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ASPECTS OF VITAMIN E
AND SELENIUM NUTRITION IN
RELATIONS TO GASTRIC ULCERS IN SWINE

presented by

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ASPECTS OF VITAMIN E AND SELENIUM NUTRITION IN RELATION TO GASTRIC ULCERS IN SWINE

By

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ABSTRACT

ASPECTS OF VITAMIN E AND SELENIUM
NUTRITION IN RELATION TO GASTRIC ULCERS IN SWINE

By

David M. Bebiak

Two experiments involving 70 weanling pigs were conducted to evaluate the effects of vitamin E (E) and selenium (Se) on the incidence and severity of gastric ulcers. Pigs were randomly assigned from litters to two dietary groups, (1) a basal ulcerogenic diet (BUD) composed of corn starch, soybean meal and corn oil adequately fortified with minerals and vitamins except Se and E and (2) the BUD + .2 ppm Se + 44 IU E/kg from d, ℓ-alpha-tocopheryℓacetate. Data were collected from animals at 5, 10 and 20 weeks of age. The effect of E-Se supplementation was determined by growth rate, serum levels of tocopherol and selenium, erythrocyte glutathione peroxidase (GSH-Px) activity, gastric tissue selenium, tocopherol, GSH-Px and cyclooxygenase, and the incidence of gastric lesions.

Supplementation of the BUD with E-Se did not affect growth rate in either experiment. Blood data of experimental animals reflected the dietary levels of E-Se such that serum tocopherol, serum selenium and erythrocyte GSH-Px values were significantly greater among supplemented animals. Likewise, tocopherol-selenium-GSH-Px levels of gastric tissue collected from several anatomic regions of the stomach reflected (significantly) dietary supplementation of the nutrients E-Se. In particular, the tocopherol and selenium concentrations and GSH-Px activity of the esophageal region appeared to be most sensitive to E-Se supplementation

and depletion. Unlike the data concerning growth and blood values which are consistent with previous work, data concerning the regional distribution of these parameters within the stomach were not available. Among all regions of the intragastric surface, and between animals of both dietary groups, the distribution of cyclooxygenase among common tissue layers was similar. Among the tissue layers of all anatomic regions examined, a relative abundance of the enzyme was present in the mucosal lamina propria, especially of the esophageal region. No previous work of this type could be located for comparison.

Finally, the stomachs of (35) unsupplemented animals in the two trials were characterized morphologically as follows: (9) normal, (20) preulcerous lesions and (6) ulcers. The stomachs of the (35) supplemented animals in the two trials were characterized as: (13) normal, (18) preulcerous lesions and (4) ulcers. The ulcerogenic effect of the BUD utilized in one trial of this study was believed to be reduced by maintaining the pigs on straw bedding.

Dedicated to my wife Kim

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INTRODUCTION

Several researchers studying the vitamin E (E)-selenium (Se) deficiency syndrome in swine have noted a high incidence of gastric ulcers among experimental animals. In general, the pathogenesis of the mucosal lesions has been attributed to several factors including genetic selection of meat-type swine, confinement rearing and the feeding of high energy finely ground rations for greater feed conversion (Muggenburg et al. 1967). Also, certain prostaglandins have been reported to protect the gastric mucosa of several species against experimental ulcerogens (Robert, 1973). The mechanism of protection is not understood and the action is described as cytoprotective (Chaudhury, 1978). Interestingly, ulcers in swine are unique in that they always occur in exactly the same anatomic region of the gastric lumenal mucosa.

In swine, gastric ulcers present a practical production problem. A conservative estimate of the incidence of esophagogastric lesions in swine would be 5 to 20 percent (Muggenburg et al., 1966, 1967). Determining more precise pathogenic factors may be useful in assisting swine producers in diminishing this problem. The curious association between E-Se deficiency, prostaglandin biology and the predictable appearance of gastric ulceration in swine inspired this research effort toward more accurately defining the ulcerogenic process.

LITERATURE REVIEW

Introduction

Gastric ulcers are an important problem in swine production as well as human health. A voluminous amount of research has been conducted on the nature of the problem, especially the physiopathologic aspects (Muggenburg, 1966). While considerable information is available on the nature of the disease, few data are available on the specific cause(s) of the problem. In swine, the problem has been associated with intensified production and the use of finely ground high energy diets intended to maximize growth and feed efficiency (Mahan, et al, 1966; Muggenburg, 1967; Perry, et al., 1963). Morbidity and mortality varies from herd to herd and from year to year without specific relation to age, sex, climate or breed (Muggenburg et al, 1967).

An unusually high incidence of ulcers has been reported in herds characterized as vitamin E (E) - selenium (Se) deficient and among E-Se deficient experimental animals. The possible relationship between E-Se status and ulcerogenesis is not defined, nor is the relationship between E-Se status and prostaglandin biology. As a class of naturally occurring compounds the prostaglandins elicit a wide range of biological effects including antiulcerogenesis (Moncada, 1978; Chaudhury, 1978). In particular, prostaglandin I_2 is a potent cytoprotective agent (Chaudhury, 1978).

This research is important in providing information which may help define the relationships mentioned above. The data and observations generated here have potential usefulness in biomedical science as well as in swine production.

VITAMIN E AND SELENIUM AS ANTIOXIDANTS

Basic to the theme of this review, and thesis, is an understanding of the free radical pathology theory (Butterfield et al., 1979). A free radical is a chemical in which the outer electron orbital has an unpaired electron which spins unopposed. This situation creates an unstable electronic distribution and hence a free radical is quite reactive. In biology, compounds are converted to free radicals by chemical agents called initiators.

The molecular structure of oxygen (O_2) may be represented as having a covalent double bond (0=0) or as being a diradical (0-0) and actually oscillates between these two forms.

The simple theoretical biological membrane containing interdigitating hydrophobic, hydrophyllic and amphipathic substances forms a lipid bilayer with a hydrophobic midzone area in which O_2 is very soluble. Hydrocarbon chains of the polyunsaturated fatty acids also exist in this hydrophobic midzone area. Thus, in the typical bilayer membrane the highest concentration of diradical oxygen exists in the hydrophobic area where it has the most destructive potential. The allylic hydrogen bonds (those involved with carbons in the β-position relative to an unsaturated C=C) are relatively weak and therefore susceptible to radical initiation reactions. Demopoulos et al. (1977) suggest that cholesterol prevents the normal plasma membrane from being destroyed by lipid peroxidation. Cholesteral enters the hydrophobic midzone area perpendicularly to the surface of the membrane. Hydrocarbon tails of the polyunsaturated fatty acids, as well as those of other lipids, wrap themselves (hydrophobic forces) around the nonpolar end of the amphipathic cholesterol. The steroid serves as a physical barrier between radical oxidative components and the susceptible

allylic bonds of the fatty acids. Apparently then, one of the many roles of cholesterol may be that of a protective antioxidant in normal plasma membranes.

The broad range of lesions which has been observed in animals under conditions of E-Se deficiency might be explained by this theory of "free radical pathology". Indeed, the role of E as a deterrent to lipid peroxidation is similar to that proposed for cholesterol in the cell membrane. Since oxygen is soluble in the membrane it may catalyze free radical peroxidation reactions which could proceed unchecked in the absence of E, ultimately disrupting membrane integrity. Normal membrane integrity is critical to membrane functions of permeability, transport, and bioenergetics. The result of free radical peroxidation would be "free radical pathology" i.e. cellular damage and necrosis. In Figure 1 the roles of E and Se in the free radical pathology theory are diagrammed. In Figure 2 the antioxidant functions of E and Se (as a component of glutathione peroxidase) are detailed.

A free radical generated in normal metabolism is capable of reacting with an allylic bond of an unsaturated fatty acid (RH). The oxygen molecule becomes stable at the expense of the lipid which itself becomes a type of radical (R) burdened with electron disruption at the reaction site. This lipid radical (R·), in the presence of molecular oxygen, forms a lipid peroxy free radical (RO_2) which is capable of initiating autocatalytic peroxidation of allylic bonds of adjacent unsaturated lipids (RH'). The products of this biochemical reaction (RO_2 + RH') are a lipid radical (R·') which again, in the presence of molecular oxygen and an adjacent unsaturated lipid, may perpetuate this cyclic autocatalytic peroxidative process. The trail of lipid hydroperoxides (ROOH) left in

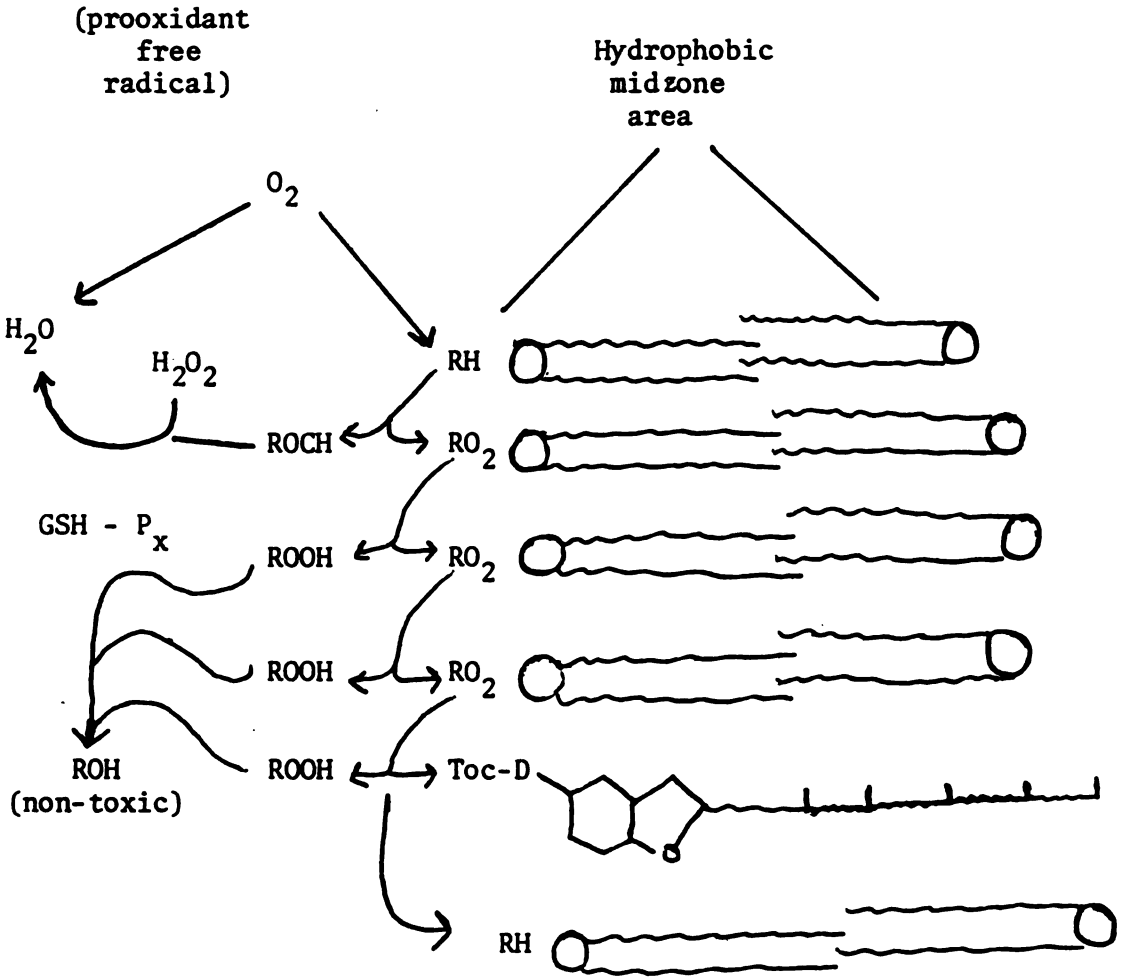


FIGURE 1. Role of vitamin E (Toc.) and selenium (GSH-Px) in free radical pathology (Adapted from Tappel, 1974). Superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) glutathione peroxidase (GSH-Px) lipid (RH) hydroperoxide (ROOH) peroxy free radical (RO_2) oxidized tocopherol (Toc-O).

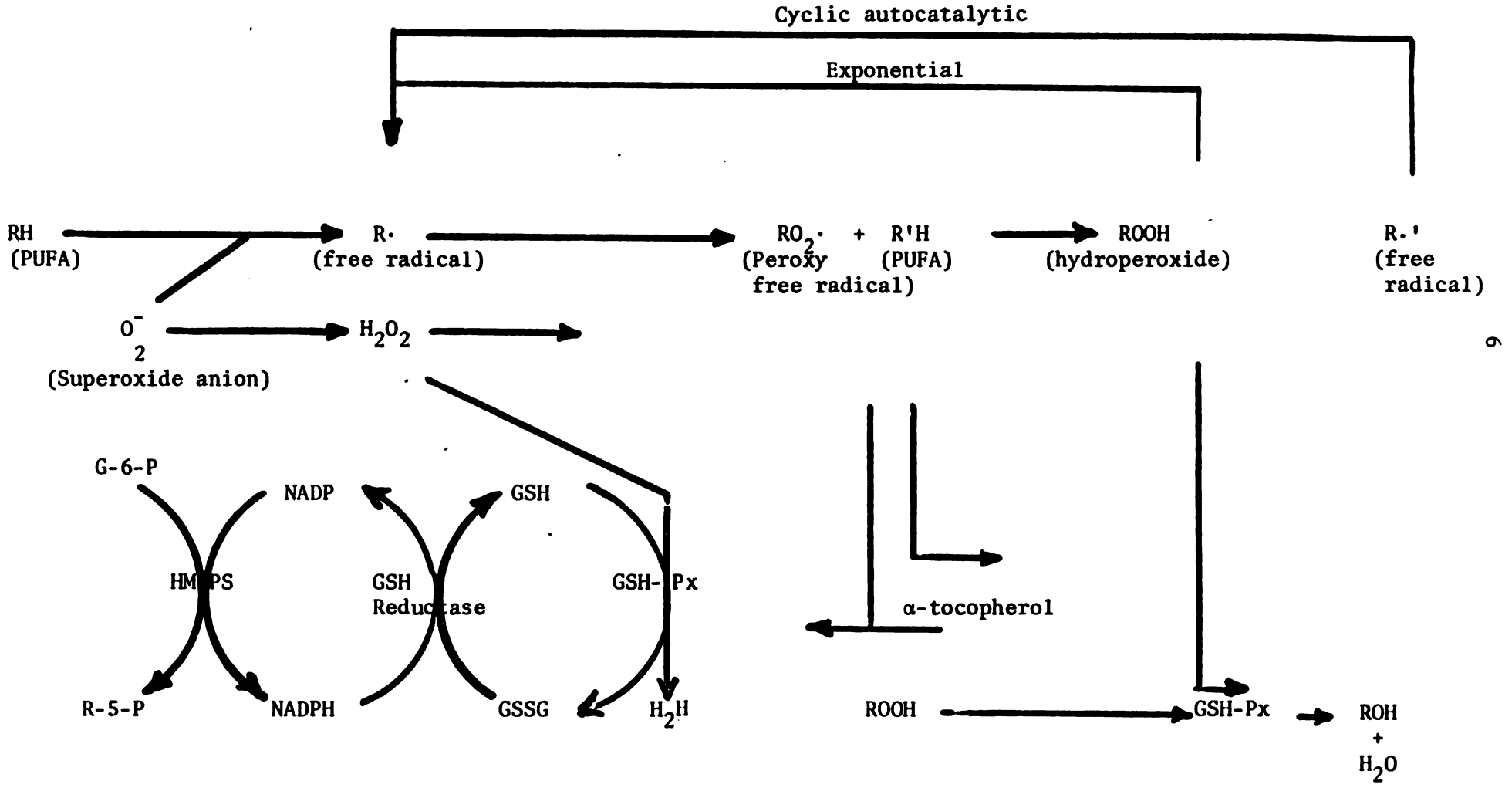


Figure 2. Vitamin E and selenium function (Adapted from Brady et al. 1979).

the wake of this peroxidative pathway presents a region of hydrophyllic polar groups in the nonpolar hydrophobic midzone of the cellular membrane. Clearly, this is disruptive to normal membrane function, and eventually the attraction of these polar groups to the water phase of the exterior surfaces of the membrane will lead to membrane-lipid decomposition.

When the propagating chain reaction meets a membrane bound molecule of E the chain reaction is broken (Tappel, 1974). The tocopherol compound accepts the oxidation reaction without generating a chain perpetuating lipid radical.

The role of Se as a limiting agent in the mechanism of "free radical pathology" is quite different from that of E. Selenium is an essential element of the enzyme glutathione peroxidase (GSH-Px). As a cytosolic enzyme with hydrophobic character, GSH-Px reacts with both cytosolic hydrogen peroxide molecules (H_2O_2) and membrane bound lipid hydroperoxides (ROOH). GSH-Px reduces the lipid hydroperoxides (ROOH) to relatively harmless hydroxy acids (ROH). Similarly the toxic hydrogen peroxides are reduced to molecules of water (Tappel, 1974).

At this point it is worthy of noting that both dietary polyunsaturated fatty acids (PuFA) and sulfur amino acids may influence E-Se status. The role of these factors in relation to E-Se status may be explained in the context of the theory of free radical pathology as discussed above. Inclusion of PuFA in the diet increases substrate (allylic bonds) involved in the initiation of the peroxidative process. Of course, this statement assumes that the composition of dietary fat influences the composition of total membrane lipids. With respect to the sulfur amino acids, their influence may be two-fold. First, through the involvement of these amino acids in the production of glutathione (GSH) a tripeptide (γ-L-glutamyl-L-cysteinylglycine) which is linked

through glutathione reductase (GSH Red) to the NADPH generating system of the cell. Second, the selenoamino acids selenocysteine and selenomethionine are significant in occurrence. Therefore, organic sources of dietary methione and cysteine may actually provide enough selenium to influence E-Se status. (Neither the negative influence of PUFA nor the positive influence of the sulfur amino acids were studied in this research).

Vitamin E and Selenium Deficiency Signs

The clinical signs which are characteristic of specific deficiencies or marginal levels of E and Se include liver necrosis (Obel, 1953), microangiopathy (Grant, 1966), yellowish brown discoloration of body fat (Davis and Gorham, 1954), sudden death in young pigs (Michel et al. 1969), exudative diathesis (Trapp et al. 1970), muscular degeneration (Lannek et al. 1961) and erythrocyte hemolysis (Sondegaard, 1966). The clinical signs of general dietary deficiencies in swine to which E and Se deficiencies are known to contribute are: slow or interrupted growth, reduced appetite, lameness or stiffness and impaired reproduction (Trapp et al. 1970). It is important to remember that a single mechanism (free radical pathology) could be responsible for the necrotic lesions observed in tissues (Butterfield, 1978).

Among experimental pigs fed E-Se deficient rations, and in field cases of E-Se deficiency, the most frequently observed gross lesions were liver necrosis and fibrosis, ulceration and preulcerous lesions of the squamous epithelium of the nonglandular esophageal region of the stomach (Michel et al. 1969). Icterus, generalized edema, and transudation were not especially evident in experimental pigs but were consistently observed in field cases.

Feed Particle Size and the Incidence of Gastric Lesions

Mahan et al. (1966) studied the effects of various physical properties of feed on the incidence of ulceration. Rations ground to a fine particle size (.16 cm) were associated with an increased incidence of ulcers.

Finely ground barley caused a strong increase in the frequency of gastric lesions in growing pigs (Simonsson, 1978). Diets containing coarsely ground barley or crushed oats caused very few lesions. Also, in this study and others, the gastric contents of pigs consuming diets of small particle size are more fluid and leave the stomach more quickly. It may be that a fluid ingesta is more accessible to the physically remote nonglandular esophageal region of the stomach. Increased exposure of this region to the acidic fluid ingesta may be responsible for the increased incidence of lesions. Gastric pH alone is not a likely causative factor in ulcerogenesis (Kowalczyk and Muggenburg, 1963).

Prostaglandins

Approximately seventeen years have passed since the structures of prostaglandin E_1 and prostaglandin F_1 (PGE_1 and PGF_1) were described (Moncada and Vane, 1978). As the biological properties of the prostaglandins were revealed, it became evident that these cyclical products of arachidonic acid metabolism had diverse but symmetrical effects. That is, PGE and PGF compounds were shown to have opposing actions in many tissues; e.g. PGE dilates blood vessels and bronchi whereas PGF constricts them. This concept of diversity and symmetry was extended by the later identification of two other classes of prostaglandins, the thromboxanes (Tx) and prostacyclin (PGI_2). Thromboxane A_2 is the principle prostaglandin

produced in the circulating blood platelets and induces platelet aggregation as well as smooth muscle constriction. Conversely, prostacyclin (PGI_2) is produced in the endothelium of blood vessel walls and is a potent antiaggregant of platelets and a smooth muscle dilator (Moncada and Vane, 1978).

With respect to ulcerogenesis, workers have shown the antiulcerogenic affects of PGI_2 (Robert, 1973; Chaudhury and Jacobson, 1978). At this point the mechanism of action is not understood however, the term "cytoprotective" (Chaudhury and Jacobson, 1978) seems appropriate. Prostacyclin (PGI_2) protects the gastrointestinal mucosa against numerous experimental ulcerogens. Among the agents which have demonstrated ulcerogenic properties, and against which PGI_2 offers protection, are aspirin [acetyl salicylic acid (ASA)] and the nonsteroidal antiinflammatory compound indomethacin. Appropriately, both of these compounds inhibit biosynthesis of endogenous prostaglandins in the mucosa (Chaudhury, 1978). Although the mechanism of inhibition of prostaglandin biosynthesis by indomethacin is not understood, that of aspirin is defined. Also, the site of action of both agents has been identified as the first unique step in prostaglandin synthesis, that of arachidonic acid conversion to PGG_2. Specifically, ASA acetylates the active site of prostaglandin cyclooxygenase. The extent of acetylation correlates with the degree of inhibition of cyclooxygenase activity. The effect of acetylation seems to be permanent as measured by its antiaggregant effect on platelets (Marcus, 1978). The overall scheme of prostaglandin metabolism is depicted in Figure 3. The reaction catalyzed by the cyclooxygenase enzyme is depicted in Figure 4.

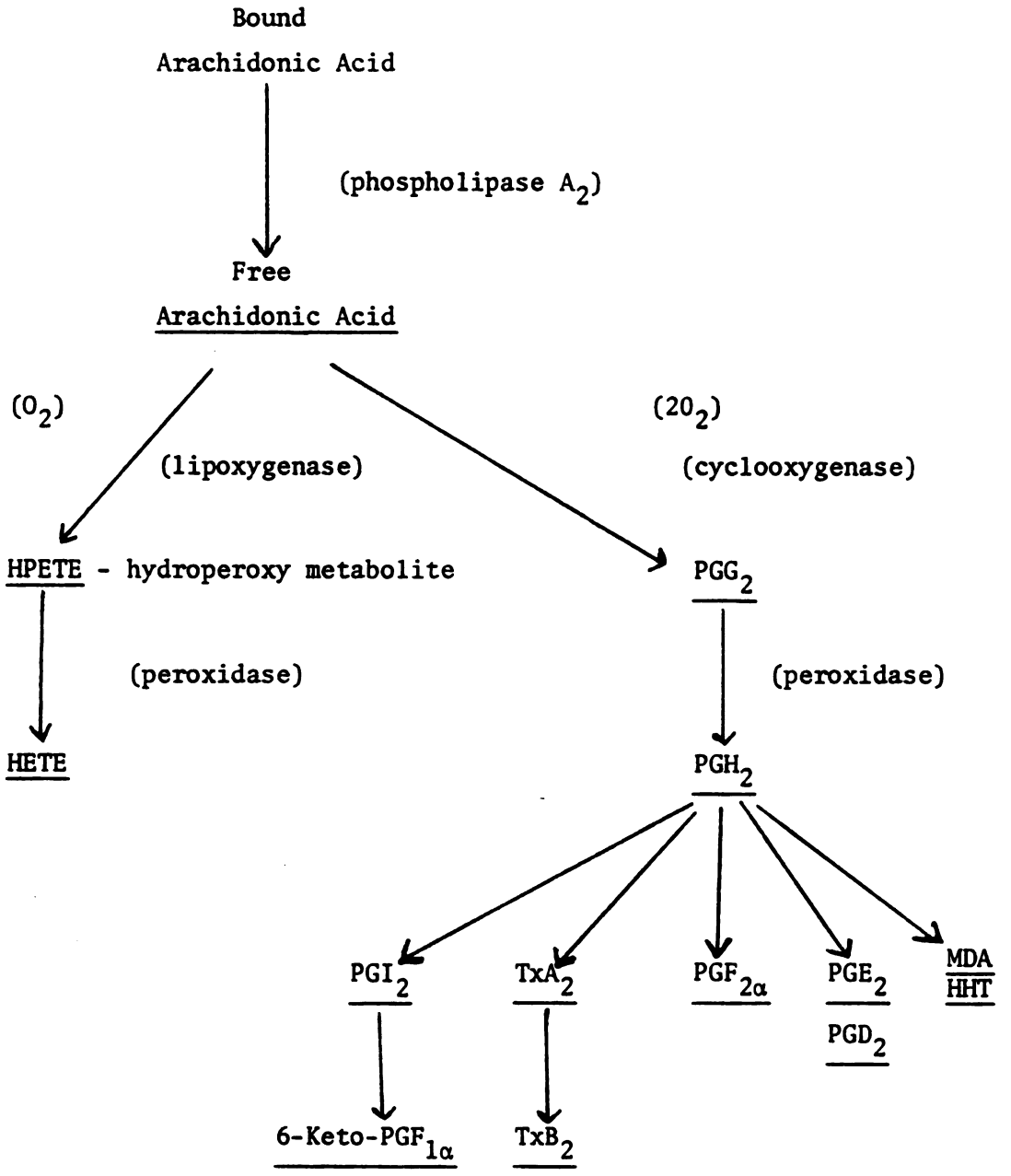
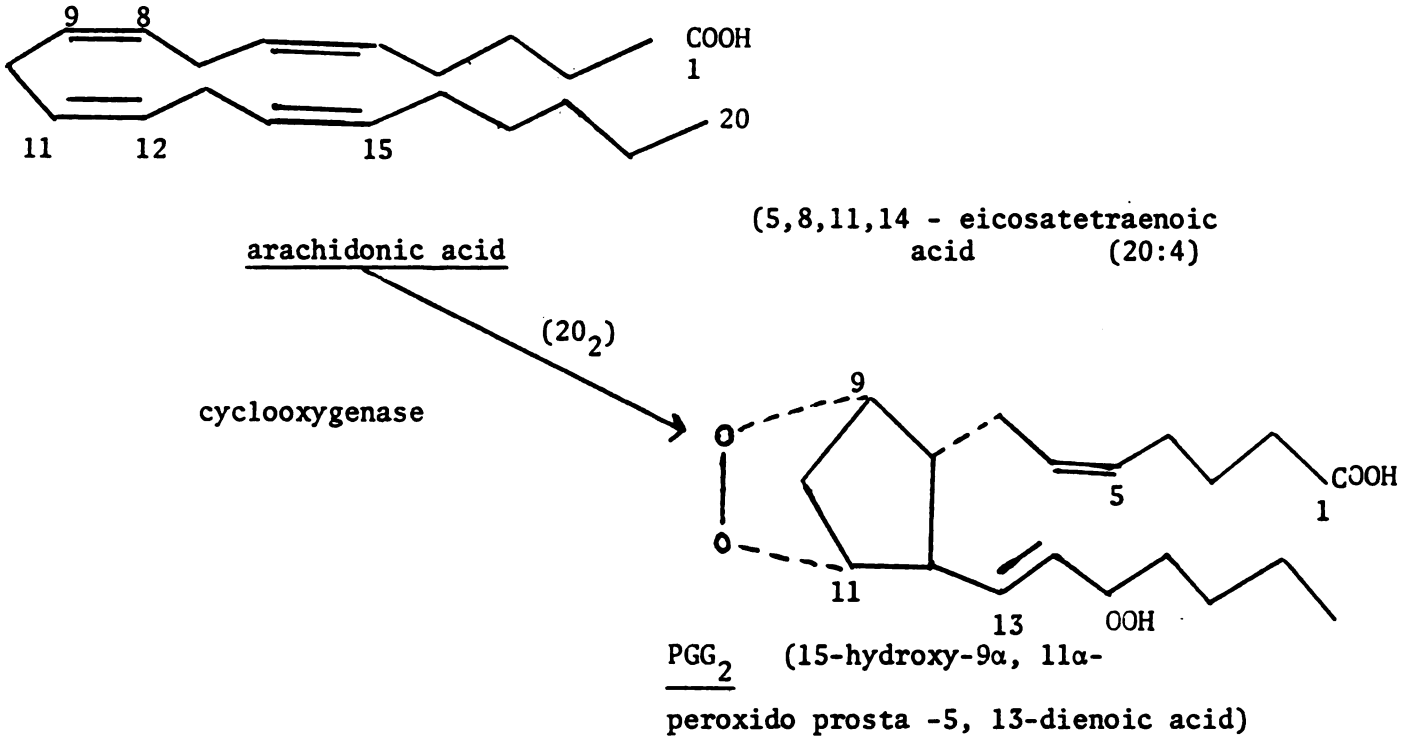


FIGURE 3. Prostaglandin metabolism



a) Oxygenation at C_{11} and C_{15}

b) Bond formation (cyclization) between C_8 and C_{12}

c) Oxygen molecule at C_{11} forms peroxide bridge with C_9

FIGURE 4. Prostaglandin forming - cyclooxygenase - catalyzed reaction.

The essential fatty acid arachidonic acid (20:4) is a component of phospholipids found in cell membranes and subcellularly. Activation of the enzyme phospholipase A_2 initiates a hydrolytic process which releases free fatty acids including arachidonic acid. Arachidonic acid is available to either lipoxygenase or cyclooxygenase enzymes and either oxygenated to form the hydroperoxide metabolite HPETE, or oxygenated and cyclized to form the endoperoxide PGG_2 respectively. Products of the lipoxygenase pathway are bioactive nonprostaglandin metabolites which will not be discussed here. All oxygenated and transformed products of the cyclooxygenase pathway must pass through the endoperoxide (PGG_2, PGH_2) stage. It should be noted that qualitative and quantitative differences exist with respect to end products among tissues.

If PGI_2 is to be implicated as a naturally occurring cytoprotective agent in the stomach, it must be demonstrated that it does occur in that tissue. Indeed, PGI_2 biosynthesis from prostaglandin endoperoxide has been demonstrated in microsomal fractions of gastric mucosa from the following species: rat, mouse, guinea-pig, rabbit and monkey (Moncada, 1977; Sun, 1977). Whittle *et al.* (1978) investigated the role of PGI_2 in the rat gastric mucosa and observed that intravenous infusion of PGI_2 increased mucosal blood flow, inhibited gastric acid secretion and inhibited indomethacin-induced gastric erosions. Another possible action of the prostaglandins in gastric tissue is that of stimulating the active transport of sodium. Data presented by Chaudhury (1978) support the hypothesis that active transport of sodium is inhibited by the ulcerogenic agent indomethacin and is stimulated by the cytoprotective agent PGE_2, the latter appearing to act via increased accumulation of intracellular

cAMP. If the inhibition of active sodium transport is related to ulcerogenesis, a possible mechanism might be that sodium accumulation promotes osmotic swelling and disruption of epithelial cells.

The interrelationship between vitamin E and prostaglandin biology, if any, is probably multifactorial and may be indirect. As noted before, one of the characteristic signs of E-Se deficiency is that of microangiopathy. Endothelial swelling and necrosis in blood vessel walls may disrupt the PGI_2 (endothelial antiaggregant) / TxA_2 (platelet proaggregant) functional symmetry which characterized prostaglandin biology. That is, disruption of vascular endothelium (removal of PGI_2 producing capacity) is a proaggregant stimulus in a "relative" proaggregant (TsA_2) environment. An episode of platelet aggregation in this microvasculature could result in microthrombi capable of occlusion and focal necrosis. [Three of 4 vitamin E deficient rabbits died from pulmonary thrombotic episodes during an intravenous injection of arachidonic acid. The fourth animal was sacrificed in a similar moribund condition. All four of the E sufficient controls survived brief periods of respiratory distress under similar conditions Nafsted (1978).] Another point of possible interrelationship between E-Se status and the prostaglandins is one of an indirect effect on prostaglandin metabolism. Lipid peroxides are strong and selective inhibitors of PGI_2 synthesis (Moncada and Vane, 1978). Lipid peroxides produced during the process of "free radical pathology" such as might occur during E-Se deficiency again may promote a situation which is predisposing to thrombus formation in vessels or noncytoprotective in gastric tissue or both simultaneously. Cornwell *et al.* (1979) has presented data which suggest that E inhibits HPETE production thus making arachidonic acid more available for endoperoxide-PG synthesis,

PGI_2 inclusive.

Gastric Ulcers in Swine

The incidence of gastric ulcers in swine ranges from 5 to 20 percent and the economics of the disease becomes significant when apparently normal pigs die suddenly (Boenker, 1967). These may develop under varying conditions of age, sex, diet, climate and feeding. In swine, lesions occur only in the nonglandular esophageal region of the stomach and are more appropriately termed esophagogastric lesions. The surface of the normal swine stomach is white, smooth, and glistening. Lesions of gastric tissue were described by Muggenburg et al. (1966) on the basis of gross and histopathologic characteristics. In order of increasing severity, Muggenburg differentiated between scars, epithelial changes, acute erosions, subacute ulcers and chronic ulcers. A detailed description of the characteristics of each class of lesion has been reviewed (Bebiak et al. 1977) with some discussion of the anatomy of the stomach.

Ulcers have been observed in the pig under a number of circumstances and consequently a number of causes have been suggested. The relationship between feed particle size and the incidence of ulcers was discussed above. Our own previous work (Bebiak et al. 1977) indicated that typical swine diets, in which corn starch supplanted ground corn, were ulcerogenic in nearly 100 percent of the animals examined. Though the mechanism is not understood, mere awareness of the ulcerogenic property of finely ground feeds is valuable in that it provides a model (negative control) for studying this health problem.

Gastric hyperacidity has been discussed as an important causative agent in ulcerogenesis (Kowalczyk 1963). A direct relationship between

gastric hyperacidity and the incidence of ulcers has not been shown consistently. In fact, most human gastric ulcer patients secrete less gastric juice, and in many cases no acid is secreted at all, compared to healthy controls (Dragstedt, 1978). Young pigs having undergone gastric vagotomy develop chronic gastric ulcers by 5 months of age. It should be noted that such an operation effectively removes the nervous phase of gastric secretion and reduces glandular response to gastrin or histamine stimulation. The lesion produced in these vagotomized pigs developed in the glandular tissue along the lesser curvature immediately distal to the nonglandular esophageal region. Gastric lesions induced through surgical manipulation of the acid environment are not representative of naturally occurring lesions. In fact, this evidence would suggest, by default, that acidity is not a principal cousative factor in naturally occurring esophagogastric ulcerogenesis.

The role of ischemia in the pathogenesis of gastric ulcers may be important (Hottenrott et al. 1978). Conscious piglets subjected to hemorrhagic shock by injection of microspheres into the left atrium developed mucosal lesions within 4 hours. The incidence and location of lesions related directly to areas of reduced blood flow indicating that local ischemia may render the mucosa susceptible to ulcerogenosis. The possible roles of vitamin E, selenium and the prostaglandins in regard to ulcerogenesis have been discussed. And in light of that discussion one cannot disregard the possible association of E-Se deficiency, PGI_2/Tx imbalance and ischemia as related pathogenic components.

Summary

In the literature reviewed here, it is clear that specific information is available concerning E-Se nutrition, prostaglandin biology and ulcers, but little specific information relating these subjects. Since the problem of gastric ulceration is important in biomedical science and swine production, and since the theoretical relationship between E-Se status-prostaglandin biology and ulcerogenesis remains untested, a study was designed with the following objectives:

1. Determine the effect of vitamin E-selenium supplementation on the incidence of gastric ulcers in swine.
2. Provide original data on the regional distribution of tocopherol, selenium, glutathione peroxidase, and cyclooxygenase in the porcine stomach.

METHODS AND MATERIALS

Experimental Design

In each experiment pigs were randomly assigned from 6 litters into 2 dietary groups. The pigs used in this experiment were born from sows which had been fed a low E-Se diet throughout gestation and lactation. These pigs were weaned to a low E-Se diet at 5 weeks of age. Two trials were conducted using 36 pigs in the first experiment while the second experiment employed 34 pigs.

The experimental diets consisted of a control ration (Table 1) demonstrated to be ulcerogenic in pigs (Wesoloski et al., 1974; Bebiak et al., 1977) and a test ration consisting of this basal ulcerogenic diet (BUD) supplemented with 44 I.U. of E/kg of feed as d,ℓ-alphatocopheryl acetate and .2 ppm of Se from sodium selenite (BUD+E+Se)

In trial I pigs were maintained in confinement on slotted floors until 10 weeks of age. After 10 weeks the pigs were maintained in confinement on straw bedding until they were killed at 20 weeks. In trial II pigs were maintained on slotted floors throughout the 20 week study. These animals were raised without the imposition of any determinable environmental stress.

Periodically (at 5, 10 and 20 weeks of age), blood was obtained from the anterior vena cava for serum E and Se analysis and for red blood cell glutathione peroxidase (RBC GSH-Px) activity determinations. Also, pigs were killed at 5, 10 and 20 weeks of age so that the stomachs could be collected for gastric tissue E, Se and GSH-Px analysis or for cyclooxygenase determination. Given certain analytical preconditions (time,

Table 1. Composition of Basal Ulcerogenic Diet. Trial 1

Ingredient	Percentage
Corn starch	70.70
Soybean meal (.49 protein)	20.00
Corn oil	3.00
Cellulose	3.00
Defluorinated phosphate	2.00
Vitamin-Trace mineral supplement*	.50
Salt	.25
ASP-250 (antibiotic)	.25
Lysine (.78)	.20
D,L-Methionine (.98)	.10
	100.00

* Composition of the Vitamin-Trace mineral supplement.

Nutrient	Amount in 10 kg
Vitamin A as retinyl palmitate	6.6×10^6 IU
Vitamin D_3	1.3×10^6 IU
Choline as choline chloride	220.0 g
Niacin as nicotinic acid	35.2 g
D-Pantothenic acid as calcium pantothenate	26.4 g
Riboflavin	6.6 g
Pyridoxine	6.6 g
Thiamin	6.6 g
Vitamin K as menadione sodium bisulfate	4.4 g
Vitamin B_{12}	39.6 mg
Zinc as zinc oxide	149.6 g
Iron as ferrous sulfate	118.8 g
Manganese as manganous oxide	74.8 g
Copper as copper sulfate	19.8 g
Iodine as potassium iodate	5.5 g
Antioxidant as BHT	99.0 g
Corn starch carrier	the balance of 10 kg

sample size, sample freshness), not all parameters could be measured on all pigs.

Samples of gastric tissue were taken from each of the anatomic regions of the stomach and either analyzed as fresh tissue or frozen for later analysis.

Tissue, Serum Analyses

The procedure for determining tissue and serum selenium levels has been described (Whetter and Ullrey, 1978) as a method modified from the procedure developed by Olson et al., (1975). The procedure for determining tissue and serum vitamin E levels has also been described (Taylor, 1976).

The coupled assay for determination of RBC GSH-Px activity was adapted from that described (Paglia and Valentine, 1967; Brady et al., 1979).

The immunohistochemical assay for the prostaglandin endoperoxide-forming cyclooxygenase was developed by Smith and Wilkin (1977). Cryostat cross sections of each anatomic region of the stomach were analyzed so that specific tissue layers could be accounted for in regard to the presence of the cylooxygenase enzyme.

Characterization of Ulcers and Tissue Sampling

The stomach was incised along the greater curvature, everted and rinsed lightly with water. The entire mucosal surface was examined and the types of lesions were recorded. The classification of gastric ulcers into five groups was based on the following gross characteristics (Muggenburg et al. 1966):

epithelial changes:	rough, corrugated, irregular shape, yellow

subacute ulcer:	rough, regular-oval to linear shape, red, shallow-extending through the mucosa, mild keratinization
chronic ulcer:	rough, regular-oval to round shape, dark red or brown, deep-extending to the muscle layer, extensive keratinization
scar:	stellate to linear shape, distorted, tough

RESULTS AND DISCUSSION

Performance

The addition of E and Se to the basal diet did not affect performance in either trial, as measured by body weight (Tables 2 and 3). Normal growth occurred among pigs in both dietary groups.

Blood Values

Serum levels of E and Se reflected dietary concentrations of those nutrients (Tables 2 and 3). At ten and twenty weeks of age, supplemented pigs in trial I had significantly higher levels of serum E ($P<.0000$). Among pigs fed the basal diet in trial I, serum tocopherol levels decreased from 2.4 mg/ml at five weeks to 1.5 mg/ml at twenty weeks. Among pigs supplemented with E-Se, serum tocopherol levels increased from 2.6 mg/ml at five weeks to 3.7 mg/ml at twenty weeks. At all ages, supplemented pigs in trial II had significantly higher serum tocopherol levels, $P<.0000$; than unsupplemented pigs. Serum tocopherol levels of unsupplemented pigs decreased from 2.0 mg/ml to 1.3 mg/ml to 3.6 mg/ml at five and twenty weeks of age, respectively. Serum selenium levels ranged from .07 ppm at the beginning to .05 ppm at the end of trial I among unsupplemented animals. Similarly, unsupplemented animals in trial II had initial and final serum selenium levels of .07 ppm and .06 ppm respectively. Supplemented animals in both trials had significantly higher serum selenium levels than controls, $P<0001$: ranging from .3 ppm to .19 ppm and from .11 ppm to .20 ppm at five and twenty weeks of age in trial I and trial II, respectively. In light of previous studies, a deficient state might be

characterized by serum values below 1.0 mg/ml tocopherol and .05 ppm selenium. Based on these figures a true E-Se deficient state may not have been accomplished with the BUD used.

At all ages, the addition of E and Se to the basal diet elevated erythrocyte glutathione peroxidase values significantly: Trial I, $P<.02$ and trial II; $P<.003$ (Tables 2 and 3). Among pigs fed the basal diet, RBC-GSH Px levels decreased from 7.0 U/mgHb at five weeks to 5.8 U/mgHb at twenty weeks in trial I. Among pigs in the same trial that were supplemented with E-Se, RBC-GSH Px levels increased from 7.6 U/mgHb at five weeks to 9.3 U/mgHb at twenty weeks. Among animals in the second trial the trends were the same: negative controls fed the basal diet decreased from 6.5 U/mgHb at five weeks to 6.0 U/mgHb at twenty weeks; positive controls supplemented with E-Se increased from 7.4 U/mgHb to 9.1 U/mgHb from five to twenty weeks.

Gastric Tissue

With regard to the Se content of the various anatomic regions of the stomach, a significant response to dietary Se supplementation was demonstrated for each tissue region, at all ages, in both trials. Again, statistical analysis was used to determine if real intraregional differences existed among animals fed common diets. Among animals fed the basal diet in trial I, the Se content of the nonglandular esophageal (NGE) region tended to be less than that of all other regions combined; .059 ppm vs .066 ppm ($P<.09$). Conversely, among animals fed the basal diet supplemented with E-Se in trial I, the Se content of the NGE region tended to be greater than that of all other regions combined; .155 ppm vs .145 ppm ($P<.228$). In trial II, the trend in intraregional selenium

differences continued. Among pigs receiving the basal diet the NGE region of stomachs sampled from these animals had significantly less Se content than all other regions; .057 ppm vs .064 ppm ($P<.048$). Among supplemented pigs, the Se content of the NGE region was significantly greater than that of all other regions combined; .167 ppm vs .146 ppm ($P<.021$; Tables 2 and 3).

The E levels measured in the various tissue regions of the stomach were significantly greater among supplemented pigs than controls at 10 and 20 weeks ($P<.036$) but not at 5 weeks of age in either trial. When the tocopherol level of the NGE region was compared with the tocopherol levels of all other regions, no significant differences were observed ($P<.29$) among unsupplemented animals. When that same comparison was made among supplemented pigs the NGE region had significantly greater tocopherol content than the other regions as a group ($P<.04$). This was the case in both trials (Tables 2 and 3).

With regard to the GSH-Px activity levels of the various anatomic regions of the stomach, a significant response to dietary Se supplementation was demonstrated for each tissue region, at all ages, in both trials ($P<.02$). Statistical analysis (analysis of variance) was applied to these data in order to determine if differences existed between anatomic regions of stomach removed from pigs receiving common diets. In trial I, the only significant intraregional difference occured among gastric tissue from pigs fed the E-Se supplemented diet. The nonglandular esophageal (NGE) region of supplemented pigs had significantly greater GSH-Px activity than all other regions, 2.04 U/g vs 1.88 U/g ($P<.02$). In a similar comparison among pigs in trial II the only significant intraregional

difference occured among pigs fed the basal diet. Again, the NGE region separated itself from all others; tending to have less GSH-Px activity, 1.07 U/g vs 1.20 U/g ($P<.10$; Tables 2 and 3).

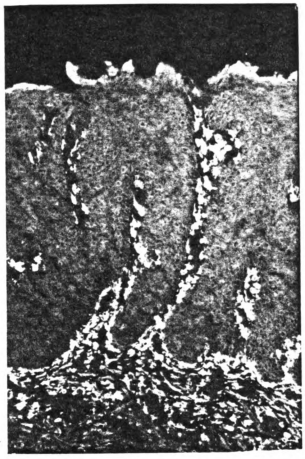
Feed Values

Vitamin E and selenium levels in the BUD ranged from 1.0 to 1.9 mg tocopherol/g feed and from .04 to .09 ppm selenium. Vitamin E and selenium levels in the E-Se supplemented ration ranged from 2.3 to 3.8 mg tocopherol/g feed and from .18 to .26 ppm selenium.

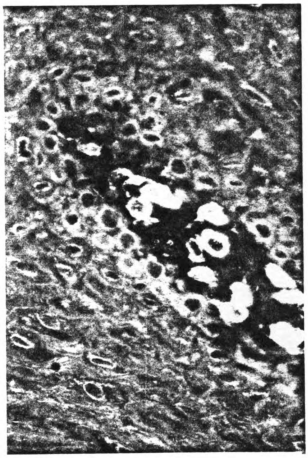
Cyclooxygenase

As an indication of prostaglandin synthesis, the entire stomach was surveyed for the prostaglandin-forming cyclooxygenase. Photographs for this semiquantitative assay were taken of each of the four tissue layers which are common to the different anatomic regions (Photographs 1-8). Fluorescence, in this assay, is an indication of the presence of cyclooxygenase.

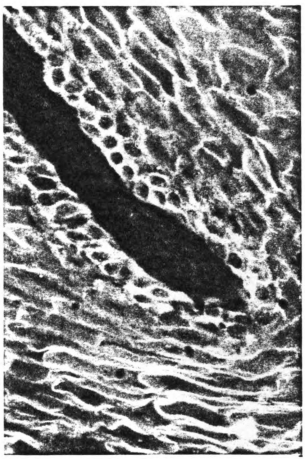
It should be noted that the epithelial layer of the cardiac, fundic and pyloric regions consists of little more than a single layer of cells. The submucosa, muscularis externa and serosa tissue layers of these regions are essentially identical to the esophageal region with respect to specific fluorescent staining and so those photographs are excluded. The occurrence of cyclooxygenase-bearing cells among the various common tissues of the various anatomic regions of the stomach is summarized in Table 4.



Photograph 1. A low power photomicrograph of the mucosal layer of the esophageal region showing the epithelial, lamina propria and muscularis mucosa. There is an abundance of positive staining cells in the lamina propria and an absence of specific staining in the epithelium and muscularis mucosa. The stratified squammous epithelium of the esophageal region is unique among the anatomic regions of the stomach.

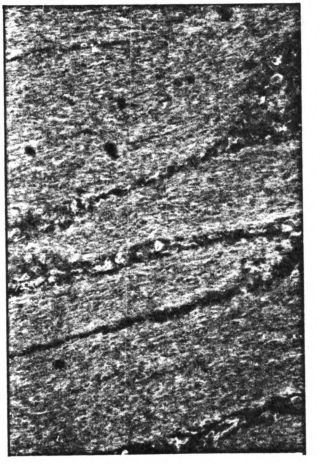


Photograph 2. A high power photomicrograph of the mucosal layer (epithelium and lamina propria) of the esophageal region. Note the perinuclear positive staining in cells of the lamina propria which have been tentatively identified as plasma cells.



Photograph 3. A photomicrograph of the mucosal layer (lamina propria and epithelium) of the esophageal region to which an absorbed antisera was applied. This represents the control used in this immunohistofluorescence assay. Note that the nonspecific staining of the epithelium remains constant (similar to that same tissue to which immune antisera was applied) while cells of the lamina propria do not contain the fluorescent indicator. Only this one photomicrograph of a negative control is included.

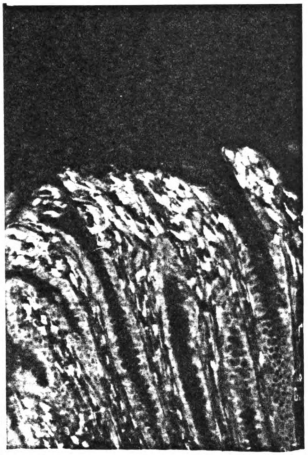
Photograph 4. A photomicrograph of the submucosa of the esophageal region. This tissue layer contains a few positive staining cells which appear to be similar to those of the lamina propria.



Photograph 5. A photomicrograph of the muscularis externa of the esophageal region. This tissue layer, like the muscularis mucosa did not appear to contain cyclo-oxygenase-bearing cells. However, the vasculature within those tissues contained a small population of positive staining cells.

Photograph 6. This photomicrograph of the serosa of the esophageal region depicts a tissue layer without specific positive staining cells.

Photograph 7. A photomicrograph of the mucosa (lamina propria and epithelium) of the fundic region of the porcine stomach. Note the positive staining cells of the lamina propria.



Photograph 8. A photomicrograph of the mucosa (epithelium and lamina propria) of the pyloric region. Note the positive staining cells of the lamina propria.

Gastric Lesions

The stomachs of all pigs were examined for ulcers. Tables 8a and 8b provide a compilation of the gross characterizations of those stomachs. In summary the stomachs of the (35) unsupplemented pigs in the two trials were characterized as follows: 9 normal, 20 preulcerous lesions and 6 ulcers. The stomachs of the 35 supplemented pigs in the two trials were characterized as: 13 normal, 18 preculcerous lesions and 4 ulcers. Among the 25 pigs in trial I maintained on straw bedding from 10 to 20 weeks of age there were 7 normal, 12 preulcerous lesions and 5 ulcers. Among the 24 pigs in trial II maintained on slotted concrete floors from 10 to 20 weeks of age, there were 4 normal, 16 preulcerous lesions and 4 ulcers.

Table 2. Summary of Data. Trial I.

	BUD			BUD + E + Se		
	5 wk	10 wk	20 wk	5 wk	10 wk	20 wk
Body wt (kg)	11.1	22.1	84.2	10.0	19.7	89.3
Serum tocopherol (mg/ml)	2.4	1.9	1.5	2.6	3.4	3.7
Serum Se (ppm)	.07	.06	.05	.13	.17	.19
RBC GSH-Px (U /mg Hb)	7.0	5.7	5.8	7.6	9.3	9.3
Gastric tissue						
tocopherol (mg/g)						
esophageal	.15	.10	.12	.18	.21	.21
gastric	.15	.13	.12	.16	.20	.20
fundic	.16	.12	.11	.15	.18	.19
pyloric	.15	.11	.12	.17	.18	.20
selenium (ppm)						
esophageal	.06	.06	.06	.13	.16	.18
gastric	.08	.06	.06	.11	.14	.17
fundic	.09	.07	.06	.11	.15	.16
pyloric	.07	.05	.05	.15	.15	.18
GSH-Px (U /g prot)						
esophageal	1.0	1.0	0.9	1.9	2.0	2.2
gastric	1.2	0.9	1.0	1.8	1.9	2.0
fundic	1.1	1.2	1.1	1.7	1.9	1.9
pyloric	1.1	1.1	1.0	1.8	1.7	2.0

Table 3. Summary of Data. Trial II.

	BUD			BUD + E + Se		
	5 wk	10 wk	20 wk	5 wk	10 wk	20 wk
Body wt (kg)	9.8	20.0	74.7	9.3	18.0	73.7
Serum tocopherol (mg/ml)	2.0	1.5	1.3	3.1	3.7	3.6
Serum Se (ppm)	.07	.07	.06	.11	.18	.20
RBC GSH-Px (U/mg HB)	6.5	6.2	6.0	7.4	9.0	9.1
Gastric tissue						
tocopherol m g/g)						
esophageal	.10	.11	.10	.18	.21	.24
gastric	.11	.12	.11	.18	.20	.18
fundic	.12	.11	.12	.17	.17	.19
pyloric	.11	.12	.09	.18	.20	.21
selenium (ppm)						
esophageal	.07	.05	.04	.13	.19	.19
gastric	.07	.06	.06	.12	.17	.19
fundic	.08	.06	.06	.11	.15	.17
pyloric	.06	.06	.05	.13	.17	.18
GSH-Px (U/g prot)						
esophageal	1.3	0.8	1.0	1.7	2.2	2.1
gastric	1.3	1.2	1.2	1.7	2.0	2.0
fundic	1.3	1.1	1.1	1.8	1.8	2.0
pyloric	1.5	1.2	0.9	1.5	1.9	2.1

Table 4. Distribution of the PG-Forming Cyclooxygenase in the Porcine Stomach.

	Esophageal	Cardiac	Fundic	Pyloric
Mucosa				
Epithelium	---	--	--	--
Lamina Propria	***	**	**	**
Muscularis Mucosa	*	*	*	*
Submucosa	*	*	*	*
Muscularis Externa	*-	*-	*-	*-
Serosa	--	--	--	--

SUMMARY

Two experiments, involving 70 weanling pigs were conducted to evaluate the effect of vitamin E and selenium on the incidence and severity of gastric ulcers. At weaning (5 weeks of age) pigs were randomly assigned from litters to two dietary groups, namely: a basal ulcerogenic diet (BUD) composed of corn starch, soybean meal and corn oil adequately fortified with minerals and vitamins without selenium and vitamin E; or, the BUD + .2 ppm selenium from sodium selenite + 44 IU of vitamin E/kg from DL-alpha-tocopherylacetate. The effect of E-Se supplementation was assessed on the basis of growth rate, serum levels of tocopherol and selenium, erythrocyte glutathione peroxidase (GSH-Px) activity, gastric tissue selenium, tocopherol, GSH-Px activity and cyclooxygenase, and the incidence of gastric lesions. Data were collected from animals at 5, 10 and 20 weeks of age. The regional distribution of tocopherol, selenium and the enzymes GSH-Px and cyclooxygenase in gastric tissue was determined.

Conclusions:

1. Supplementation of the BUD with E-Se did not affect growth rate in either experiment.
2. Blood data of experimental animals reflected the dietary levels of E-Se such that serum tocopherol, serum selenium and erythrocyte GSH-Px values were significantly greater among supplemented pigs than non supplemented pigs. The conspicuous absence of classical E-Se deficiency signs, accompanied by serum tocopherol and selenium values which are not indicative

of a deficient state, suggests that we failed to induce a deficient negative control group. Serum levels of less than 1.0 mg/ml tocopherol and .05 ppm selenium are indicative of deficiency. In contrast, at 20 weeks of age, serum levels of pigs considered negative controls were 1.4 mg/ml tocopherol and .06 ppm selenium.

3. Tocopherol, Se and GSH-Px analyses of gastric tissue collected from each of the anatomic regions of the stomach correlated significantly with dietary supplementation of the nutrients E-Se. In particular, the tocopherol, selenium and GSH-Px content of the esophageal region appeared to be most sensitive to E-Se "supplementation and depletion". However, since the process of erosion in this area does alter the quality of the tissue, and since it does not occur randomly among anatomic regions, this effect may be artificial. That is, analyzing that esophageal tissue which remains after an erosive process amounts to an analysis of serosa and keratin in contrast to the analysis of normal cardiac, fundic and pyloric tissues.
4. Among all regions of the gastric lumen, and between animals of both dietary groups, the distribution of cyclooxygenase among common tissue layers was similar. Among the tissue layers of all anatomic regions, a relative abundance of the enzyme was present in the

mucosal lamina propria, especially of the esophageal region. If a cyclooxygenase product is cytoprotective of the gastric mucosa, and if the accessibility of that product (likely PGI_2) to the mucosa is a factor contributing to cytoprotection, then, the presence of a greatly thickened esophageal epithelium may be indirectly responsible for regional (esophageal) gastric ulcerogenesis by disallowing the lamina propriae-produced cytoprotective agent acess to the site of effectiveness (the gastric mucosa).

5. The presence of dietary vitamin E and selenium did reduce the number and severity of gastric ulcers and preulcerous lesions. Among the stomachs of 35 unsupplemented pigs in the two trials, there were: 9 normal, 20 preulcerous lesions and 6 ulcers. The stomachs of 35 supplemented pigs were characterized as: 13 normal, 18 preulcerous lesions and 4 ulcers.
6. The ulcerogenic effect of the BUD utilized in this study was reduced in trial I by maintaining the pigs on straw bedding. Pigs in this trial did consume large amounts of straw, however, this straw consumption did not appear to affect E-Se status. This observation lends support to the idea that the physical quality (fineness) of the BUD is the principle ulcerogenic factor and that nutritional status (E-Se) is secondary.

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APPENDIX

Table 1a. Body weight (kg). Trial I.

BUD Pig No.	5 wk	10 wk	20 wk
162-01	12.0	23.0	86.0
162-03	11.0	19.0	80.0
162-07	11.0	23.0	86.0
162-13	8.5	18.0	79.0
167-10	11.5	20.0	83.0
168-11	11.5	25.0	91.0
162-02	11.0	22.0	84.2 ± .04
162-05	10.5	19.0	P<1.0
167-01	12.5	26.0	
168-01	11.5	24.0	
169-10	11.0	25.0	
169-11	10.5	21.0	
162-06	11.5	22.1 ± .11	
162-04	8.5	P<.1170	
162-10	11.5		
162-11	11.5		
167-02	11.5		
168-10	12.5		
	*11.1 ± .37		
	P<.0435		

BUD + E + Se Pig No.	5 wk	10 wk	20 wk
163-01	11.0	23.0	105.0
163-14	12.5	29.0	107.0
169-13	9.0	19.0	86.0
171-03	8.5	17.0	76.0
171-11	7.0	15.0	77.0
171-12	10.5	18.0	85.0
163-10	11.5	21.0	89.3 avg
169-02	11.5	18.0	
169-03	9.5	22.0	
169-04	8.5	12.0	
171-02	9.5	23.0	
171-10	11.5	19.0	
163-11	13.0	19.7 avg	
163-12	12.0		
171-01	6.5		
169-01	8.5		
169-06	8.5		
169-14	10.5		
	10.0		

*At 5 weeks of age, deficient pigs (BUD) weighed more than E-Se supplemented pigs. P<.0435

Table 1b. Body Weight (kg) Trial II.

BUD Pig No.	5 wk	10 wk	20 wk
143-12	12.0	23.0	83.0
143-10	11.5	21.0	70.0
145-01	14.0	28.0	83.0
144-11	13.5	28.0	66.0
146-04	9.0	17.0	74.0
145-04	8.0	16.0	72.0
145-14	9.0	16.0	74.7 ± .27
145-12	13.0	26.0	P<1.0
147-01	10.0	19.0	
144-02	7.5	16.0	
147-05	9.0	16.0	
146-06	5.5	14.0	
144-01	13.0	20.0 ± .13	
146-10	8.0	P<.2604	
143-01	9.0		
146-01	8.0		
146-07	7.5		
	9.8 ± .53		
	P<1.0		

BUD + E + Se Pig No.	5 wk	10 wk	20 wk
146-02	9.0	17.0	71.0
144-04	10.0	18.0	66.0
143-14	11.0	23.0	83.0
146-07	7.5	14.0	71.0
144-12	7.0	14.0	73.0
147-07	8.5	15.0	78.0
146-03	13.0	14.0	73.7
145-11	9.5	23.0	
145-13	9.5	20.0	
145-02	10.5	22.0	
143-03	13.0	17.5	
144-05	7.5	18.0	
146-13	9.5	18.0	
147-04	8.5		
143-11	7.5		
144-03	11.0		
145-03	7.5		
	9.3		

No significant weight differences were observed between treatment groups of any age.

Table 2a. Serum vitamin E (mg/ml). Trial 1.

BUD Pig No.	5 wk	10 wk	20 wk
162-01	1.9	2.4	1.6
162-03	2.5	1.6	1.8
162-07	2.2	1.5	1.2
162-13	3.0	2.1	1.7
167-10	-	2.0	1.8
162-11	1.8	1.7	1.1
162-02	1.8	1.7	1.5 ± .15
162-05	2.7	2.0	P<.0001
167-01	2.6	1.7	
163-01	2.3	2.0	
169-10	2.0	2.2	
169-11	3.0	2.1	
162-06	2.0	1.9 ± .10	
162-14	2.2	P<.0001	
162-10	3.1		
162-11	1.9		
167-02	2.8		
168-10	2.9		
	2.4 ± .11		
	P<.1347		

BUD + E + Se Pig No.	5 wk	10 wk	20 wk
163-01	3.0	3.6	3.7
163-14	3.2	3.4	3.2
169-13	2.1	2.9	3.4
171-03	1.8	2.8	3.5
171-14	2.7	3.7	4.1
171-12	2.8	4.1	4.2
163-10	3.0	4.0	*3.7
169-02	3.4	2.9	
169-03	2.1	3.2	
169-04	2.4	3.6	
171-02	2.4	3.3	
171-10	2.5	3.4	
163-11	2.9	*3.4	
163-12	2.8		
171-01	3.1		
169-01	3.0		
169-06	1.9		
169-14	2.4		
	2.6		

*At 10 and 20 weeks of age, supplemented animals had elevated serum tocopherol levels. P<.0001

Table 2b. Serum vitamin E (ng/ml). Trial II.

BUD Pig No.	5 wk	10 wk	20 wk
143-12	2.3	1.7	1.1
143-10	2.2	1.4	1.1
145-01	1.5	1.2	1.0
144-11	2.1	1.2	1.4
146-04	1.8	2.1	1.6
145-04	1.8	1.8	1.4
145-14	1.8	1.4	1.3 ± .09
145-12	1.3	1.1	P<.0001
147-01	2.0	1.2	
144-02	2.2	1.7	
147-05	1.8	1.3	
146-06	2.5	1.8	
144-01	-	1.5 ± .07	
146-10	2.0	P<.0001	
143-01	-		
146-01	2.2		
146-07	2.0		
	2.0 ± .09		
	P<.0001		

BUD + E + Se Pig No.	5 wk	10 wk	20 wk
146-02	3.5	3.9	3.7
144-04	2.9	3.3	4.1
143-14	2.7	3.0	3.5
146-07	3.2	3.6	2.9
144-12	4.4	4.3	3.7
147-07	3.3	3.7	-
146-03	2.4	3.3	*3.6
145-11	2.8	4.1	
145-13	2.3	4.3	
145-02	3.3	3.4	
143-02	3.0	3.7	
144-05	2.5	3.8	
146-13	4.6	*3.7	
147-04	2.9		
143-11	2.3		
144-03	3.7		
145-03	3.2		
	*3.1		

*At all ages, supplemented animals had elevated serum tocopherol. P<.0001

Table 3a. Serum selenium (ppm). Trial I.

BUD

Pig No.	5 wk	10 wk	20 wk
162-01	.07	.06	.05
162-03	.08	.06	.06
162-07	.09	.05	.05
162-13	.08	.05	.04
167-10	-	.07	.06
162-11	.06	.05	.06
162-02	.05	.07	.05 ± .004
162-05	.05	.08	P<.0001
167-01	.06	.06	
163-01	.09	.06	
169-10	.06	.07	
169-11	.10	.08	
160-06	.05	.06 ± .003	
162-14	.07	P<.0001	
162-10	.07		
162-11	.07		
167-02	.08		
168-10	.08		
	.07 ± .003		
	P<.0001		

BUD + E + Se

Pig No.	5 wk	10 wk	20 wk
163-01	.12	.19	.19
163-14	.13	.17	.18
169-13	.11	.18	.20
171-03	.12	.17	.19
171-14	.12	.16	.18
171-12	.10	.17	.22
163-10	.14	.16	*.19
169-02	.16	.15	
169-03	.11	.18	
169-04	.12	.17	
171-02	.13	.21	
171-10	.13	.17	
163-11	.14	*.17	
163-12	.12		
171-01	.11		
169-01	.15		
169-06	.15		
169-14	.15		
	*.13		

*At all ages, supplemented animsls had elevated serum selenium levels. P<.0001

Table 3b. Serum selenium (ppm). Trial II

BUD Pig No.	5 wk	10 wk	20 wk
143-12	.07	.07	.07
143-10	.06	.06	.06
145-01	.08	.07	.06
144-11	.05	.07	.05
146-04	.10	.09	.07
145-04	.07	.06	.06
145-14	.09	.08	.06 ± .005
145-12	.09	.09	P<.0001
147-01	.07	.07	
144-02	.10	.08	
147-05	.05	.07	
146-06	.06	.05	
144-01	-	.07 ± .003	
146-10	.04	P<.0001	
143-01	-		
146-01	.08		
146-07	.08		
	.07 ± .003		
	P<.0001		

BUD + E + Se Pig No.	5 wk	10 wk	20 wk
146-02	.07	.15	.16
144-04	.10	.16	.19
143-14	.13	.19	.22
146-07	.11	.19	.21
144-12	.06	.18	.19
147-17	.12	.16	-
146-03	.13	.19	*.20
145-11	.12	.19	
145-13	.14	.21	
145.02	.11	.17	
143-02	.09	.19	
144-05	.10	.20	
146-13	.12	*.18	
147-04	.12		
143-11	.14		
144-03	.13		
145-03	.09		
	*.11		

*At all ages, supplemented animals had elevated serum selenium levels. P<.0001

Table 4a. Red blood cell glutathione peroxidase (u/mg Hb). Trial I.

BUD Pig No.	5 wk	10 wk	20 wk
162-01	7.0	7.0	6.0
162-03	6.5	6.0	-
162-07	6.0	6.5	6.0
162-13	5.0	5.5	6.5
167-10	7.0	6.5	5.5
168-11	7.5	6.0	5.0
162-02	6.5	6.0	5.8 ± .21
162-05	8.0	5.0	P<.0001
167-01	7.5	5.5	
168-01	8.0	5.0	
169-10	6.5	4.5	
169-11	7.0	5.0	
162-06	6.0	5.8 ± .31	
162-04	8.0	P<.0001	
162-10	-		
162-11	7.5		
167-02	-		
168-10	7.0		
	7.0 ± .17		
	P<.0124		

BUD + E + Se Pig No.	5 wk	10 wk	20 wk
163-01	7.0	8.5	8.5
163-14	8.5	9.0	9.5
169-13	-	10.0	9.5
171-03	6.5	8.5	9.0
171-11	7.0	-	10.0
171-12	8.0	5.5	9.5
163-10	7.0	8.0	*9.3
169-02	6.5	9.5	
169-03	8.5	10.0	
169-04	8.0	11.0	
171-02	8.0	11.5	
171-10	7.0	10.0	
163-11	8.0	*9.3	
163-12	8.5		
171-01	7.5		
169-01	7.5		
169-06	7.0		
169-14	8.0		
	*7.6		

*At all ages, supplemented animals had elevated levels of GSH-Px (P<.02)

Table 4b. Red blood cell glutathione peroxidase activity (U/mg Hb). Trial II

BUD Pig No.	5 wk	10 wk	20 wk
143-12	-	6.0	5.5
143-10	7.5	6.5	-
145-01	6.0	6.5	6.0
144-11	7.0	7.0	6.5
146-04	9.0	6.5	6.0
145-04	7.5	7.0	6.0
145-14	6.0	6.5	6.0 ± .27
145-12	6.5	6.0	P<.0001
147-01	5.0	5.0	
144-02	7.0	5.5	
147-05	6.0	5.0	
146-06	6.5	-	
144-01	-	6.2 ± .24	
146-10	7.0	P<.0001	
143-01	5.5		
146-01	6.0		
146-07	6.0		
	6.5 ± .20		
	P<.0026		

BUD + E + Se Pig No.	5 wk	10 wk	20 wk
146-02	-	-	8.5
144-04	8.5	8.5	8.0
143-14	8.0	-	10.5
146-07	8.0	-	9.0
144-12	6.0	6.5	9.0
147-07	6.5	8.5	9.5
146-03	7.5	9.5	*9.1
145-11	8.0	10.0	
145-13	9.0	10.5	
145-02	8.5	8.5	
143-02	8.0	10.5	
144-05	7.0	8.5	
146-13	7.5	*9.0	
147-04	6.5		
143-11	6.5		
144-03	6.5		
145-03	6.0		
	*7.4		

*At all ages, supplemented animals had elevated levels of GSH-Px activity. P<.003.

Table 5a. Stomach tissue vitamin E (mg/g). Nonglandular esophageal (NGE), Gastric (G), Fundic (F) and Pyloric (P) regions. Trial I.

BUD Pig No.	5 wk NGE	G	F	P	10 wk NGE	G	F	P	20 wk NGE	G	F	P
162-01									.17	.07	.15	.14
162-03									.09	.10	.08	.10
162-07									.14	.14	.07	.12
162-13									.10	.19	.14	.13
167-10									-	-	-	-
162-11									-	-	-	-
162-02					.12	.11	.16	.11	$\bar{x}$ .12	.12	.11	.12
162-05					.11	.18	.09	.09	SE .01	.01	.01	.01
167-01					.08	.14	.11	.10	P< .0004	.0133	.0002	.0/
163-01					.11	.09	.10	.13				
169-10					-	-	-	-				
169-11					-	-	-	-				
162-06	.08	.09	.16	.15	$\bar{x}$ .10	.13	.12	.11				
162-14	.17	.15	.12	.14	SE .01	.02	.08	.01				
162-10	.14	.20	.22	.16	P< .0001	.0356	.0013	.0001				
162-11	.22	.16	-	.16								
167-02	-	-	-	-								
168-10	-	-	-	-								
$\bar{x}$	.15	.15	.16	.15								
SE	.02	.01	.02	.01								
P<	.1925	1.0	1.0	1.0								

Table 5b. Stomach tissue vitamin E (mg/g). Nonglandular esophageal (NGE), Gastric (G), Fundic (F), and Pyloric (P) regions. Trial I.

BUD + E + Se	5 wk				10 wk				20 wk			
Pig No.	NGE	G	F	P	NGE	G	F	P	NGE	G	F	P
163-01									.19	.16	.17	.21
163-14									.20	.21	.19	.16
169-13									.28	.23	.20	.23
171-03									.19	.17	.21	.19
171-11									-	-	-	-
171-12									-	-	-	-
163-10					.26	.20	.19	.16	$\bar{x}$ .21	.20	.19	.20
169-02					.21	.15	.14	.20				
169-03					.22	.24	.21	.19				
169-04					.17	.20	.16	.18				
171-02					-	-	-	-				
171-10					-	-	-	-				
163-11	.11	.11	.07	.08	$\bar{x}$ .21	.20	.18	.18				
163-12	.18	.16	.13	.21								
171-01	.24	.19	.21	.20								
169-01	.21	.20	.17	.17								
169-06	-	-	-	-								
169-14	-	-	-	-								
	$\bar{x}$ .18	.16	.15	.17								

Table 5c. Stomach tissue vitamin E (mg/g). Nonglandular esophageal (NGE), Gastric (G), Fundic (F), and Pyloric (P) regions. Trial II.

BUD	5 wk				10 wk				20 wk			
Pig No	NGE	G	F	P	NGE	G	F	P	NGE	G	F	P
143-12									.06	.12	.16	.11
143-10									.10	.09	.11	.14
145-01									.08	.10	.11	.08
144-11									.14	.13	.09	.05
146-04									-	-	-	-
145-04									-	-	-	-
145-14					.17	.15	.15	.17	$\bar{x}$ .10	.11	.12	.09
145-12					.10	.14	.11	.08	SE .01	.00	.01	.01
147-01					.06	.09	.10	.08	P< .001	.001	.001	.001
144-02					.09	.09	.08	.13				
147-05					-	-	-	-				
146-06					-	-	-	-				
144-01	.07	.11	.12	.13	$\bar{x}$ .11	.12	.11	.12				
146-10	.08	.06	-	.09	SE .02	.01	.01	.01				
143-01	.16	.15	.12	.10	P< .0112	.0087	.0096	.008				
146-01	-	-	-	-								
146-07	-	-	-	-								
$\bar{x}$	.10	.11	.12	.11								
SE	.02	.009	.01	.01								
P<	.0075	.0011	.0031	.0004								

Table 5d. Stomach tissue vitamin E (mg/g). Nonglandular esophageal (NGE), Gastric (G), Fundic (F), and Pyloric (P) regions.

BUD + E + Se	5 wk				10 wk				20 wk			
Pig No.	NGE	G	F	P	NGE	G	F	P	NGE	G	F	P
146-02									.32	.19	.23	.21
144-04									.24	.18	.19	.21
143-14									.21	.19	.17	.26
146-07									.20	.18	.19	.17
144-12									-	-	-	-
147-07									-	-	-	-
146-03					.19	.20	.14	.17	$\bar{x}$ .24	.18	.19	.21
145-11					.21	.20	.25	.26				
145-13					.29	.25	.16	.20				
145-02					.15	.14	.12	.17				
143-03					-	-	-	-				
144-05					-	-	-	-				
146-13	.13	.14	.13	.15	$\bar{x}$ .21	.20	.17	.20				
147-04	.25	.20	.19	.17								
143-11	.20	.17	.21	.21								
144-03	-	-	-	-								
145-03	-	-	-	-								
	$\bar{x}$ .18*	.18	.17	.18								

Table 6a. Stomach tissue selenium (ppm). Nonglandualr esophageal (NGE), Gstric (G), Fundic (F), and Pyloric (P) regions. Trial I.

BUD Pig No.	5 wk NGE	G	F	P	10 wk NGE	G	F	P	20 wk NGE	G	F	P
162-01									.05	.07	.06	.06
162-03									.08	.06	.07	.04
162-07									.06	.06	.07	.06
162-13									.04	.04	.05	.05
167-10									-	-	-	-
162-11									-	-	-	-
162-02					.05	.06	.07	.08				
162-05					.08	.09	.06	.04				
167-01					.04	.05	.07	.05				
163-01					.06	.06	.09	.05				
169-10					-	-	-	-				
169-11					-	-	-	-				
162-06	.06	.06	.06	.09								
162-14	.08	.09	.10	.06								
162-10	.06	.07	.08	.07								
162-11	.05	.06	.09	.07								
167-02	-	-	-	-								
168-10	-	-	-	-								

	5 wk NGE	G	F	P	10 wk NGE	G	F	P	20 wk NGE	G	F	P
$\bar{x}$	.06	.08	.09	.07	.06	.06	.07	.05	.06	.06	.06	.05
SE	.001	.01	.01	.00	.01	.01	.01	.01	.01	.01	.01	.01
P<	.001	.063	.011	.001	.001	.0001	.0001	.01	.01	.01	.01	.01

Table 6b. Stomach tissue selenium (ppm). Nonglandular esophageal (NGE), Gastric (G), Fundic (F), and Pyloric (P) regions. Trial I.

BUD + E + Se	5 wk				10 wk				20 wk			
Pig No.	NGE	G	F	P	NGE	G	F	P	NGE	G	F	P
163-01									.21	.21	.20	.18
163-14									.17	.14	.11	.16
169-13									.16	.17	.17	.18
171-03									.19	.16	.15	.18
171-11									-	-	-	-
171-12									-	-	-	-
163-10					.12	.13	.12	.14				
169-02					.16	.11	.15	.14				
169-03					.20	.18	.16	.16				
169-04					.15	.12	.19	.14				
171-02					-	-	-	-				
171-10					-	-	-	-				
163-11	.11	.09	.10	.12								
163-12	.12	.10	.11	.10								
171-01	.14	.14	.14	.12								
169-01	.13	.11	.11	.14								
169-06	-	-	-	-								
169-14	-	-	-	-								
$\bar{x}$	.13	.11	.11	.12	$\bar{x}$ .16	.14	.15	.15	$\bar{x}$ .18	.17	.16	.18

Table 6c. Stomach tissue selenium (ppm). Nonglandular esophageal (NGE), Gastric (G), Fundic (F), and Pyloric (P) regions. Trial II.

BUD Pig No.	5 wk NGE	5 wk G	5 wk F	5 wk P	10 wk NGE	10 wk G	10 wk F	10 wk P	20 wk NGE	20 wk G	20 wk F	20 wk P
143-12									.03	.04	.06	.07
143-10									.04	.06	.07	.04
145-10									.06	.06	.05	.05
144-11									.03	.06	.06	.05
146-04									-	-	-	-
145-04									-	-	-	-
145-14					.06	.05	.04	.06	$\bar{x}$ .04	.06	.06	.05
145-12					.05	.07	.07	.07	SE .01	.01	.01	.01
147-01					.07	.06	.08	.06	P< .01	.01	.01	.01
144-02					.04	.06	.06	.05				
147-05					-	-	-	-				
146-06					-	-	-	-				
144-01	.05	.07	.07	.05	$\bar{x}$ .05	.06	.06	.06				
146-10	.07	.06	.10	.09	SE .01	.01	.01	.01				
143-01	.07	.08	.08	.04	P< .01	.01	.01	.01				
146-01	-	-	-	-								
146-07	-	-	-	-								
$\bar{x}$	.07	.07	.08	.06								
SE	.01	.01	.01	.01								
P<	.0001	.0006	.0003	.01								

Table 6d. Stomach tissue selenium (ppm). Nonglandular esophageal (NGE), Gastric (G), Fundic (F), and Pyloric (P) regions. Trial II.

BUD + E + Se	5 wk				10 wk				20 wk			
Pig No.	NGE	G	F	P	NGE	G	F	P	NGE	G	F	P
146-02									.17	.16	.18	.21
144-04									.20	.19	.17	.17
143-14									.19	.21	.20	.16
146-07									.21	.20	.14	.18
144-12									-	-	-	-
147-07									-	-	-	-
146-03					.17	.16	.18	.17	$\bar{x}$ .19	.19	.17	.18
145-11					.18	.21	.15	.15				
145-13					.19	.17	.14	.16				
145-02					.21	.16	.15	.19				
143-03					-	-	-	-				
144-05					-	-	-	-				
146-13	.10	.11	.14	.14	$\bar{x}$ .19	.17	.15	.17				
147-04	.16	.12	.06	.10								
143-11	.13	.17	.11	.11								
144-03	-	-	-	-								
145-03	-	-	-	-								
	$\bar{x}$ .13	.12	.11	.13								

Table 7a. Stomach tissue GSH-Px (U./g). Nonglandular esophageal (NGE), Gastric (G), Fundic (F), and Pyloric (P) regions. Trial I.

BUD Pig No.	NGE	G	F	P		NGE	G	F	P		NGE	G	F	P
162-01											0.7	0.6	0.9	0.8
162-03											1.0	1.2	1.1	1.0
162-07											1.3	1.1	1.1	1.0
162-13											0.5	1.4	1.2	1.2
167-10											-	-	-	-
168-11											-	-	-	-
162-02						0.9	0.9	1.4	1.1	$\bar{x}$	0.9	1.0	1.1	1.0
162-05						1.0	1.2	0.9	1.4	SE	.09	.13	.06	.09
167-01						1.1	0.6	1.2	0.8	P<	.0001	.0027	.01	.0002
168-01						1.2	1.1	1.4	1.1					
169-10						-	-	-	-					
169-11						-	-	-	-					
162-06	1.0	1.0	1.2	1.4	$\bar{x}$	1.0	0.9	1.2	1.1					
162-04	0.9	1.3	1.1	0.8	SE	.06	.05	.06	.08					
162-10	1.4	1.2	1.2	1.2	P<	.01	.01	.001	.0001					
162-11	0.9	1.3	1.0	1.0										
167-02	-	-	-	-										
168-10	-	-	-	-										
$\bar{x}$	1.0	1.2	1.1	1.1										
SE	.08	.05	.05	.07										
P<	.0004	.0004	.0002	.0003										

Table 7b. Stomach tissue GSH-Px (U./g). Nonglandular esophageal (NGE), Gastric (G), Fundic (F), and Pyloric (P) regions. Trial I.

BUD + E + Se	5 wk				10 wk				20 wk			
Pig No.	NGE	G	F	P	NGE	G	F	P	NGE	G	F	P
163-01									2.8	1.7	2.1	2.3
163-14									2.0	2.2	2.1	2.5
169-13									2.1	2.0	1.5	1.7
171-03									1.9	2.1	2.0	1.7
171-11									-	-	-	-
171-12									-	-	-	-
163-10					2.1	1.8	1.4	2.0	$\bar{x}$ 2.2	2.0	1.9	2.0
169-02					2.2	1.9	2.1	1.2				
169-03					1.7	2.1	2.1	2.1				
169-04					2.3	1.7	1.7	1.4				
171-02					-	-	-	-				
171-10					-	-	-	-				
163-11	1.8	1.7	2.0	1.8	$\bar{x}$ 2.0	1.9	1.9	1.7				
163-12	2.2	1.6	1.7	1.7								
171-01	1.5	1.6	1.6	2.2								
169-01	1.9	2.1	1.5	1.6								
169-06	-	-	-	-								
169-14	-	-	-	-								
$\bar{x}$	1.9	1.8	1.7	1.8								

Table 7c. Stomach tissue GSH-Px (U/g). Nonglandular esophageal (NGE), Gastric (G), Fundic (F) and Pyloric (P) regions. Trial II.

	5 wk				10 wk				20 wk			
BUD Pig No.	NGE	G	F	P	NGE	G	F	P	NGE	G	F	P
143-12									0.7	1.0	0.9	0.9
143-10									1.1	1.8	1.0	0.9
145-01									1.2	1.1	1.4	0.8
144-11									0.9	1.0	1.1	1.2
146-04									-	-	-	-
145-04									-	-	-	-
145-14					1.0	1.2	1.3	1.3	$\bar{x}$ 1.0	1.2	1.1	0.9
145-12					0.9	1.3	1.1	1.5	SE .15	.09	.08	.09
147-01					-	1.2	1.1	1.4	P< .0007	.0002	.0001	.0001
144-02					0.5	0.9	1.0	0.7				
147-05					-	-	-	-				
146-06					-	-	-	-				
144-01	1.1	1.0	1.3	1.0	$\bar{x}$ 0.8	1.2	1.1	1.2				
146-10	1.6	1.3	1.6	1.5	SE .07	.07	.07	.12				
143-01	1.3	1.7	0.9	1.9	P< .01	.01	.001	.0056				
146-01	-	-	-	-								
146-07	-	-	-	-								
$\bar{x}$	1.3	1.3	1.3	1.5								
SE	.06	.06	.07	.11								
P<	.0135	.0193	.0083	.2589								

Table 7d. Stomach tissue GSH-Px (U/g). Nonglandular esophageal (NGE), Gastric (G), Fundic (F), and Pyloric (P) regions. Trial II.

BUD + E + Se	5 wks				10 wks				20 wks			
Pig No.	NGE	G	F	P	NGE	G	F	P	NGE	G	F	P
146-02									2.5	1.7	1.9	2.0
144-04									1.9	1.5	2.1	1.7
143-14									2.3	2.6	2.5	2.7
146-07									1.7	2.3	1.7	2.1
144-12									-	-	-	-
147-07									-	-	-	-
146-03									-	-	-	-
145-11					2.1	2.0	1.9	1.8				
145-13					2.6	2.3	2.1	2.4				
145-02					2.1	1.9	2.2	2.1				
143-03					1.9	1.7	1.2	1.4				
144-05					-	-	-	-				
146-13	1.7	1.6	2.1	1.8								
147-04	1.4	1.5	1.8	1.5								
143-11	2.0	1.9	1.4	1.1								
144-03	-	-	-	-								
145-03	-	-	-	-								
$\bar{x}$	1.7	1.7	1.8	1.5	2.2	2.0	1.8	1.9	2.1	2.0	2.0	2.1

Table 8a. Gross characterization of stomach surface (mucosa). Trial I.

BUD Pig No.		BUD + E + Se Pig No	
5 wks		5 wks	
162-06	epithelial change	163-11	epithelial change
162-04	normal	163-12	normal
162-10	normal	171-01	epithelial change
162-11	epithelial change	169-01	epithelial change
167-02	epithelial change	169-06	normal
168-10	epithelial change	169-14	normal
10 wks		10 wks	
162-02	subacute ulcer	163-10	acute erosion
162-05	epithelial change	169-02	subacute ulcer
167-01	acute erosion	169-03	acute erosion
168-01	acute erosion	169-04	epithelial change
169-10	subacute ulcer	171-02	acute erosion
169-11	subacute ulcer	171-10	normal
20 wks		20 wks	
162-01	normal	163-01	epithelial change
162-03	acute erosion	163-14	normal
162-07	subacute ulcer	169-13	normal
162-13	normal	171-03	acute erosion
167-10	normal	171-11	acute erosion
168-11	acute erosion	171-12	normal

Table 8b. Gross characterization of stomach surface (mucosa). Trial II.

BUD Pig No.		BUD + E + Se Pig No.	
5 wks		5 wks	
144-01	normal	146-13	normal
146-10	epithelial change	147-04	acute erosion
143-01	normal	143-11	subacute ulcer
146-01	normal	144-03	normal
146-07	epithelial change	145-03	normal
10 wks		10 wks	
145-14	epithelial change	146-03	acute erosion
145-12	normal	145-11	acute erosion
147-01	epithelial change	145-13	normal
144-02	subacute erosion	145-02	epithelial change
147-05	epithelial change	143-03	epithelial change
146-06	acute erosion	144-05	normal
20 wks		20 wks	
143-12	acute erosion	146-02	normal
143-10	epithelial change	144-04	chronic ulcer
145-01	acute erosion	143-14	epithelial change
144-11	subacute ulcer	146-07	chronic ulcer
146-04	epithelial change	144-12	acute erosion
145-01	chronic ulcer	147-07	epithelial change

Vita

The author was born in Lansing, Michigan on July 17, 1953. Graduating from Lansing Waverly High School in 1971 the author enrolled at Kalamazoo College, a private liberal arts college, in Kalamazoo, Michigan. While at Kalamazoo College, he had the opportunity to spend time at Michigan State University in East Lansing, Michigan, at the Upjohn Company in Kalamazoo, Michigan and at L'universite' de Caen in Caen, France. In 1975 the author graduated from Kalamazoo College and returned to Michigan State University to enter graduate school in the Department of Animal Husbandry. The author obtained the degree of Master of Science from that department in 1977 and is currently pursuing the degree of Doctor of Philosophy from that department in conjunction with the Michigan State University Institute of Nutrition.

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