972. A radioimmunoassay for measurement of thyroxine in unextracted serum. J. Clin. Endocrinol. and Metab. 34:938.

Convey, E. M., L. Chapin, J. S. Kesner, and D. Hillman. 1977. Serum thyrotropine and thyroxine after thyrotropine releasing hormone in dairy cows fed varying amounts of iodine. J. Dairy Sci. 60:975.

Coplan, H. M. and M. M. Sampson. 1935. The effects of a deficiency of iodine and vitamin A on the thyroid gland of the albino rat. J. of Nutr. 9:469.

Correa, P., and R. A. Welsh. 1960. The effect of excessive iodine intake on the thyroid gland of the rat. Arch of Path. 70:247.

Dann, W. J. 1932. CXXV. The transmission of vitamin A from parents to young in mammals. Biochem. J. 26:1072.

Davis, R. E. and L. L. Madsen. 1941. Carotene and vitamin A in cattle blood plasma with observations on reproductive performance at restricted levels of carotene intake. J. of Nutr. 21:135.

DeLuca, L. and G. Wolf. 1969. Vitamin A and protein synthesis in mucous membranes. Amer. J. Clin. Nutr. 22:1050.

Drew, B., W. P. Barber, and D. G. Williams. 1975. The effect of excess dietary iodine on pregnant mares and foals. The Vet. Rec. 97:93.

Eaton, H. D., J. J. Lucas, S. W. Nielsen, and C. F. Helmboldt. 1970. Association of plasma or liver vitamin A concentrations with the occurrence of parotid duct metaplasia or of ocular papilledema in holstein male calves. J. Dairy Sci. 53:1775.

Erwin, E. S., T. R. Varnell, and H. M. Page. 1959. Relationship of vitamin A and carotene to bovine serum proteins. Soc. for Exp. Biol. and Med. Proc. 100:373.

Fisher, D. A. and J. H. Dussault. 1974. Development of the mammalian thyroid gland. Handbook of Physiology. Section 7: Endocrinology. Vol. III. Thyroid. Eds. M. A. Greer and D. H. Solomon. American Physiological Society, Washington, D. C. p. 21.

Fountain, F. C., D. B. Parrish, F. W. Atkeson, and J. S. Hughes. 1948. The effect of a ration limited to pasture during the dry-rest period on the vitamin A and carotenoid content of the blood of the newborn calf. J. Anim. Sci. 7:525.

Galton, V. A. and R. Pitt-Rivers. 1959. The effect of excessive iodine on the thyroid gland of the rat. Endocrinol. 64:835.

Ganguly, J. 1960. Absorption, transport, and storage of vitamin A. Vit. and Horm. 18:387.

Ganguly, J. 1969. Absorption of vitamin A. Am. J. of Clin. Nutr. 22:923.

Glover, J. 1973. Retinol-binding proteins. Vit. and Horm. 31:1.

Goodman, D. S. 1969. Biosynthesis of vitamin A from B-carotene. Amer. J. Clin. Nutr. 22:963.

Gorbman, A., S. Lissitzky, O. Michel, R. Michel, and J. Roche. 1952. Metabolism of radioiodine by the near-term bovine fetus. Endocrinol. 51:546.

Guilbert, H. R. and G. H. Hart. 1934. Storage of vitamin A in cattle. J. of Nutr. 8:25.

Gilbert, H. R. and G. H. Hart. 1935. Minimum vitamin A requirements with particular reference to cattle. J. Nutr. 10:409.

Hale, F. 1933. Pigs born without eye balls. J. of Heredity. 24:105.

Hayes, K. C. 1969. Comments. Am. J. Clin. Nutr. 22:1081.

Hernandez, M. V., K. M. Etta, E. P. Reineke, W. D. Oxender, and H. D. Hafs. 1972. Thyroid function in prenatal and neonatal bovine. 34:780.

Herrick, J. B. 1972. What role for EDDI (ethylene diamine dihydriodide) in bovine respiratory disease complex? Vet. Med. Small Animal Clin. 67:480.

Hillman, D., D. Bolenbaugh, and E. M. Convey. 1976. Iodine toxicity and thyroid disturbance in dairy cattle. Dept. of Dairy Sci., Michigan State University. Personal Communication.

Horvat, A., V. Vidović, P. Milutinović, and R. Buzina. 1959. Effect of potassium iodide and vitamin A on the thyroidal uptake and urinary excretion of I^{131} in goitrous subjects on the island of Krk. J. Nutr. 68:647.

Ismadi, S. D. and J. A. Olson. 1975. Vitamin A transport in human fetal blood. Am. J. of Clin. Nutr. 28:967.

Johnson, R. M. and C. A. Baumann. 1947. The effect of thyroid on the conversion of carotene into vitamin A. J. Biol. Chem. 171:513.

Kahl, S., T. R. Wrenn, and J. Bitman. 1977. Plasma tri-iodothyronine and thyroxine in young growing calves. J. of Endocrinol. 73:397.

Kanai, M., A. Raz, and D. S. Goodman. 1968. Retinol-binding protein: the transport protein for vitamin A in human plasma. J. Clin. Invest. 47:2025.

Kalter, H. and J. Warkany. 1959. Experimental production of congenital malformations in mammals by metabolic procedure. Physiol. Rev. 39:69.

Kimble, M. S. 1939. The photocolorimetric determination of vitamin A and carotene in human plasma. J. of Lab. and Clin. Med. 24:1055.

Koneff, A. A., C. W. Nichols, J. R., J. Wolff, and I. L. Chaikoff. 1949. The fetal bovine thyroid: morphogenesis as related to iodine accumulation. Endocrinol. 45:242.

Kunde, M. M. 1926. Studies on experimental cretinism. III. Nutritional disturbances, pellagra and xeropthalmia. Proc. Soc. Exp. Biol. Med. 23:812.

Lewis, R. C. and N. P. Ralston. 1953. Changes in the plasma level of protein-bound iodine in the young calf. J. Dairy Sci. 36:363.

Logaras, G. and J. C. Drummond. 1938. Vitamin A and the thyroid. Biochem. J. 32:964.

Lipsett, M. B. and R. Winzler. 1947. Effects of vitamin A deficiency on thyroid function studied with radioactive iodine. Endocrinol. 41:494.

Madsen, L. L. and I. P. Earle. 1947. Some observations on beef cattle affected with generalized edema or anasarca due to vitamin A deficiency. J. Nutr. 34:603.

Mayberry, W. E. and T. J. Hockert. 1968. Excess iodide ingestion and thyroid function in chicks. Pro. Soc. Exp. Biol. Med. 129:370.

McCauley, E. H., D. W. Johnson, and I. Alhadji. 1972. Disease problems in cattle associated with rations containing high levels of iodide. Bovine Practitioner. 7:22.

McCauley, E. H., J. G. Linn, and R. D. Goodrich. 1973. Experimentally induced iodide toxicosis in lambs. Am. J. Vet. Res. 34:65.

Mead, S. W. and W. M. Regan. 1931. Deficiencies in rations devoid of roughage for calves. J. Dairy Sci. 14:382.

Miller, J. K., E. W. Swanson, P. W. Aschbacher, and R. G. Cragle. 1967. Iodine transfer and concentration in the prepartum cow, fetus, and neonatal calf. J. Dairy Sci. 50:1301.

Moore, L. A. and M. H. Berry. 1944. Effect of colostrum on the vitamin A and carotene of blood plasma of newborn calves. J. Dairy Sci. 27: 867.

Moore, L. A., C. F. Huffman, and C. W. Duncan. 1935. Blindness in cattle associated with a constriction of the optic nerve and probably of nutritional origin. J. Nutr. 9:533.

Moore, T. 1931. XXXIV. Vitamin A and carotene. VII. The distribution of vitamin A and carotene in the body of the rat. Biochem. J. 25:275.

Moore, T. 1957. Vitamin A. Elsevier Publishing Company, New York.

Moore, T. 1971. Vitamin A transfer from mother to offspring in mice and rats. Internat'l J. for Vit. and Nutr. Res. 41:301.

Moore, T., and I. M. Sharman, J. R. Todd, and R. H. Thompson. 1972. Cooper and vitamin A concentrations in the blood of normal and cu-poisoned sheep. Br. J. Nutr. 28:23.

Morriss, G. M. 1976. Vitamin A and congenital malformations. Internat'l J. for Bit. and Nutr. Res. 46:220.

Morton, R. A. 1960. Summary discussion. Vit. and Horm. 18:543.

Muto, Y. and D. Goodman. 1972. Vitamin A transport in rat plasma. J. of Biol. Chem. 247:2533.

Muto, Y., J. E. Smith, P. O. Milch, and D. S. Goodman. 1972. Regulation of retinol-binding protein metabolism by vitamin A status in the rat. J. Biol. Chem. 247:2542.

Nagataki, S. 1974. Effect of excess quantities of iodide. Handbook of Physiology. Section 7: Endocrinology. Vol. III. Thyroid. Eds. M. A. Greer and D. H. Solomon. American Physiological Society, Washington, D. C. p.329.

Nathanielsz, P. W. 1969. Peripheral utilization of thyroxine by the young growing calf. J. of Physiol. 204:43.

Nathanielsz, P. W. 1970. Thyroxine utilization in the new-born lamb. J. Physiol. 211:157.

Nathanielsz, P. W. and A. L. Thomas. 1973. Plasma triiodothyronine concentration in the newborn calf. Experientia. 29:1426.

Newton, G. L. and A. J. Clawson. 1974. Iodine toxicity: physiological effects of elevated dietary iodine on pigs. J. Anim. Sci. 39:879.

Newton, G. L., E. R. Barrick, R. W. Harvey, and M. B. Wise. 1974. Iodine toxicity. Physiological effects of elevated dietary iodine on calves. J. Anim. Sci. 38:449.

N.R.C. 1978. Nutrients Requirements of Domestic Animals. No. 3. Nutrient Requirements of Dairy Cattle. National Research Council, Washington, D. C.

Oliver, J. W. and G. M. Neher. 1971. Experimentally induced athyreosis in swine: clinical signs, radiographic changes, and necropsy observations. Am. J. Vet. Res. 32:905.

Olson, J. A. 1969. Metabolism and function of vitamin A. Fed. Proc. 28:1670.

Oppenheimer, J. H. 1968. Role of plasma proteins in the binding, distribution and metabolism of the thyroid hormones. New Eng. J. of Med. 278:1153.

Palludan, B. 1976. The influence of vitamin A deficiency on foetal development in pigs with special reference to eye organogenesis. Internt'l J. for Vit and Nutr. Res. 46:223.

Parrish, D. B., G. H. Wise, and J. S. Hughes. 1948. Vitamin A and carotenoids in the blood serum of dairy cattle--chemical methods for determination. Anal. Chem. 20:231.

Peterson, P. A. 1971. Characteristics of a vitamin A-transporting protein complex occurring in human serum. J. of Biol. Chem. 246:34.

Raz, A. and D. Goodman. 1969. The interaction of thyroxine with human plasma prealbumin and with the prealbumin-retinol-binding protein complex. J. Biol. Chem. 244:3230.

Raz, A., T. Shiratori, and D. S. Goodman. 1970. Studies on the protein-protein and protein-ligand interactions involved in retinol transport in plasma. J. of Biol. Chem. 245:1903.

Reap, M., C. Cass, and D. Hightower. 1978. Thyroxine and triiodothyronine levels in ten species of animals. Southwest Vet. 31:31.

Reineke, E. P. and C. W. Turner. 1944. Non-permeability of mammary gland to thyroid hormone. J. Dairy Sci. 27:793.

Remington, R. E. P. L. Harris, and C. L. Smith. 1942. Relationship between vitamin A and iodine metabolism in the rat. J. Nutr. 24:597.

Robbins, J. and J. E. Rall. 1960. Proteins associated with the thyroid hormones. Physiol. Rev. 40:415.

Rodbard, D. 1974. Statistical quality control and routine data processing for radioimmunoassays and immuno-radiometric assays. Clin. Chem. 20:402.

Roels, O. A., O. R. Anderson, N. S. T. Lui, D. O. Shah, and M. E. Trout. 1969. Vitamin A and membranes. Amer. J. Clin. Nutr. 22:1020.

Rowlands, G. J., R. Manston, R. M. Pocock, and S. M. Dew. 1975. Relationships between stage of lactation and pregnancy and blood composition in a herd of dairy cows and the influences of seasonal changes in management on these relationships. J. Dairy Res. 42:349.

Sadhu, D. P. and S. Brody. 1947. Excess vitamin A ingestion, thyroid size and energy metabolism. Amer. J. of Physiol. 149:400.

Serif, G. and A. Brevik. 1960. Effects of butyl-4-hydroxy-3, 5-diiodobenzoate on the conversion of β-carotene to vitamin A in the rat. J. Biol. Chem. 235:2230.

Seward, C. R., G. V. Mitchell, and E. L. Hove. 1969. Some aspects of vitamin A deficiency or toxicity in intermediary metabolism. Amer. J. Clin. Nutr. 22:1014.

Smith, F. R. and D. S. Goodman. 1971. The effects of diseases of the liver, thyroid, and kidneys on the transport of vitamin A in human plasma. J. Clin. Invest. 50:2426.

Smith, D. C. and J. M. Perman. 1940. Effect of throxin combined with carotene upon the oxygen consumption of cats. Endocrinol. 27:110.

Spielman, A. A., J. W. Thomas, J. K. Loosli, C. L. Norton, and K. L. Turk. 1946. The placental transmission and fetal storage of vitamin A and carotene in the bovine. J. Dairy Sci. 29:707.

Steel, R. G. D. and J. H. Torrie. 1960. Principles and procedures of statistics. McGraw-Hill Book Company., Inc., New York.

Stöckl, M. Schuh, and S. Schmid. 1975. Über das verhalten von glucose, thyroxine, vitamin A, β-carotin, methiomin and vitamin B_{12} im blut erstgebärender rinder während der puerperalphase. Z. Tierphysiol., Tierernährg u. Futtermittelkde. 35:281.

Sutton, T. S., H. E. Kaeser, and P. A. Soldner. 1945. Changes in the level of vitamin A and carotene in the blood plasma of dairy cows associated with parturition and beginning lactation. J. Dairy Sci. 28:933.

Sutton, T. S. and P. A. Soldner. 1943. The effect of parturition and beginning lactation on the level of carotene and vitamin A in the blood plasma of dairy cows. J. Dairy Sci. 26:740.

Swanson, E. W., G. G. Martin, F. E. Pardue, and G. M. Gorman. 1968. Milk production of cows fed diets deficient in vitamin A. J. Anim. Sci. 27:541.

Takahashi, Y. I., J. E. Smith, M. Winick, and D. S. Goodman. 1975. Vitamin A deficiency and fetal growth and development in the rat. J. of Nutr. 105:1299.

Tanabe, Y., T. Ishii, and Y. Tamaki. 1969. Comparison of thyroxine-binding plasma proteins of various vertebrates and their evolutionary aspects. Gen. and Compar. Endocrinol. 13:14.

Thompson, J. N. 1969. Vitamin A in development of the embryo. Amer. J. of Clin. Nutr. 22:1063.

vanJaarsveld, P. P., H. Edelhoch, D. S. Goodman, and J. Robbins. 1973. The interaction of human plasma retinol-binding protein with prealbumin. J. Biol. Chem. 248:4698.

Warkany, J. 1945. Manifestations of prenatal nutritional deficiency. Vit. and Horm. 3:73.

Woeber, K. A. and S. H. Ingbar. 1974. Interactions of thyroid hormones with binding proteins. Handbook of Physiology. Section 7: Endocrinology. Vol. III. Thyroid. Eds. M. A. Greer and D. H. Solomon. American Physiological Society, Washington, D. C. p. 187.

Wohl, M. G. and J. B. Feldman. 1939. Vitamin A deficiency in disease of the thyroid gland: its detection by dark adaptation. Endocrinol. 24:389.

Wolff, J. 1969. Iodide goiter and the pharmacologic effects of excess iodide. Am. J. of Med. 47:101.

Wolff, J. and I. L. Chaikoff. 1948. Plasma inorganic iodide as a homeostatic regulator of thyroid function. J. Biol. Chem. 174:555.

Wolff, J., I. L. Chaikoff, and C. W. Nichols, Jr. 1949. The accumulation of thyroxine-like and other iodine compounds in the fetal bovine thyroid. Endocrinol. 44:510.

Zile, M., E. C. Bunge, and H. F. DeLuca. 1977. Effect of vitamin A deficiency on intestinal cell proliferation in the rat. J. Nutr. 107:552.

VITA

Patricia Kate White was born in Anniston, Alabama on September 14, 1954. Most of her life has been spent in Kingsport, Tennessee, where she was graduated from Dobyns-Bennett High School in 1972.

After attending East Tennessee State University for 2 years, she transferred to the University of Tennessee in the pre-veterinary curriculum. She earned a Bachelor of Science degree, with high honors, in Animal Science in June 1974.

Having developed an interest in dairy cattle, she pursued a Master of Science degree in dairy cattle nutrition and physiology. She received a research fellowship from the Ralston Purina Company to financially assist her in the obtainment of this degree which she received in August 1978.

Kate White was elected to membership in Alpha Zeta, Gamma Sigma Delta, and Phi Kappa Phi honorary societies. She is an affiliate member of the American Dairy Science Association and the American Society of Animal Science.