CONVERSION OF INTRAVENOUSLY ADMINISTERED CAROTENE TO VITAMIN A IN SHEEP

By

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CONVERSION OF INTRAVENOUSLY ADMINISTERED CAROTENE TO VITAMIN A BY SHEEP

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CHAPTER I

INTRODUCTION

A site of conversion of orally administered carotene to vitamin A has now definitely been demonstrated to be the intestinal mucosa of the jejenum section of the small intestine. Previous reviews of this subject have covered this matter thoroughly (24, 25, 29).

It has also been established that intravenously administered, aqueous dispersions of carotene can be converted to vitamin A by some types of animals, such as: sheep, goats, rabbits, rats, pigs and possibly calves, provided the particle size of the dispersed carotene is sufficiently small. Since the work of Drummond, Gilding and MacWalter (16), it has been known that when colloidal carotene is introduced directly into the blood stream of animals, the liver rapidly removes the pigment as it would other colloidal material. Lease, Lease, Steenbock and Baumann (26), and Sexton, Mehl and Deuel (30), found that such colloidal carotene is essentially unavailable to the animal as a source of vitamin A and may be found in the liver after the animal had died from an apparent deficiency of the vitamin. In sheep, as in most of the other animal species mentioned above, the actual site of conversion has not yet been determined for parenteral administrations of carotene, but presumably either extra-intestinal sites of conversion exist or the carotene finds its way into the gut.

Mattson, Mehl and Deuel (28) original proposed the latter possibility

when they suggested that parenterally administered carotene was secreted into the small intestine by way of the bile duct and was there utilized in a manner analogous to orally administered carotene. Kirschman (24), however, found no significant decrease in conversion by sheep following total enterectomization, thus discounting a direct function of the intestine in the conversion of parenterally administered carotene, and indicating the existence of one or more extra-intestinal sites of conversion. Bieri and Pollard (7) have also shown that in the rat the formation of vitamin A from injected aqueous carotene dispersions occurred essentially unimpaired after ligation of the bile duct, removal of the small intestine or kidneys, or removal of up to 75% of the liver. In addition, Worker (36) has shown that hepatectomy in the rat and rabbit, or total evisceration in the rat seems to have no adverse effect on the conversion of intravenously injected, aqueous dispersions of carotene to vitamin A. Worker likewise reported decapitation or removal of the lungs of rats to have little affect on the conversion (37). Hentges, Grummer and Sorensen (19) found that ligation of the anterior and posterior mesenteric, and coeliac arteries, and cannulation of the bile duct did not prevent injected carotene from being converted to vitamin A in the pig.

Since neither the sheep nor pig normally circulates more than trace amounts of carotene in the blood, it was thought that these animals might possibly metabolize an injected aqueous dispersion of carotene in a similar manner. Thus, experiments were designed, following those of Hentges et al. (19), in an attempt to establish the extra-intestinal site or sites of conversion in sheep.

It was also thought desirable to study the affect of materials

known or suspected to influence the process of vitamin A formation such as the thyroid-influencing drugs, thiourea and iodinated casein, and the avitaminosis A-inducing polychlorinated naphthalenes, on the rate of conversion of carotene. Relative blood carotene and vitamin A levels following administration of dispersed carotene were used as the means of evaluating the influence of these materials.

Arnich (2), with dogs, and Arnrich and Morgan (3), with dogs and rats, found thyroid activity to have little if any effect on the conversion of orally administered carotene; however, Arnich, did find a significant increase in circulating carotene and vitamin A in hypothyroid dogs. In contrast, Smith, Niedermeier and Schultz (31) found thyroid activity to be of major importance in the conversion of orally administered carotene in the goat, as did Chanda, Clapham, McNaught and Owen (13) in the cow and goat. Drill and Truant (15) found thyroidectomy impaired conversion in the rat. Cama and Goodwin (11) found thyroid activity to control intestinal absorption of carotene in the rabbit. Thyroid activity has no effect on the storage of vitamin A in rats, according to Johnson and Baumann (21); however, they found that when carotene was fed to hyperthyroid rats, there was more vitamin A stored than in normal rats.

Worker (36) and McGillivray, Thompson and Worker (27) found thyroid activity to have little, if any, effect on the extra-intestinal conversion of intravenously administered, aqueous dispersions of carotene, based on the vitamin A levels of the liver and blood following the injection of a single dose of carotene into normal, hyperthyroid and hypothyroid rats. In the rat, thyroid activity seems to affect only the intestinal conversion, possibly through diminished (hypothyroid), or enhanced (hyperthyroid) absorption.

The differing observations of the effect of thyroid activity on carotene conversion may be due to the influence of the particular drug used to produce the desired thyroid state. Thyroxine, thyroid preparations or extracts, or iodinated proteins are commonly used to produce a hyperthyroid state, whereas thiourea or thiouracil produce a hypothyroid state in animals.

Chanda and Owen (14) found indications that thyroxine stimulates carotene conversion in the intestinal mucosa of cows, and Chanda et al. (13) observed the digestibility of carotene preparations to be markedly increased. In cows, serum vitamin A and carotene increase during thyroxine treatment according to Chanda (12), and von Euler and Klussmann (33) noted a marked decrease in liver carotene content. Desiccated thyroid stimulated carotene absorption in rabbits, but did not affect plasma vitamin A levels, or the plasma-liver equilibrium according to Cama and Goodwin (11). Allen, Wise and Jacobson (1) could find no evidence of increased conversion in calves fed iodinated casein, whereas Swick, Grummer and Baumann (32) found pigs stored more vitamin A following a carotene injection than did normal ones which did not receive the iodinated material.

On feeding thiourea to sheep, Bolin and Bolin (9) observed a marked drop in serum vitamin A, and could detect no rise in blood vitamin A following feeding of carotene. Administration of thiourea and thiouracil prevented storage of vitamin A in rats (21), and they appeared to interfer with carotene conversion in lambs, according to Barrick, Andrews, Beeson and Harper (4), as did thiouracil in rats (22). Allen et al. (1) found thiouracil to give a slight rise in blood vitamin A in calves, whereas Bieri and Schultze (8), with rats, and Cama and Goodwin (11),

with rabbits, could find no significant effect of thiouracil on plasma vitamin A levels. Worker (36) observed significantly higher liver vitamin A storage in rats administered thiouracil, but Swick et al. (32) found pigs stored less vitamin A following a carotene injection than did pigs not fed thiouracil. Chanda and Owen (14) found a retarded rate of hepatic store vitamin A depletion in rats, cows and goats. Cama and Goodwin (11) found that thiouracil increased the amount of carotene excreted in the feces, thus indicating decreased carotene absorption. This observation is supported by Chanda et al. (13), who observed the digestibility of carotene preparations to be markedly reduced by thiouracil.

Thus, the effects of the various thyroid-influencing drugs seem to vary appreciably from animal to animal, and possibly do not indicate a direct role of thyroid activity in carotene conversion, but rather, as mentioned previously, the effect of the particular drug used to induce the thyroid state. Conversely, this variation may reflect a true biochemical difference between species.

Hyperkeratosis-producing substances, such as the polychlorinated naphthalenes, seem to prevent the conversion of orally administered carotene to vitamin A. Hansel, McEntee and Olafson (18) found that plasma carotene increased when large doses of carotene were fed cattle, but that plasma vitamin A did not. They suggested the possibility that the hyperkeratosis-producing factor exerts an antivitamin A affect by interfering with the conversion of carotene to vitamin A. They also found that when vitamin A was fed in large amounts to cattle with hyperkeratosis, the liver and plasma vitamin A levels increased rapidly, but fell rapidly when vitamin A feeding was stopped. The hyperkeratosis-producing substances were found to produce a prolonged depressing effect on plasma

vitamin A.

Continued feeding of large amounts of vitamin A alleviated the symptoms of hyperkeratosis (17) and accelerated the eventual cure in cattle. Hoekstra, Hall and Phillips (20) found that is was necessary to feed high levels of vitamin A, since mere maintenance of the normal vitamin A level in calves by feeding of the vitamin while feeding limited amounts of hyperkeratosis-producing substances did not prevent the hyperkeratosis syndrome from developing, or its fatal termination. Ferrando (17) suggested that vitamin A is concerned in the detoxication process, and thus, large amounts of the vitamin are necessary in order to supply both the normal body requirements and that needed for the detoxication process.

It is interesting to note that the typical symptoms of bovine hyperkeratosis are not duplicated in sheep; instead a syndrome differing substantially in external symptoms and of markedly different character insofar as vitamin A is concerned, is encountered. Extensive post-mortem changes are also observed, expecially in the liver, following the fatal termination of the poisoning (10), but these are not typical of avitaminosis A in the same animal.

It was felt that polychlorinated naphthalenes might affect the conversion of intravenously administered carotene in sheep in a manner analogous to that observed for orally administered carotene.

CHAPTER II

MATERIALS AND METHODS

Injection Materials

From results reported in the literature, it was considered advisable to use a carotene preparation in these experiments in which the carotene existed in a subcolloidal dispersion. This was approached in the preparation described by Bieri (5), where Tween 40 (polyoxyethylene sorbitan monopalmitate)[1] acted as the dispersing agent. The preparation was made in the following manner: One hundred mg. of crystalline carotene (90% beta and 10% alpha)[2] was dissolved in 2 ml. of chloroform. Twenty ml. of Tween 40 at 100° C was added with constant stirring and the mixture was maintained at this temperature until the chloroform was driven off. It was important to remove all of the chloroform, otherwise a stable solution could not be made. After the chloroform was removed, the solution was taken to 100 ml. with distilled water, also at 100° C. The solution as made up contained 1 mg. of carotene per ml., in a 20% Tween 40 solution. This solution was prepared within 24 hours prior to use and stored under refrigeration in a brown glass bottle.

Thiourea

The commercially available material (Merck) was placed in a gelatin

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[1] Atlas Powder Company, Wilmington, Delaware.

[2] Barnett Laboratories, Long Beach, California.

capsule and given orally at the rate of 6 g. per day for 12 days to induce a hypothyroid state in the sheep (9).

Iodinated Casein

A commercial preparation, Libidoxin (60% iodinated casein)[3], was given orally in gelatin capsules at the rate of 5 g. per 100 lb. body weight per day for 12 days to induce a hyperthyroid state in the sheep (1).

Polychlorinated Naphthalenes

Halowax 1014[4], containing predominately hexachloronaphthalene, was dissolved in corn oil to make a 10% solution, and given orally by gelatin capsule at the rate of 1 g. per 100 lb. body weight for 7 days. This dosage was calculated to give slight symptoms of toxicity without producing acute poisoning and extensive post-mortem changes (10).

Surgical Techniques

Isolation of the Liver, Intestine, Spleen and Pancreas From the Systemic Blood Circulation

The blood supply of the liver is provided by the hepatic artery, which arises from the posterior aorta just anterior to the kidney. The venous return is provided by the hepatic veins, which join the inferior vena cava; the portal vein drains the small intestine and enters the liver at the hilus. Ligation of the hepatic artery and the portal vein would effectively isolate the liver, but such a procedure led to severe congestion of the area drained and increased surgical shock. To over-

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[3]Jensen-Salsbery Laboratories, Inc., Kansas City, Missouri.

[4]Halowax Products Division of Union Carbide and Carbon, Corp.

come these adverse effects, the blood vessels supplying the gastrointestinal tract (anterior and posterior mesenteric and coeliac arteries) were ligated.

Prior to the operation, the animals were deprived of water for 12 hours. At the time of the operation, they were restrained in a left, lateral, recumbant position, and anaesthetised with sodium pentobarbital, given by slow intravenous injection, until the proper neurological response had been obtained. To maintain a free airway and to facilitate resuscitation, an endotracheal tube with inflatable cuff was inserted in the trachea. Anaesthesia was maintained by additional injections of sodium pentobarbital. It was interesting to note that no additional anaesthesia was needed, once the liver was isolated. Blood sugar and electrolyte levels were maintained by slow intravenous drip of a 2.5% solution of glucose in N/2 saline. Automatic resuscitation with oxygen was employed during the experiment to prolong post-operative life and to improve the impaired venous return resulting from operative shock.

The peritoneal cavity was opened by a right, lateral, paracostal incision. The vessels to be ligated were approached by a peritoneal incision dorsal and just anterior to the kidney. The right crus of the diaphragm was exposed by blunt dissection and was severed at the distal, tendinous portion and reflected forward to expose the posterior aorta. The aorta was followed forward until the anterior mesenteric, hepatic, and coeliac arteries were palpated. They were then ligated at their origin. The posterior mesenteric artery, which was not always present, was located by following the aorta posteriorly from the original site of exposure. This, when present, was also ligated. The anterior and posterior mesenteric, coeliac and hepatic arteries having been ligated,

the portal vein was exposed at the hilus of the liver and similarily ligated. The laparotomy incision was then closed. All operations were terminal and the sites of the ligatures were checked at autopsy.

This procedure effectively isolated the liver, small intestine, stomach, spleen, pancreas and part of the colon from the systemic circulation. By the use of ligatures instead of excision of the necessary viscera, the operation was simplified and the surgical shock minimized. The animals lived for 4 to 6 hours following the operation.

Isolation of the Entire Viscera and Posterior Extremities From the Systemic Circulation

Preoperative preparation, restraint, anaesthesia, resuscitation and fluid therapy were identical to that in the previous procedure. The total viscera and the posterior extremities were isolated from the systemic circulation by ligation of the posterior aorta and the inferior vena cava just anterior to the diaphragm. This procedure was followed instead of the total evisceration described by Worker (36) in order to minimize the extensive shock and technical problems encountered when the entire viscera were removed from the sheep.

A right, lateral, thoracic incision was made between the seventh and eighth ribs. The region anterior to the diaphragm was exposed by reflecting the right lobe of the lungs anteriorly. The posterior aorta and the inferior vena cava were exposed and ligated. The thoracotomy incision was then closed. All operations were terminal and the sites of the ligatures were checked at autopsy.

This procedure effectively isolated the abdominal viscera and the posterior extremities from the systemic circulation. Leakage of the injected carotene into the viscera was not detected. The animals lived

for 3.5 to 4.5 hours following the operation.

Rations Fed to Experimental Animals

The sheep were partially depleted in their vitamin A stores by placing them on a grain-mix and straw diet. The grain-mix was composed of: Purina Omolene[5], bran and oats, in a 1:1:1 ratio.

Blood Analysis

The blood samples were drawn from the jugular vein by hypodermic syringe and placed in tubes containing lithium citrate as the anticoagulant. The blood tubes were prepared by adding 1 ml. per 10 ml. of blood collected, of a lithium citrate solution containing 57 g. of lithium citrate per 500 ml. of distilled water, to the collecting tube and then taking the tubes to dryness in a 300° F, forced draft drying oven (1.5 hours). The samples were centrifuged as soon as possible and the plasma was removed from the cells, frozen and stored at -14° C until analysis was made.

The determinations for carotene and vitamin A were carried out according to the method of Kimble (23). The concentrations were expressed in micrograms per 100 ml. of plasma (mcg. %).

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[5]Grain supplement ration, Ralston Purina Co., St. Louis, Missouri.

CHAPTER III

INVESTIGATION OF POSSIBLE EXTRA-INTESTINAL SITES FOR CONVERSION OF CAROTENE TO VITAMIN A

The purpose of these experiments was to ascertain the effect of the abdominal viscera, and specifically of the liver, on the rate of disappearance from the blood of intravenously injected carotene. It was assumed that disappearance of carotene from the blood was directly associated with the appearance there of vitamin A, as had been found in the normal, intact animal. Therefore, this disappearance was accepted as indicative of some degree of carotene metabolism, and subsequent formation of vitamin A, even though no net increase in plasma vitamin A was observed. Any direct effect of oxygen resuscitation or of the anaesthetic agent, sodium pentobarbital, on the rate of carotene disappearance was not significant, according to the results presented in Figure 1 (Table 1).

All experimental animals were maintained on a carotene-free diet for a period of at least 4 weeks prior to operation. This time was sufficient to lower the plasma vitamin A level to approximately 35 mcg. percent or lower. No attempt was made to lower the vitamin A level below 20 mcg. percent, as this usually led to lessened ability to withstand surgical shock.

FIGURE 1 PLASMA CAROTENE AND VITAMIN A LEVELS FOLLOWING INTRAVENOUS INJECTION OF AN AQUEOUS CAROTENE DISPERSION IN NORMAL SHEEP AND ANAESTHETIZED SHEEP GIVEN OXYGEN

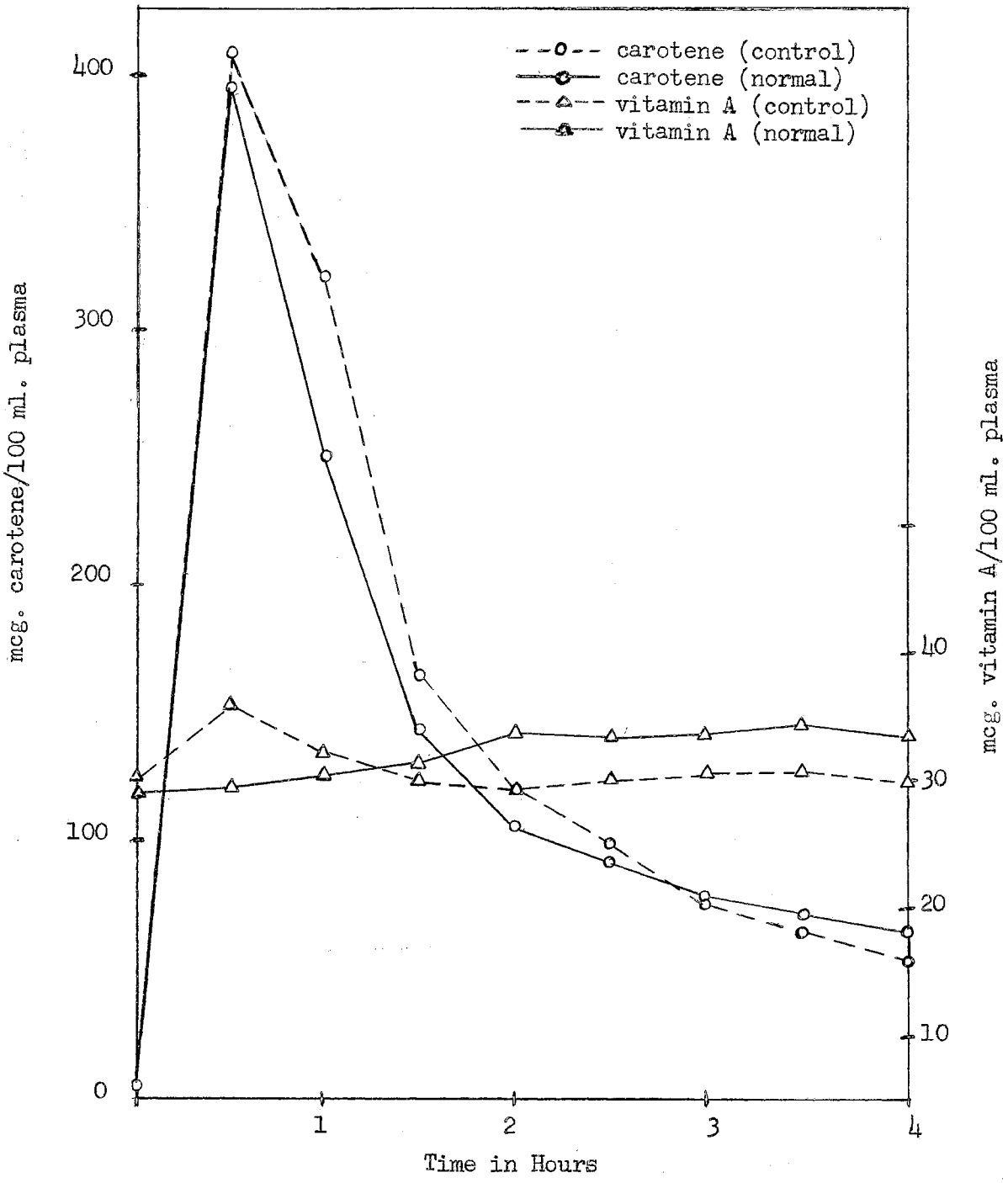

TABLE 1 PLASMA CAROTENE AND VITAMIN A LEVELS FOLLOWING INTRAVENOUS INJECTION OF AN AQUEOUS CAROTENE DISPERSION IN NORMAL SHEEP AND ANAESTHETIZED SHEEP GIVEN OXYGEN

mcg. carotene/100 ml. plasma

Time Interval (hours)	Normal Sheep	Anaesthesia-O_2 control
0	3.7	4.5
1/2	395.7	410.8
1	252.0	322.3
1 1/2	144.7	167.6
2	108.0	122.4
2 1/2	96.1	100.2
3	81.0	78.3
3 1/2	72.5	65.2
4	65.0	55.3

mcg.vitamin A/100 ml. plasma

Time Interval (hours)	Normal Sheep	Anaesthesia-O_2 control
0	29.4	29.9
1/2	29.4	35.8
1	30.6	32.2
1 1/2	31.6	30.1
2	33.9	29.4
2 1/2	33.7	30.3
3	34.0	30.7
3 1/2	34.6	31.2
4	33.8	30.3

Metabolism of Intravenously Administered Carotene by Sheep in Which the Liver, Intestine, Spleen, Pancreas and Stomach Were Isolated From the Systemic Blood Circulation

Three experimental sheep and one operation-control were used for this experiment. The operation-control differed from the experimental animals in that no carotene was injected.

As is observed from Figure 2 (Table 2), carotene metabolism was diminished by the isolation of the liver, intestine, spleen, pancreas and stomach from the systemic circulation. The vitamin A levels were essentially the same in both the experimental and control animals. The gradual decrease observed in the vitamin A plasma levels was not thought to be indicative of lack of conversion, but rather of an increased rate of storage or utilization induced by surgical shock. Figure 3 (Table 3) shows an initial sharp drop in the vitamin A level when no attempt was made to minimize surgical shock. Thus, shock seems to enhance storage or utilization of vitamin A. It was interesting to note that little net carotene disappearance could be demonstrated in this case.

The vitamin A levels obtained during the first hour following the carotene injection show some inconsistency (Figure 2). Sheep E showed a definite initial increase in vitamin A, whereas sheep I showed only a slight increase. In contrast, sheep F showed a steady decrease. After the first hour, vitamin A disappeared from the plasma at essentially the same rate in all three animals.

In this experiment no attempt was made to ligate the hepatic veins. The liver sinusoids are known to store a substantial amount of blood, which is released slowly into the blood stream at the onset of shock (34). This release of blood, and possibly liver vitamin stores into the cir-

FIGURE 2 PLASMA CAROTENE AND VITAMIN A LEVELS FOLLOWING INTRAVENOUS INJECTION OF AN AQUEOUS CAROTENE DISPERSION IN SHEEP WITH PARTIALLY ISOLATED ABDOMINAL VISCERA
Control Sheep Not Injected

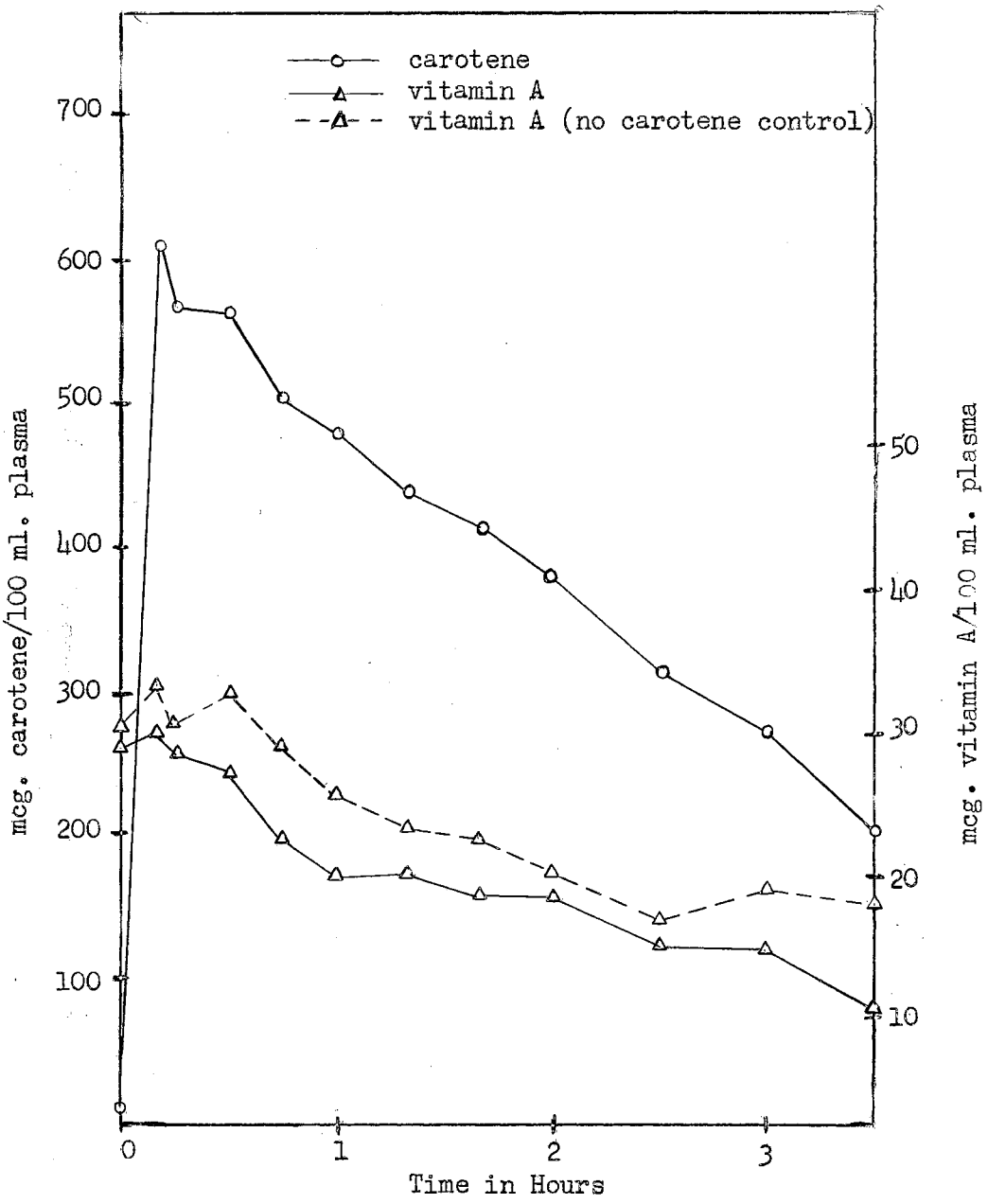

TABLE 2 PLASMA CAROTENE AND VITAMIN A LEVELS FOLLOWING INTRAVENOUS INJECTION OF AN AQUEOUS CAROTENE DISPERSION IN SHEEP WITH PARTIALLY ISOLATED ABDOMINAL VISCERA

Control Sheep Not Injected

mcg. carotene/100 ml. plasma

Time Interval (hours)	Sheep E	Sheep F	Sheep I	Average	Operation control
0	5.1	8.7	5.5	6.4	
1/6	557.1	693.6	580.9	610.5	
1/4	544.2	653.4	505.4	567.7	
1/2	544.2	663.3	487.6	565.0	
3/4	516.3	549.0	449.8	505.0	
1	481.5	522.3	437.9	480.6	
1 1/3	435.0	494.4	387.3	438.9	
1 2/3	426.0	471.6	354.5	417.4	
2	411.0	414.0	322.7	382.6	
2 1/2	346.0	334.5	267.7	316.3	
3	271.8	297.0	250.0	272.9	Insignificant
3 1/2	---	185.7	227.5	206.6	

mcg. vitamin A/100 ml. plasma

Time Interval (hours)	Sheep E	Sheep F	Sheep I	Average	Operation control
0	25.3	38.3	22.2	28.6	30.1
1/6	31.0	38.3	19.7	29.7	33.2
1/4	30.7	35.0	20.6	28.8	30.3
1/2	32.1	32.7	16.9	27.2	32.5
3/4	28.8	24.3	14.5	22.5	28.9
1	24.9	24.4	10.5	19.9	25.5
1 1/3	24.8	24.7	11.0	20.2	23.3
1 2/3	23.6	18.8	13.1	18.5	22.4
2	23.5	20.3	11.6	18.5	20.0
2 1/2	18.9	17.0	9.3	15.1	16.9
3	20.7	13.7	10.2	14.9	19.0
3 1/2	---	12.6	9.3	11.0	18.0

FIGURE 3 PLASMA CAROTENE AND VITAMIN A LEVELS FOLLOWING INTRAVENOUS INJECTION OF AN AQUEOUS CAROTENE DISPERSION IN SHEEP WITH PARTIALLY ISOLATED ABDOMINAL VISCERA
No Attempt Made to Minimize Shock

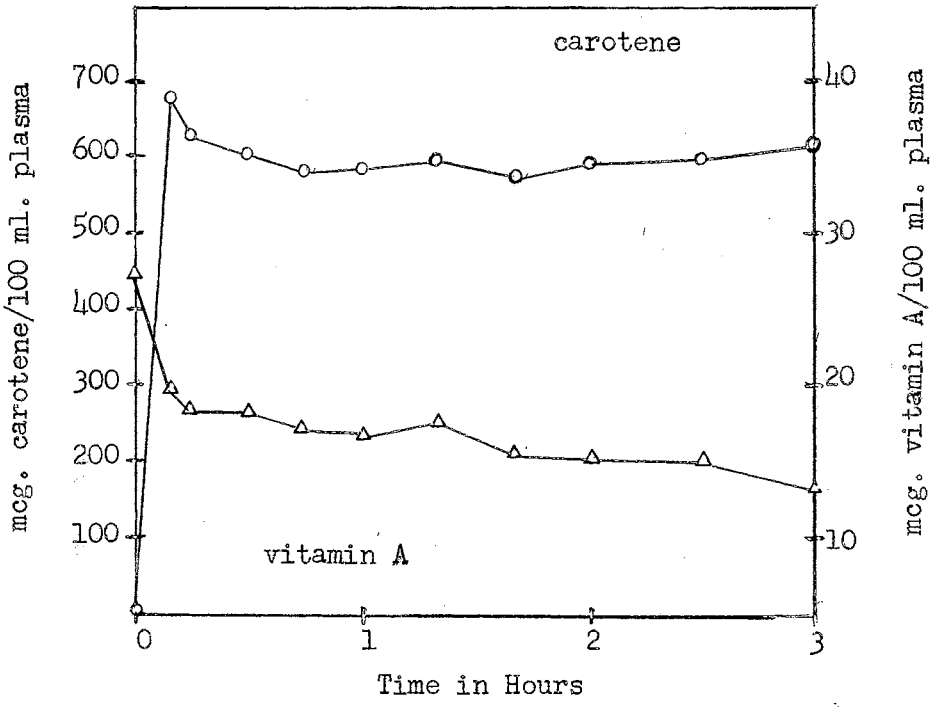

TABLE 3 PLASMA CAROTENE AND VITAMIN A LEVELS FOLLOWING INTRAVENOUS INJECTION OF AN AQUEOUS CAROTENE DISPERSION IN SHEEP WITH PARTIALLY ISOLATED ABDOMINAL VISCERA
No Attempt Made to Minimize Shock
mcg./100 ml. plasma

Time Interval (hours)	Carotene	Vitamin A
0	7.5	27.6
1/6	675.0	20.0
1/4	629.7	18.6
1/2	610.8	18.2
3/4	589.8	17.2
1	589.8	16.7
1 1/3	597.9	17.5
1 2/3	580.8	15.5
2	597.9	15.2
2 1/2	597.9	15.2
3	619.5	13.5

culatory system, via the hepatic veins, could be an explanation for the initial variation in plasma vitamin A.

Isolation of the liver, intestine, spleen, pancreas and stomach from the systemic blood circulation was found to retard the rate of carotene disappearance. However, there was sufficient decrease in the plasma carotene level to indicate conversion of carotene to vitamin A. A net increase in plasma vitamin A could not be demonstrated after the first few minutes of the experiment. Since in this experiment the liver was not completely isolated and since the kidneys, sex organs and the rectal portion of the large intestine were not isolated, the following experiment was designed.

Metabolism of Intravenously Administered Carotene by Sheep in Which the Entire Viscera and Lower Extremities Were Isolated From the Systemic Blood Circulation

The purpose of this experiment was to make a further study of the role of the viscera in carotene metabolism. By ligating the posterior aorta and the inferior vena cava anterior to the diaphragm, the possibility of blood leakage from the liver sinusoids into that portion of the circulatory system which was still functional was eliminated. In addition to the previously isolated organs, the kidneys, sex organs, rectal portion of the large intestine and the lower extremities were isolated. Postmortem examination showed complete isolation of the entire viscera, and in addition, isolation of practically all tissues posterior to the diaphragm. The only portion of the viscera not isolated was a short section of the esophagus, posterior to the diaphragm.

Two experimental sheep and one operation-control were used for this experiment.

As in the previous experiment, the data presented in Figure 4

(Table 4) indicate that carotene metabolism was retarded. The apparent rate of carotene disappearance was less in this experiment than in the previous one. In addition, the vitamin A levels did not decline so rapidly as in the previous experiment. This indicates that in the previous experiment either the blood volume leaking from the liver sinusoids may have been sufficiently large to give a significant dilution of the vitamin A present, or that vitamin A storage or utilization was enhanced more than in the present experiment.

In contrast to the previous experiment, the initial vitamin A concentration rose in each of the animals observed. Sheep T gave a much greater initial rise than did sheep P; however, after one hour the rate of decrease of plasma vitamin A was similar in experimental and control animals.

The rate of carotene disappearance and the initial rise in plasma vitamin A concentration is an indication that carotene conversion does occur in sheep in which the entire viscera have been isolated from the systemic blood circulation. The extent of such conversion, based on the rate of disappearance of carotene, is not so great as in the normal animal. We believe that this retarded rate of metabolism is indicative of a site or sites of conversion in the tissues isolated. Shock could also account for a small part of the observed decrease in conversion, as it would be expected to retard all metabolic processes to some extent.

These results are like those of Hentges et al. (19) with pigs, in which the anterior and posterior mesenteric and coeliac arteries were ligated and the bile duct cannulated. They are not like the findings of Worker (36) with eviscerated rats and hepatectomized rats and rabbits, or the work of Bieri and Pollard (7) with partially hepatectomized or

FIGURE 4 PLASMA CAROTENE AND VITAMIN A LEVELS FOLLOWING INTRAVENOUS INJECTION OF AN AQUEOUS CAROTENE DISPERSION IN SHEEP WITH LIGATED POSTERIOR AORTA AND INFERIOR VENA CAVA
Control Sheep Not Injected

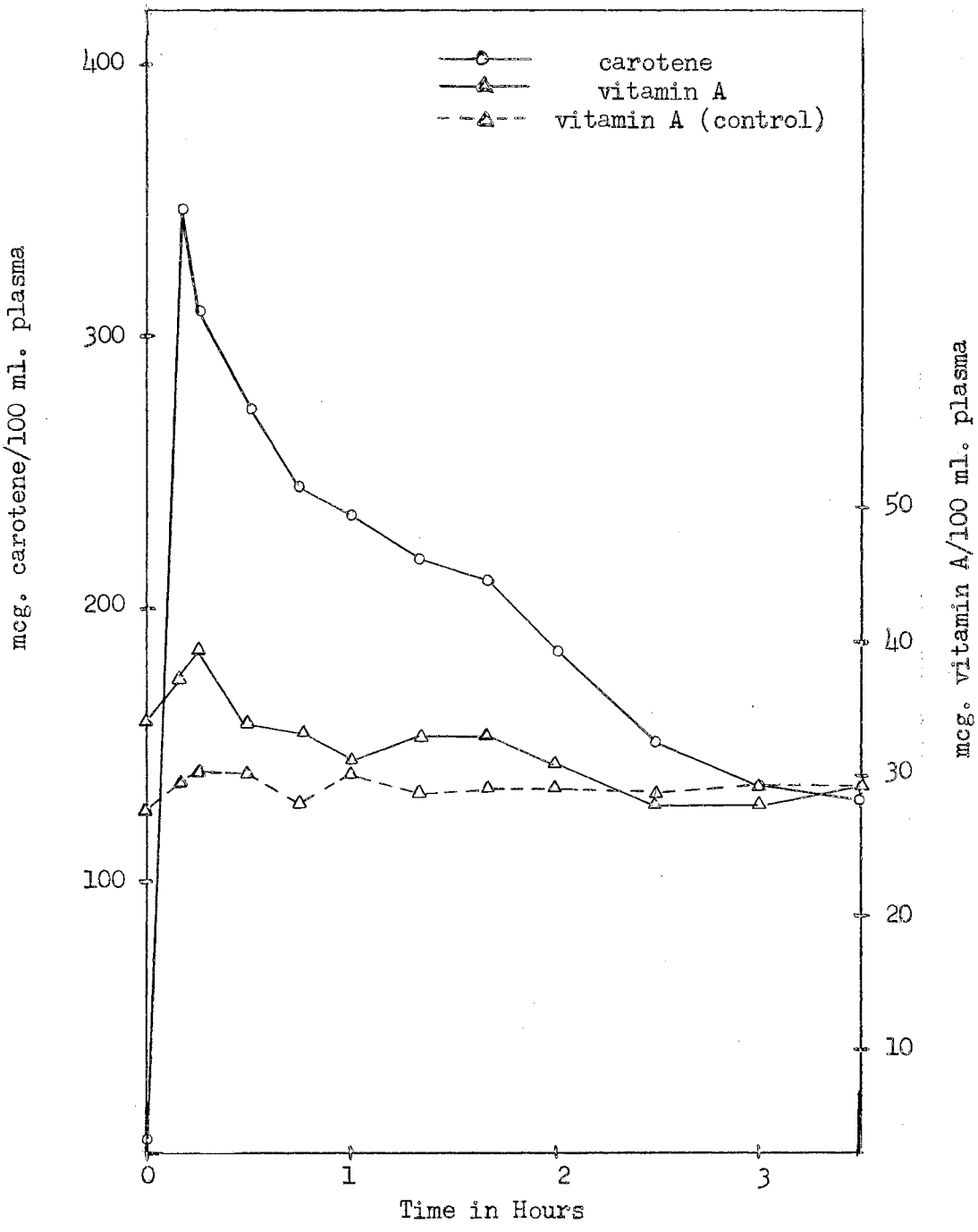

TABLE 4 PLASMA CAROTENE AND VITAMIN A LEVELS FOLLOWING INTRAVENOUS INJECTION OF AN AQUEOUS CAROTENE DISPERSION IN SHEEP WITH LIGATED POSTERIOR AORTA AND INFERIOR VENA CAVA

Control Sheep Not Injected

mcg. carotene/100 ml. plasma

Time Interval (hours)	Sheep P	Sheep T	Average	Operation control
0	4.5	4.4	4.4	
1/6	351.6	340.0	345.8	
1/4	303.0	319.9	311.4	
1/2	275.7	270.8	273.2	
3/4	248.1	242.4	245.2	
1	242.4	229.4	235.9	
1 1/3	220.2	214.9	217.6	
1 2/3	213.3	211.4	212.4	
2	166.2	201.0	183.6	
2 1/2	114.0	190.9	152.4	
3	96.3	176.0	136.2	
3 1/2	80.4	180.8	130.6	

Insignificant

mcg. vitamin A/100 ml. plasma

Time Interval (hours)	Sheep P	Sheep T	Average	Operation control
0	34.1	35.0	34.5	27.9
1/6	35.4	39.5	37.4	30.1
1/4	34.1	45.0	39.6	30.6
1/2	30.6	37.5	34.0	30.6
3/4	31.0	35.8	33.4	28.4
1	28.5	34.3	31.4	30.6
1 1/3	29.0	37.3	33.2	28.9
1 2/3	29.0	37.6	33.3	29.5
2	27.5	34.7	31.1	29.5
2 1/2	25.9	30.7	28.3	28.9
3	25.1	31.9	28.5	29.5
3 1/2	27.0	31.5	29.2	29.4

totally enterectomized or nephrectomized rats, or Kirschman (24) with totally enterectomized sheep.

CHAPTER IV

UTILIZATION OF INTRAVENOUSLY ADMINISTERED CAROTENE BY SHEEP FED THYROID-INFLUENCING DRUGS

The purpose of these experiments was to determine the affect of thyroid activity, as induced by chemical agents, on the metabolism of intravenously administered carotene by sheep. The thyroid-influencing drugs used were iodinated casein (inducing a hyperthyroid state) and thiourea (inducing a hypothyroid state).

In each of the following experiments, two sheep were placed on a carotene-deficient diet for at least 4 weeks prior to the initial injection of carotene. Single carotene injections were then given at 0 and 2 weeks to determine the normal metabolic pattern for each sheep. One week following the second carotene injection, oral administration of the thyroid-influencing drug was begun. In all experiments, the drug was fed daily for a period of 12 days. On the thirteenth day following the beginning of the treatment, a final injection of carotene was given each animal.

Metabolism of Intravenously Administered Carotene by Sheep Rendered Hyperthyroid With Iodinated Casein

The purpose of this experiment was to determine the effect of hyperthyroidism, as induced by oral administration of iodinated casein, on the metabolism of intravenously administered carotene by sheep.

Following the determination of the normal carotene metabolic

pattern for each sheep, iodinated casein treatment was started. By the last day of the treatment, an external syndrome of iodine poisoning had appeared (perfuse nasal discharge which turned from a clear to a yellowish color as the treatment progressed, and which was accompanied by inflammation of the nasal membranes). Marked changes were also noted in the feces, which became light brownish-yellow in color and assumed a plastic consistency, being greatly increased in volume.

This state of hyperthyroidism was associated with an enhanced rate of carotene metabolism, as can be seen in Figure 5 (Table 5). Carotene disappeared more rapidly from the plasma of hyperthyroid sheep than from the plasma of normal sheep. There was a significant increase in plasma vitamin A in the hyperthyroid sheep. These results indicate that carotene metabolism can be stimulated by a hyperthyroid state induced by iodinated casein.

These observations, however, are not like those reported by Allen et al. (1), who conducted studies with calves; they are also unlike those reported by Cama and Goodwin (11), who fed desiccated thyroid to rabbits. Both groups of workers administered carotene orally. These differences thus might be due to the method of administration of the carotene, rather than to the actual state of thyroid activity induced (thyroid activity is known to have a definite effect on the ability of an animal to perform intestinal absorption). The results of the present study are in agreement with those reported by Chanda and Owen (14) and Chanda (12), who used thyroxine to induce hyperthyroidism in cows.

Metabolism of Intravenously Administered Carotene by Sheep Rendered Hypothyroid With Thiourea

The purpose of this experiment was to determine the effect of hypo-

FIGURE 5 PLASMA CAROTENE AND VITAMIN A LEVELS FOLLOWING INTRAVENOUS INJECTION OF AN AQUEOUS CAROTENE DISPERSION IN NORMAL AND HYPERTHYROID SHEEP

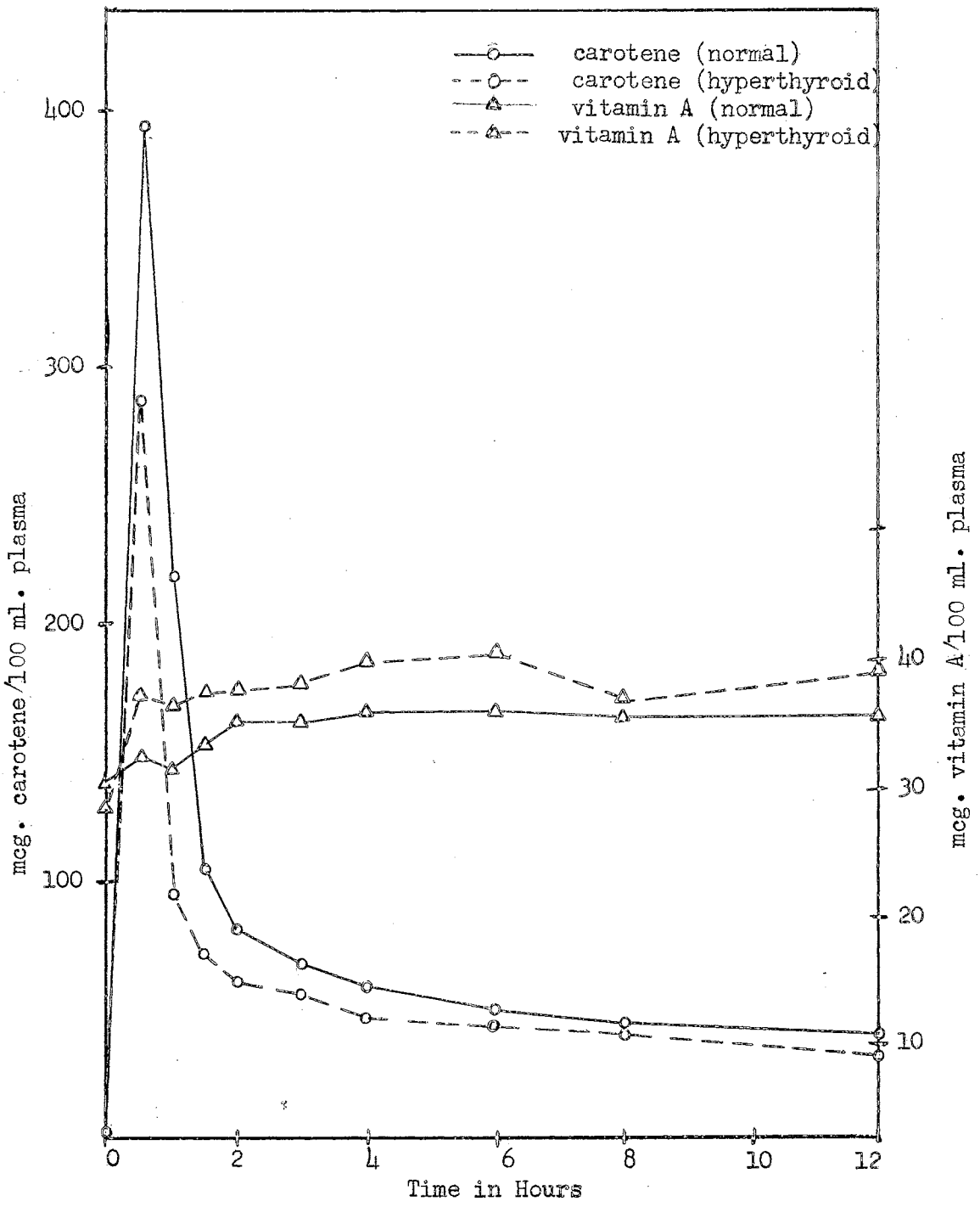

TABLE 5 PLASMA CAROTENE AND VITAMIN A LEVELS FOLLOWING INTRAVENOUS INJECTION OF AN AQUEOUS CAROTENE DISPERSION IN NORMAL AND HYPERTHYROID SHEEP

mcg. carotene/100 ml. plasma

Time Interval (hours)	Normal							Hyperthyroid		
	Sheep 1449			Sheep 1450			Ave.	Sheep 1449	Sheep 1450	Ave.
	#1	#2	Ave.	#1	#2	Ave.				
0	0	3.3	1.6	4.4	1.1	2.8	2.2	3.3	7.6	5.4
1/2	467.9	389.7	428.8	373.6	342.1	357.8	393.3	373.6	200.1	286.8
1	284.4	279.9	282.2	173.4	139.1	156.2	219.2	90.7	98.8	94.8
1½	107.1	124.0	115.6	96.2	90.9	93.6	104.6	68.8	75.2	72.0
2	92.2	82.9	87.6	82.9	70.1	76.5	82.0	57.6	66.2	61.9
3	75.2	70.1	72.6	73.9	55.1	64.5	68.6	52.7	60.1	56.4
4	61.3	60.1	60.7	61.3	51.4	56.4	58.6	43.1	50.1	46.6
6	56.4	52.7	54.6	51.4	41.9	46.6	50.6	40.7	46.7	43.7
8	51.4	45.5	48.4	44.3	41.9	43.1	45.8	37.1	43.1	40.1
12	47.9	41.9	44.9	39.5	40.7	40.1	42.5	31.3	35.9	33.6

mcg. vitamin A/100 ml. plasma

Time Interval (hours)	Normal							Hyperthyroid		
	Sheep 1449			Sheep 1450			Ave.	Sheep 1449	Sheep 1450	Ave.
	#1	#2	Ave.	#1	#2	Ave.				
0	32.2	32.0	32.1	23.3	33.2	28.2	30.2	30.9	26.2	28.6
1/2	35.7	32.5	34.1	26.3	33.3	29.8	32.0	40.7	33.5	37.1
1	35.6	33.0	34.3	22.5	33.4	28.0	31.2	39.4	33.1	36.2
1½	37.4	33.7	35.6	26.2	36.4	31.3	33.4	40.4	34.1	37.2
2	39.2	33.5	36.4	30.1	36.2	33.2	34.8	39.0	36.0	37.5
3	37.0	33.9	35.4	28.7	40.4	34.6	35.0	42.3	34.2	38.2
4	38.7	37.0	37.8	28.4	38.9	33.6	35.7	41.9	37.8	39.8
6	39.1	35.3	37.2	30.4	37.9	34.4	35.8	43.3	38.1	40.7
8	38.9	35.3	37.1	28.7	38.5	33.6	35.4	38.3	35.5	36.9
12	39.8	33.4	36.6	30.2	39.8	35.0	35.8	40.5	38.4	39.4

thyroidism, as induced by feeding thiourea, on the metabolism of intravenously administered carotene.

Following the determination of the normal carotene metabolic pattern for each sheep, the thiourea treatment was begun. By the end of the treatment period, the nasal membranes of the sheep were observed to be dry and the feces had become hard, black and greatly reduced in size and volume. In addition, urination was slight and infrequent.

Carotene conversion was significantly depressed in the hypothyroid state, as indicated by the reduced rate of disappearance of carotene shown in Figure 6 (Table 6). The initial plasma vitamin A level was markedly lowered in both animals during the thiourea treatment period. The carotene level remained higher than the normal level for at least 12 hours following the carotene injection. The relative shapes of the vitamin A curves are similar, possibly indicating some release of stored vitamin A in the treated animal. The important fact indicated by these data is that hypothyroidism, induced by thiourea, slows conversion of carotene to vitamin A but does not prevent it.

The mechanism of carotene metabolism seems not to be changed by either hyper- or hypothyroidism, as indicated by the close similarity between the carotene and vitamin A curves for the experimental and control animals. The effect of thyroid activity seems to be to modify the rate of carotene metabolism.

The results obtained in this experiment are in agreement with those obtained by Bolin and Bolin (9) with thiourea-treated sheep, and by Barrick et al. (4) who fed thiourea and thiouracil to lambs and rats. Allen et al. (1) also obtained comparable results with thiouracil-treated calves. Conversely, Bieri and Schultze (8), with rats, and Camma and

FIGURE 6 PLASMA CAROTENE AND VITAMIN A LEVELS FOLLOWING INTRAVENOUS INJECTION OF AN AQUEOUS CAROTENE DISPERSION IN NORMAL AND HYPOTHYROID SHEEP

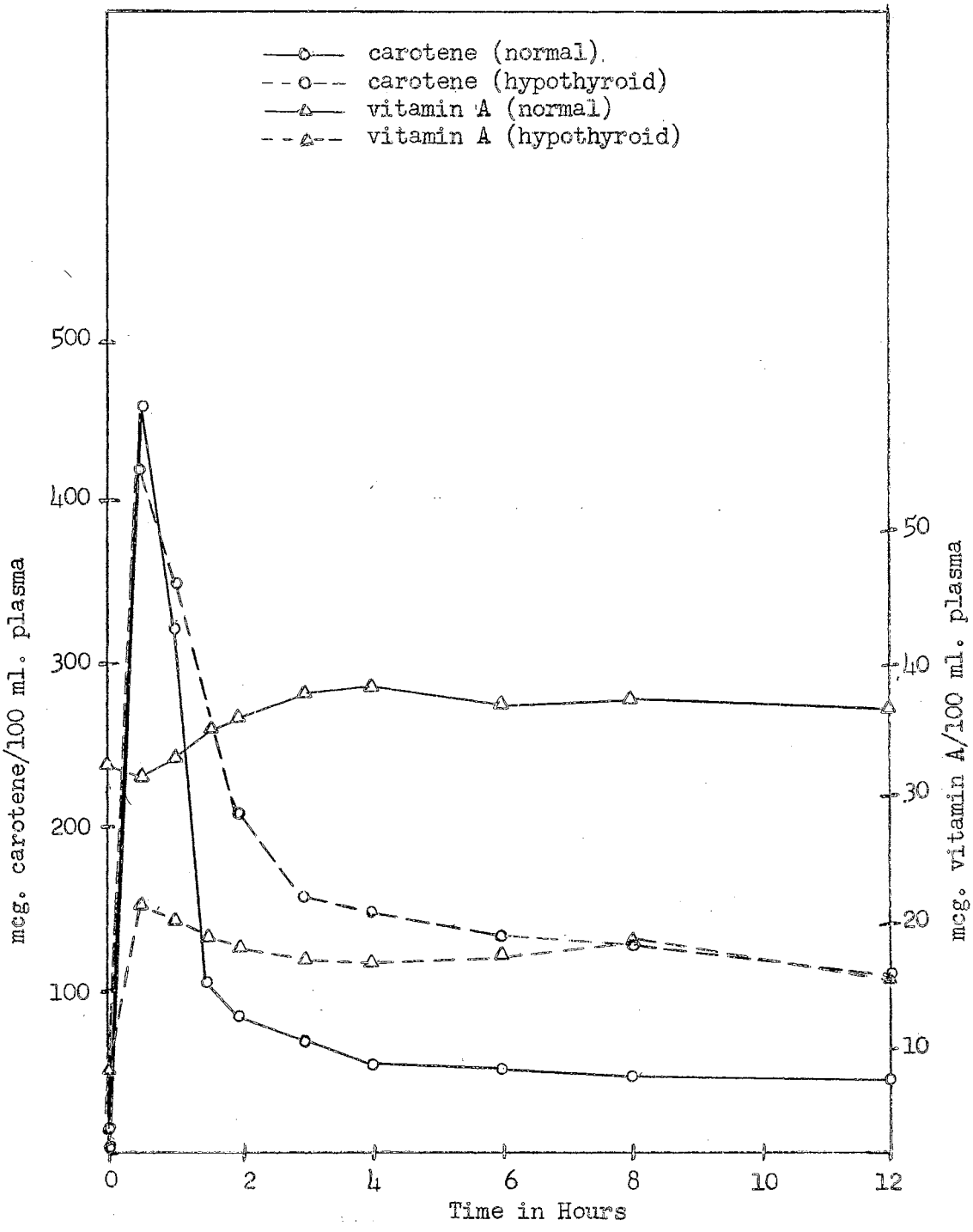

TABLE 6 PLASMA CAROTENE AND VITAMIN A LEVELS FOLLOWING INTRAVENOUS INJECTION OF AN AQUEOUS CAROTENE DISPERSION IN NORMAL AND HYPOTHYROID SHEEP

mcg. carotene/100 ml. plasma

Time Interval (hours)	Normal							Hypothyroid		
	Sheep 3221			Sheep 1449			Ave.	Sheep 3221	Sheep 1449	Ave.
	#1	#2	Ave.	#1	#2	Ave.				
0	4.4			0	3.3	1.6	3.0	7.6	22.1	14.8
1/2	490.3			467.9	389.7	428.8	459.6	474.1	368.6	421.4
1	362.9			284.4	279.9	282.2	322.6	349.9	352.5	351.2
1½	93.5			107.1	124.0	115.6	104.6	218.5	311.8	265.2
2	80.3			92.2	82.9	87.6	84.0	156.9	265.7	211.3
3	70.1			75.2	70.1	72.6	70.4	100.3	222.0	161.2
4	51.4			61.3	60.1	60.7	56.0	94.8	207.8	151.3
6	53.9			56.4	52.7	54.6	54.2	80.3	189.2	134.8
8	46.7			51.4	45.5	48.4	47.6	77.8	179.2	128.5
12	45.5			47.9	41.9	44.9	45.2	62.6	160.1	111.4

Faulty injection

mcg. vitamin A/100 ml. plasma

Time Interval (hours)	Normal							Hypothyroid		
	Sheep 3221			Sheep 1449			Ave.	Sheep 3221	Sheep 1449	Ave.
	#1	#2	Ave.	#1	#2	Ave.				
0	33.0			32.2	32.0	32.1	32.6	10.9	6.3	8.6
1/2	29.1			35.7	32.5	34.1	31.6	18.4	25.3	21.8
1	31.6			35.6	33.0	34.3	33.0	16.0	25.1	20.6
1½	36.1			37.4	33.7	35.6	35.8	15.4	23.5	19.4
2	36.0			39.2	33.5	36.4	36.2	16.5	20.6	18.6
3	40.4			37.0	33.9	35.4	37.9	15.1	20.1	17.6
4	39.5			38.7	37.0	37.8	38.6	16.6	18.4	17.5
6	37.5			39.1	35.3	37.2	37.4	19.9	16.0	18.0
8	38.1			38.9	35.3	37.1	37.6	18.5	19.6	19.0
12	37.0			39.8	33.4	36.6	36.8	16.5	15.7	16.1

Faulty injection

Goodwin (11), with rabbits, obtained results different from these. Their results may be related to the method of carotene administration (oral), as hypothyroidism significantly affects intestinal absorption. These results for hypo- and hyperthyroid sheep support the work of Smith et al. (31) with goats, and Chanda et al. (13) with cows and goats. They do not agree with the findings of Johnson and Baumann (21), Worker (36), or McGillivray, Thompson and Worker (27), with rats, who were unable to show an effect of thyroid activity on the metabolism of intravenously administered carotene. The thyroid state did, however, seem to affect intestinal conversion of carotene.

In conclusion, it appears that thyroid activity affects carotene metabolism in the sheep, as based on the rate of carotene disappearance from the plasma. Hyperthyroidism was observed to accelerate slightly both the rate of plasma carotene disappearance and of vitamin A appearance. Hypothyroidism markedly reduced the rate of both plasma carotene disappearance and vitamin A appearance.

CHAPTER V

UTILIZATION OF INTRAVENOUSLY ADMINISTERED CAROTENE BY SHEEP FED SUB-LETHAL DOSES OF POLYCHLORINATED NAPHTHALENES

The purpose of this experiment was to determine the effect of polychlorinated naphthalenes at sub-lethal levels on metabolism of intravenously administered carotene by sheep.

Three sheep were placed on a carotene-deficient diet for at least 4 weeks prior to the initial injection of carotene. Single carotene injections were then given at 0 and 2 weeks to determine the normal metabolic pattern for each sheep. One week following these injections, polychlorinated naphthalenes were fed for a period of 7 days, at which time a toxicity syndrome was evident. A description of this syndrome has been given by Brock et al. (10). On the eighth day following the beginning of the polychlorinated naphthalene treatment, a single carotene injection was again given each sheep.

Polychlorinated naphthalenes seemed to lower the initial plasma vitamin A level slightly. Carotene metabolism did not seem to be substantially altered by these materials, except in the case of sheep #3216 which showed a more rapid rate of disappearance of injected carotene than did the other animals. As indicated by the similarity between the carotene and vitamin A curves for the experimental and control animals, polychlorinated naphthalenes do not seem to alter the mechanism of carotene metabolism.

Because of the variable results obtained, further experiments are necessary to ascertain the significance of these observations. The apparently increased rate of carotene metabolism, as indicated by the slightly accelerated rate of disappearance of plasma carotene and the rapid initial increase in plasma vitamin A, could, if significant, indicate an accelerating effect of polychlorinated naphthalenes on carotene metabolism. The results shown in Figure 7 and individual results in Table 7 (Sheep 3216 and 1450), point in this direction.

The decrease in plasma vitamin A during treatment, accompanied by the rapid decrease in vitamin A following the early increase observed in the carotene-injected animals, may support the hypothesis of Ferrando (17), who assigned vitamin A a role in the detoxication of polychlorinated naphthalenes. This initial increase in plasma vitamin A, followed by a subsequent decrease, supports the work of Hansel et al. (18) with cattle; however, the effect in sheep is not so spectacular as that observed in cattle.

In conclusion, polychlorinated naphthalenes seem to affect the rate of carotene conversion only slightly. The initial increase in plasma vitamin A, following injection of carotene, indicates carotene metabolism does occur in the intoxicated sheep.

FIGURE 7 PLASMA CAROTENE AND VITAMIN A LEVELS FOLLOWING INJECTION OF AN AQUEOUS CAROTENE DISPERSION IN NORMAL AND POLYCHLORINATED NAPHTHALENE-INTOXICATED SHEEP

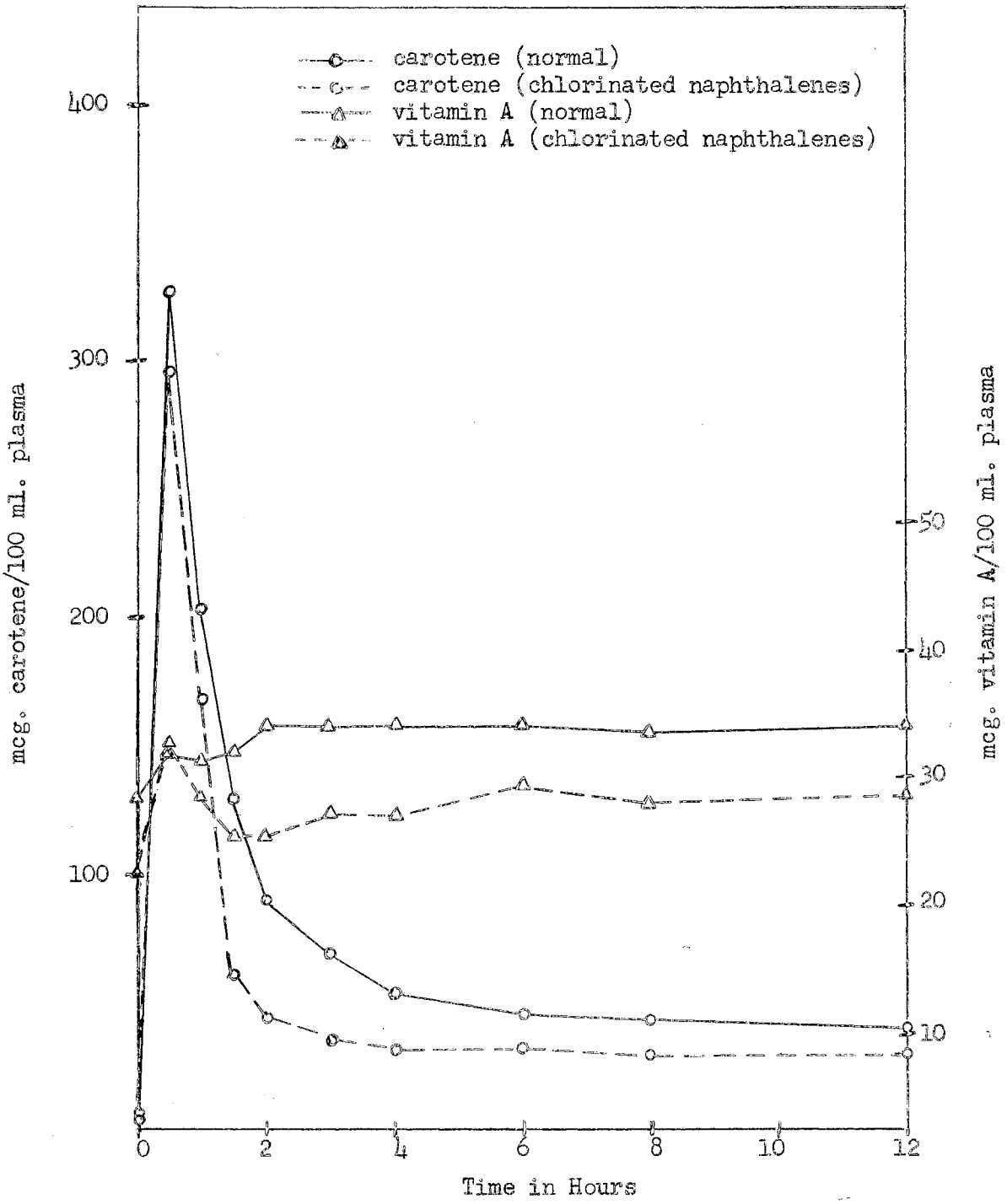

TABLE 7 PLASMA CAROTENE AND VITAMIN A LEVELS FOLLOWING INTRAVENOUS INJECTION OF AN AQUEOUS CAROTENE DISPERSION IN NORMAL AND POLYCHLORINATED NAPHTHALENE-INTOXICATED SHEEP

mcg. carotene/100 ml. plasma

Time Interval (hours)	Normal										Polychlorinated Naphthalenes			
	Sheep 3216			Sheep 3218			Sheep 1450			Ave.	Sheep 3216	Sheep 3218	Sheep 1450	Ave.
	#1	#2	Ave.	#1	#2	Ave.	#1	#2	Ave.					
0	5.5	5.5	5.5	4.4	6.6	5.5	4.4	1.1	2.8	4.6	3.3	2.2	15.4	7.0
1/2	526.3	322.7	424.5	147.7	257.8	202.8	373.6	342.1	357.8	328.4	352.5	234.3	300.6	295.8
1	526.3	201.0	363.6	70.1	115.5	92.8	173.4	139.1	156.2	204.3	234.3	96.2	173.4	168.0
1½	403.2	63.8	233.5	63.8	53.9	58.8	96.2	90.9	93.6	128.6	34.9	65.0	82.9	60.9
2	251.9	60.1	156.0	51.4	30.2	40.8	82.9	70.1	76.5	91.1	16.5	53.9	58.9	43.1
3	126.9	52.7	89.8	65.0	39.5	52.2	73.9	55.1	64.5	68.8	18.7	37.1	52.7	36.2
4	100.3	45.5	72.9	47.9	22.1	35.0	61.3	51.4	56.4	54.8	10.9	40.7	45.5	32.4
6	71.3	38.3	54.8	41.9	24.4	33.2	51.4	41.9	46.6	44.9	23.3	35.9	40.7	33.3
8	65.0	40.7	52.8	37.1	26.7	31.9	44.3	41.9	43.1	42.6	16.5	31.3	39.5	29.1
12	53.9	33.7	43.8	38.3	34.9	36.6	39.5	40.7	40.1	40.2	24.4	25.5	35.9	28.6

mcg. vitamin A/100 ml. plasma

0	28.0	34.6	31.3	27.5	31.7	29.6	23.3	33.2	28.2	28.7	28.7	16.8	22.9	22.8
1/2	27.4	41.0	34.1	29.5	39.0	34.2	26.3	33.3	29.8	32.7	34.7	23.8	41.1	33.2
1	29.4	40.3	34.8	31.7	32.1	31.9	22.5	33.4	28.0	31.6	35.9	19.2	30.7	28.6
1½	38.0	40.3	34.2	29.4	33.5	31.4	26.2	36.4	31.3	32.3	28.9	21.1	27.3	25.8
2	33.1	40.6	36.8	32.0	34.3	33.2	30.1	36.2	33.2	34.4	27.6	21.5	27.5	25.5
3	28.3	39.9	34.1	34.3	34.1	34.2	28.7	40.4	34.6	34.3	31.3	20.7	30.2	27.4
4	31.0	40.0	35.5	35.7	32.7	34.2	28.4	38.9	33.6	34.4	29.2	22.5	30.3	27.3
6	31.6	40.5	36.0	32.8	32.5	32.6	30.4	37.9	34.4	34.3	35.4	24.5	29.0	29.6
8	30.4	38.6	34.5	32.6	33.4	33.0	28.7	38.5	33.6	33.7	31.5	21.7	31.3	28.2
12	31.8	38.0	34.9	30.3	34.5	32.6	30.2	39.8	35.0	34.2	35.8	21.6	29.4	28.9

SUMMARY

It is postulated that the absence of carotene in the circulation of animals reflects the existence of extra-intestinal sites of carotene conversion. In support of this hypothesis, it was found that sheep in which the liver, intestine, spleen, pancreas and stomach had been isolated from the systemic blood circulation were able to metabolize intravenously administered, aqueous dispersions of carotene in a manner similar to the normal animal. These animals, however, were not able to metabolize the injected carotene as efficiently as did the normal sheep, based on the reduced rate of plasma carotene disappearance. Sheep, in which all tissues posterior to the diaphragm had been isolated from the systemic blood circulation, with the exception of a short section of the esophagus, were also found to metabolize intravenously injected, aqueous dispersions of carotene in a manner similar to the normal animal, though again at a diminished rate.

A hyperthyroid state, induced by feeding iodinated casein to sheep, was found to accelerate the conversion of an intravenously administered, aqueous dispersion of carotene, as indicated by the increased rate of disappearance of plasma carotene and of appearance of plasma vitamin A. In contrast, a hypothyroid state, as induced by thiourea, was observed to decrease the rate of disappearance of plasma carotene and of appearance of plasma vitamin A, following an intra-

venous injection of an aqueous dispersion of carotene. Thus thyroid activity was found to influence the rate of carotene conversion in the sheep.

Polychlorinated naphthalenes were not found to markedly affect the rate of carotene conversion in sheep, though there was some indication that the rate of carotene disappearance was accelerated in the intoxicated animal.

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