EFFECT OF HYPOGLYCEMIC COMPOUNDS UPON FATTENING SWINE

by

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INTRODUCTION

Swine and swine products have been closely associated with the affairs of man since the earliest development of human society. As this society developed, it became increasingly dependent upon the domestication of the forerunners of our modern day swine for food, warmth, and other necessities in the home. Consequently, this dependency became more acute and man began to realize the importance of attempting to improve the productivity of the pig. This increased productivity was sought in the forms of increased growth rate and was enhanced largely through breeding, feeding, and management.

During the past several decades, improvement in efficiency of livestock and its increased suitability to man's needs have been truly remarkable. However, the livestock industry is constantly striving to improve the knowledge, abilities, and skills of efficiency and productiveness per unit of feed. The advent of superior applied and basic research, since World War II, has had an affirmative and advantageous effect upon these goals.

Unlike the ruminant animals, swine are, for the most part, incapable of utilizing large percentages of roughage in their diet. Consequently, they are dependent upon a high energy concentrate ration consisting of carbohydrates, fats, and proteins. The attempt to improve the growth rate and feed efficiency of swine by altering the anabolic and catabolic rate of these compounds relentlessly continues under the administration of various types of hormones and feed additives such as thyroxine, synthetic and purified estrogens, androgens, progestogens,

growth hormones, arsenic compounds, and enzymes. Favorable results have been obtained in many cases with ruminants and, in a few instances, with swine.

Recently, several workers indicated an interest in the hormonal protein insulin as a growth stimulant. Successful results have been shown with rats and other species of animals including mice, dogs, and pigs.

The studies in these experiments were designed to investigate the effects of feeding oral hypoglycemic compounds and injecting protamine zinc insulin into swine. The objectives of the experiment were as follows: (1) to investigate the oral hypoglycemic compound Diabenese, (chloropropamide), and Dymelor, (acetohexamide), and subcutaneous and intramuscular injections of protamine zinc insulin and their effects on blood glucose and urea levels of fattening swine; and (2) to determine what effect protamine zinc insulin, given intramuscularly and subcutaneously, will have on growth rate, feed intake, feed efficiency, average daily gain, and backfat thickness of both heavy and lighterweight fattening swine.

REVIEW OF LITERATURE

History of Insulin

The name insuline was suggested by de Meyer (1909) for the hypothetical internal secretion of the pancreas, the search for which had been stimulated by von Mering's and Minkowski's findings (1889). Banting and Best (1922) were the first to obtain a preparation containing the

antidiabetic hormone in a form which constantly alleviated all signs of diabetes in completely depancreatized dogs. He'don (1927) and Scott (1934) also obtained very suggestive results pertaining to curtailment of diabetes.

For many years, insulin was thought to be composed of four chains of amino acids made up of two pairs of identical chains with a molecular weight of 12,000. In 1954, the first complete description of the insulin molecule was achieved by the English biochemist Frederick Sanger and a small group of workers at Cambridge University (Sanger, 1959; and Thompson, 1955). By utilizing hydrolysis, techniques, labeling the end amino acid in a peptide, chromotography, and electrophoresis, they were able, in 10 years of study, to develop and describe the entire insulin molecule. Sanger showed that the compound is protein in nature and consists of two chains of amino acids instead of two pairs of chains. One chain, (glycine chain), is made up of 21 amino acids, while the second chain, (phenylalanine chain), is composed of 30 amino acids. Two disulfide linkages connect the chains while 17 different amino acids make up the entire molecule.

Other workers have verified Sangers findings and have acknowledged that the insulin molecule is built up entirely, or almost entirely, of amino acids. They found it to be richer in the amino acids leucine, glutamic acid, and cystine than most other proteins. Methionine, tryptophane, and hydroxy-proline, common to many proteins, are completely absent in the insulin molecule.

The insulin obtained from various species appears to be identical on the basis of immunological tests, thus indicating a lack of species

specificity for this hormone (Wasserman and Mirsky, 1942). Structural differences, however, appear to exist between the insulin obtained from several species of fish and that isolated from beef (Wilson and Dixon, 1961).

The Source of Insulin

In the mammal, the pancreas appears to be the only organ manufacturing or storing insulin in more than minute amounts. This feat is accomplished in the region of the Islets of Langerhans. Several workers have proven that this hormone is produced and stored in the beta cells. Best and Taylor (1961) summarized their main points of evidence as follows: (1) The islets are glandular structures; an obvious outlet for the secretion of insulin into the blood stream. (2) Tumors of the islet cells will form in cases of hyperinsulinism. However, when these are removed the blood sugar content is maintained at higher levels. (3) The injection of anterior pituitary extracts leads to destructive changes in the islet cells, chiefly in the beta cells, while there is little or no effect on the alpha cells. (4) Alloxan and other chemical substances destroy the islet cells leaving the other cells essentially intact with an increase in blood glucose concentration. (5) When approximately nine-tenths of the pancreas was removed from a dog, characteristic glycogen lesions were noted in the beta cells of the remnant, however, the administration of insulin eliminated these lesions.

The pancreases from a number of dogs treated with diabetogenic materials have been assayed for their insulin content and the values

obtained were roughly proportional to the concentration of granules in the beta cells as determined by the histological studies of these tissues (Best and Taylor, 1961). Hartroft and Wrenshall (1955) suggested that a good agreement between the amount of extractable insulin and the size and number of granules in the beta cells of the human pancreas are also obtainable.

Regulation or Liberation of Insulin Secretion

The arrangement of the capillary loops about the islet cells and the reported scarcity of the lymph channels provide morphological evidence in favor of the capillary blood stream as the pathway by which insulin reaches the systemic circulation (Best and Taylor, 1961).

Many experiments support the conclusion that the level of blood sugar is an important factor in the regulation of insulin liberation. The major control of insulin secretion is executed by a feedback effect of the blood glucose level directly on the pancreas (Ganong, 1965). The production of hyperglycemia, glycogen infiltration of the beta cells of the islets, and permanent diabetes by the intraperitoneal administration of glucose (Lukens and Dohan, 1938), suggests an overstimulation of the pancreatic islets by the raised blood sugar level.

Obdyke et al. (1942) indicated that a linear relation between the hypoglycemic action of insulin and the logarithm of the dose of insulin definitely exists in chicks. Preparations other than intact animals such as hypophysectomized-adrendemedullated-alloxan diabetic rats have been used in assays to increase the sensitivity of animals to insulin.

These animal preparations were sensitive to insulin doses of 0.001-1 I.U./100 gm. body weight. The results, according to Vallance-Owen (1954), indicate a variation in blood hormone content dependent upon the dietary state of the species and test animal preparation used for the assay. However, such studies have shown that a rise in blood insulin levels occurs after glucose administration. Though glucose does increase the circulating level of insulin, Brown et al. (1952) and Vallence-Owen (1960) have shown that only a major change in blood sugar concentration seems able to stimulate pancreatic activity, and some mechanism other than glucose level may be responsible for insulin release.

Among the six carbon sugars, Ganong (1965) has indicated that glucose and mannose will stimulate insulin secretion. Fructose has a moderate stimulating effect. Galactose and the five carbon sugars D-xylose and L-arabinose do not stimulate the secretion of insulin. Neither do a variety of citric acid cycle intermediates and non-metabolizable sugars.

Experimental evidence also indicates the possibility that a decrease in the rate of discharge of sugar from the liver may also be produced when the blood sugar level is raised (Best and Taylor, 1961). The injection of small amounts of glucose into the artery supplying a pancreas grafted into the neck of a depancreatized dog or into the pancreatic artery in a decerebrate cat causes a prompt lowering of the blood sugar. This latter case was not obtained when the splenic or portal vein was used.

According to Ganong (1961) and others, additional stimuli also have an effect on the liberation of insulin from the pancreas.

Tolbutamide and other sulfonylurea derivatives such as chloropropamide will lower the blood glucose level when the pancreas is present by stimulating insulin secretion. Induced islet cell hypergranulation and hyperplasia occurs when these compounds are administered over prolonged periods of time. The effect of exogenous administration of inculin to normal animals induces the insulin content of the pancreas to drop, but when the treatment is stopped, the beta cells are hypersensitive, as if they had been "rested."

Genuth et al. (1965) observed that corticotropin administration yielded a five to ten fold increase in plasma insulin levels accompanied by a decrease in blood sugar and an increase in blood ketones. The rise in insulin levels was due to pancreatic secretion increases in the plasma insulin levels and was a result of direct stimulus of pancreatic insulin release. These workers confirmed the above results when they incubated mouse pancreases in a medium with 10 ug./ml. of corticotropin and successfully affirmed a twofold increase of insulin secretion when compared to the controls.

Mechanism of Action of Insulin

The biologic activity of insulin seems to be a function of the whole molecule rather than being attributable to specific groupings within it (Turner, 1961). Potency is lost even after slight alterations in molecular structure such as reductions of the disulfide linkages, treatment with alkali, proteolytic enzymes, or acid hydrolysis. No satisfactory method has yet been found to protect insulin from

hydrolysis in the alimentary tract, consequently, it must be administered by injection.

Mirsky (1956), Mirsky et al. (1956), and Mirsky (1957) have shown that insulin is rapidly degraded in the liver by an enzyme system, insulinase, which is relatively specific in catalyzing the hydrolysis of this hormone. This system contains a factor that can competitively inhibit the action of insulin both in vitro and in vivo commonly referred to as the "insulinase inhibitor." Hendley et al. (1957), Madison et al. (1958), and Skom et al. (1958) observed that the effectiveness of insulin depends on the balance between these two principles, the binding of insulin to circulatory protein, and various factors that compete with or antagonize the action of the hormone at the cellular level.

The site of action of insulin will vary in different tissues. It has been found that insulin becomes firmly bound to certain target tissues (Haugard et al., 1954 and Lee et al., 1959) while not on others. Stadie (1957) in his experiments with rats, suggested that in peripheral tissue, such as the rat diaphragm, the exposure or binding of insulin for as little as 10 minutes produced an increased glucose uptake; whereas insulin action in the liver and adipose tissue was much slower.

Rafaelson et al. (1965) stated that the insulin binding effect of the apididymal adipose tissue and rat diaphragm muscle supported the hypothesis of the importance of insulin binding to tissues as a factor controlling the responsiveness of individual tissues to insulin.

Two important events must occur before glucose can be utilized

for energy production, fat synthesis and glycogen synthesis. It must first enter the cell and then be phosphorylated to glucose-6-phosphate by adenosine tri-phosphate in the presence of hexokinase. Because the various metabolic pathways diverge at glucose-6-phosphate, most hypotheses have assumed that insulin acts at, or prior to, the formation of this compound (Stetton et al. 1955).

The exact mechanism of the utilization of glucose by insulin action is not known, but two views of this concept have received considerable experimental support; the glucose transport hypothesis (Levine et al., 1955 and 1958) and the intracellular enzyme hypothesis. According to the transport hypothesis, the main action of insulin is to facilitate the transfer of glucose across the cell membrane (Levin et al., 1958; Levine et al., 1950; and Henderson, 1963). Using isotopic glucose, methods have been developed for studying the effect of insulin upon intracellular free glucose in rat diaphragm, heart, and skeletal muscle in vitro (Park, 1953; and Park et al., 1955). These experiments have indicated that insulin accelerates the transport of glucose and various other sugars, with the same first three carbon configurations as glucose, (Ganong, 1965; Park et al., 1955; Ross, 1952; and Ross, 1953), across cell membranes, and that this step precedes the phosphorylation of glucose by the hexokinase reaction (Park et al., 1955). Stadie (1957) confirmed this hypothesis when he observed that the rapidity of the response of muscle to insulin, both in the binding of the hormone and in glucose uptake and glycogen deposition, indicated that the hormone acts at the cell surface to aid glucose transport. This phenomena may be explained by the possibility that the sulfhydryl bonds of

the insulin molecule unite with the sulfhydryl groups in the membrane. Oganesgan (1963) showed, in his experimental work with dogs, that adenosine triphosphate activity in the kidney and skeletal muscle increased 20 to 29.5% under the influence of insulin. He concluded that this enzyme has an important role in the transport of glucose and that it represents part of the glucose transporting mechanism in the kidney and muscle. The explanation was that the influence of insulin on the membrane adenosine triphosphatase caused the adenosine triphosphate to break up, thus yielding its energy to the glucose carrier which, in turn, initiated the reaction of the insulin disulfide group with the sulfhydryl group of the receptor protein, probably adenosine triphosphatase.

The concepts of the intracellular enzyme hypothesis emphasize the key position of glucose-6-phosphate in the carbohydrate metabolism of the liver (Ashmore, et al., 1956). There is some evidence that insulin speeds up the conversion of glucose to glucose-6-phosphate. It has been proposed that insulin might accelerate the glucokinase reaction by counteracting the inhibitory effect of an anterior pituitary factor even though the phosphorylation hypothesis of insulin action has not received experimental confirmation.

In contradiction to this hypothesis, Stadie et al. (1947) investigated the relation between insulin and glucohexokinase in rabbit muscle and failed to show any influence of the pancreatic or adrenal hormone on the enzyme. Attention, by several workers, has also been drawn to the enzyme glucose-6-phosphatase. In rat liver slices, the release of glucose from glucose-6-phosphate is related to the activity of the

glucose-6-phosphatase, (Ashmore et al., 1956). The administration of adrenal glucocorticoids have been found to increase the activity of the enzyme whereas insulin reduces its activity.

Rabkino (1964) found, in experimental work with normal rats, that autoradiographical labeled insulin distribution was prevalent in (1) the kidneys of the convoluted tubules; (2) the liver; and (3) the muscles.

Worthington et al. (1964) suggested that there is a distinct affinity of elastic tissue for insulin or its breakdown products, and generally a non-uniform distribution of this hormone or its breakdown products in connective tissue.

Effect of Insulin on Body Metabolism

The primary action of insulin is on carbohydrate metabolism. This hormone also exerts an effect on fat and protein metabolism by both a direct and indirect action. Hall (1959) implies that the metabolic pathways involved in the oxidation of carbohydrates are linked with those of fat and protein metabolism, hence a modification of carbohydrate metabolism would be expected to reflect some change in fat and protein utilization.

According to Hall (1959), the effects of insulin administration can be summarized as follows: (1) increased conversion of glucose to glycogen in the liver and muscle; (2) increased uptake and oxidation of glucose by peripheral tissues; (3) increased rate of conversion of carbohydrates to fat; and (4) increased rate of protein synthesis. Turner

(1961) indicated the administration of insulin will also reduce the blood sugar level, inhibit excessive ketogenesis, and decrease the concentration of potassium and inorganic phosphate in the blood.

Bishop et al. (1965), in his experimental work with dogs, showed that glucose C^{14} was the source of almost all C^{14} of glycogen in the liver without passage through a three carbon intermediate. He also observed that intravenous infusion of insulin at 0.1-0.2 U./kg./hr., along with glucose to limit hypoglycemia, stopped glycogen loss and decreased glucose release from the liver while also increasing glucose uptake from the plasma by the tissues.

Rafaelson (1964) found that the intraperitoneal injection of 1 ml. of undiluted human serum in 100 gm. intact rats leads to an increase of diaphragm glycogen. He postulated this action can be assumed, due to the representation of insulin activity present in the serum. In another experiment with 100 gm. rats, he suggested that the intraperitoneal injection of 100 uU. and 10,000 uU. of insulin caused a 25 - 50% and 200 - 400% increase in diaphragm glycogen, respectively. These doses did not affect blood glucose levels. Intravenous injections at the level of 10,000 uU./100 gm. weight yielded a 25% increase in diaphragm glycogen and heart glycogen plus a significant fall in the blood glucose level. Gemmill (1940) earlier confirmed these results.

Mann (1922) found that hypoglycemia can be produced by the removal of the liver. The effects of large doses of insulin is the same as those due to hypoglycemia produced by other means.

Asplund et al. (1962) in his experimental work with baby pigs showed that 400 oral units of both insulin and protamine zinc insulin,

lowered the blood glucose level. Pekas et al. (1959) verified these results when he injected 0.5 - 1.0 units of insulin per kg. body weight to baby pigs.

The main action of insulin is to increase glucose utilization or glucose uptake. Park et al. (1952) found that insulin increases glucose uptake of the normal rat diaphragm in Krebs-bicarbonate solution from 3.6 mg./gm./hr. to 6.6 mg./gm./hr. Conversely, muscle from diabetic animals has a lower than normal glucose uptake. Friatt et al. (1964) also observed that insulin increases the glucose uptake up to 300% more than the control values in rats.

Brady et al. (1951) proposed that insulin promotes the synthesis of fatty acids in cats. In total pancreatectomy, however, a virtual abolishment of the incorporation of acetate into fatty acids and the rate of ketone body formation increased fivefold (Stadie, 1947; and Stadie, et al., 1940). In such pancreatectomized animals, hypophysectomy reduces the rate of ketone formation and restores the ability of the liver to synthesize fatty acids from the acetate fragment. Friatt, et al. (1964) showed that the addition of insulin to rats increased fatty acid synthesis 500% as compared to controls. Fain et al. (1965) indicated that insulin injected subcutaneously stimulated, within thirty minutes, fatty acid synthesis in the liver adipose tissue, and carcass in pancreatectomized rats deprived of insulin for 17 hours. Using the technique of isotopic tracers, Stetten (1953) has calculated that in the well-nourished rat only about 3% of the glucose injected each day is converted to glycogen, while 30% is used to make fatty acids.

Beaton et al. (1965) submitted daily subcutaneous injections of protamine zinc insulin to Wistar rats for 25 days at a level of 2 U./100 gm. body weight. Under these conditions, he observed that body fat increased markedly on both a low-protein and normal diet. He also showed that the food intake and growth rate increased. Kumaresan (1965), in his experimental work with normal female rats, observed that subcutaneous injections of graded levels of protamine zinc insulin, from 0.5 U. to 60 U., increased body weight gains and feed consumption per day and per 100 gm. of body weight. With these increasing levels, there was also a gradual increase up to 48%, in mean total daily feed intake.

Observations by Bulatao and Carlson (1924), Quigiley et al. (1929), Mayer and Bates (1951), Van Itallie et al. (1953), and Stunkard and Wolff (1954), have shown that there is an inverse relationship between blood glucose concentration and food intake. That is, as the blood glucose concentration decreases, the food intake will increase.

Protein is formed in the absence of insulin, however, the net formation of protein is accelerated by insulin. Luken (1964) and Fritz et al. (1964) suggest that the effects of insulin on protein metabolism occur independently of the transport of glucose or amino acids into the cell, of glycogen synthesis, and of stimulation of high energy phosphate formation. Lostrok (1964) showed that the effect of insulin on protein synthesis in the uteri from ovarectomized rats in the cells of both endometrium and myometrium responded with a net increment of 60% in the basal medium alone and 80% when insulin was included. Akedo et al. (1963) discussed the nature of insulin action on

amino acid uptake by the isolated diaphragm. He found that insulin enhances the uptake of at least eight amino acids, including the naturally occurring amino acids glycine, L-methionine and L-proline. Allen (1922) has demonstrated that a linear relationship exists between the insulin dose and nitrogen retention in depancreatized dogs.

Most of the work on this thesis was based on studies initiated in Russia by Kosvalevskaja et al. (1962), and Obydennov (1963) on feeder pigs. Also observed were the findings suggested by Pekas (1959) on newborn pigs. The results from work done by the Russians indicate that injected insulin will stimulate growth rate, improve feed efficiency and improve backfat quality. Pekas et al. (1959) has shown that there is an inverse relationship between blood glucose concentration and food intake under the influence of insulin.

The purpose of the study was (1) to investigate the effects of oral hypoglycemic compounds chloropropamide (Diabenese), and acetohexamide (Dymelor), and subcutaneously and intramuscularly injected protamine zinc insulin effect on blood glucose and urea levels in fattening swine, and (2) to determine the effect protamine zinc insulin given intramuscularly and subcutaneously on growth rate, feed intake, feed efficiency, average daily gain, and backfat thickness on both heavy and light weight fattening swine.

MATERIALS AND METHODS

Experiment I

Three pigs, one Poland China Barrow and two Poland China gilts, weighing an average of 68.3 kilograms, were randomly placed in individual wooden, slot floor pens (3.5 x 10 feet) from April 27, 1965, to June 6, 1965, a period of 40 days. All animals were fed, free choice, a ground ration (Table 1) composed of 89.8% sorghum grain (10% protein), 7.0% soybean oil meal (44% solvent), plus a 2% mineral and 1% vitamin premix. Water was constantly available to the animals. The weight and feed consumed per animal was determined at periodic intervals of from one to two weeks.

Each pig served as its own control and was assigned one of the following specific hypoglycemic treatments: (1) protamine zinc insulin (Eli Lilly) injected subcutaneously in the back or intramuscularly in the ham at a level of 0.5 U./kg. body weight; (2) Chloropropamide (Diabenese from Pfizer Laboratories) given orally in the feed at increasing levels of 25 to 200 mg./lb. of feed; and (3) Acetohexamide (Dymelor from Eli Lilly and Company) given orally in the feed at increasing levels of 100 to 800 mg./lb. of feed. The oral compounds were pre-mixed and then added to the complete ration.

The hypoglycemic agents were administered continuously in the feed. A single injection was made at 7 A.M. All pigs were without feed for six hours prior to blood sample collections. Blood samples were collected at 1:00 p.m. daily and glucose and urea determinations made

immediately at 24 hour intervals for the next 3 days. The Nelson (1944) method was used for determining blood glucose concentration and both the Coulombe-Favreau (1963) and Haver-Lockhart Laboratory methods were used in determining blood urea concentrations.

Two drops of heparin were added to each collection tube to prevent blood coagulation. One 5 ml. sample was withdrawn from the external jugular vein of each animal by means of a 10 ml. syringe attached to a two inch needle and quickly deposited in the tubes. The collection tubes were immediately stoppered with rubber caps and gently shaken to assure a homogenous blood sample. Quadruplicate determinations were performed for each animal at each level and the average represented the blood glucose and urea concentrations. These values were reported as milligrams of glucose or urea per 100 ml. of blood.

Experiment II

Two feed-lot trials were conducted on 15 heavy and 15 light weight crossbred pigs. For each weight group, the animals were allotted by weight and litter into three lots of five animals each, consisting of: (1) control; (2) protamine zinc insulin (subcutaneous); and (3) protamine zinc insulin (intramuscular). The average weight of the lots obtained from three consecutive weighings during two days preceding the start of the experiment, did not differ by more than 0.9 kg. for both trials. The initial weight of the heavier pigs (Trial 1) was 64.4 kg. while that of the lighter pigs (Trial 2) was 42.9 kg.

Trial 1 lasted from October 7, 1965, to November 24, 1965, or a period of 47 days, while Trial 2 began on October 7, 1965, and terminated on January 18, 1965, or a period of 103 days. The ration used for this experiment was identical to that of Experiment I. Water was constantly available to the animals. The average weight and feed consumed per animal were determined each week.

Protamine zinc insulin was administered to each animal at the same time each week. The level of this hormone was 0.5 U./kg. body weight. The subcutaneous injections were administered in the back while intramuscular injections were in the ham.

An average of two weights of each animal, determined on the last two days of both trials, was recorded as the animals finished weight. Thirty-six hours elapsed between the termination of the experiment and slaughter. The animals were given only water during the last 16 hours of this period and were slaughtered in a commercial plant; Maurer-Neuer Meat Packers, Arkansas City, Kansas.

All carcass data reported were obtained by personnel from the Animal Husbandry Department, with the cooperation of the packing plant staff.

Table 1. Composition of the basal ration.

Ingredient	Amount/500 lbs. or 222.27 kg. Individual Lbs.	kg.	Percentage
Bulk			
Sorghum grain (10% protein)	449.0	227.3	89.8
Soybean oil meal (44% solvent)	35.0	15.9	7.0
Premix A			
Dicalcium phosphate	5.0	2.3	
Limestone	3.5	1.6	2.0
Salt	2.5	1.1	
Trace Mineral	0.25	0.1	
	Premix added		
Premix B (gm.)			
Vitamin D (15,000)	5.0		
Vitamin A (10,000)	75.0		
B Vitamin (Merck 1233)	75.0		1.0
B_{12} (Proferm 20)			
Aurofac 10	227.0		
Sorghum grain	1863.0		
	Premix added		

RESULTS AND DISCUSSION

Experiment I

Visual Observations. Each animal came through its respective treatment during the spring months in good condition. The pig injected intramuscularly with protamine zinc insulin showed possible signs of hallucinatory depression and a lack of limb coordination within 15 minutes after the administration; however, only for a short period of time. This reaction may have been due to the depressing effect of the hormone on blood glucose levels, thereby causing a decrease in the amount of available energy to the central nervous system.

Neither the pig injected subcutaneously nor the other two pigs receiving chloropropamide or acetohexamide exhibited any of these symptoms.

Blood Glucose Levels. The normal level of the blood glucose concentration for swine is from 45-75 mg. percent. All of the pigs in this experiment were within this range when the two control values for each animal were averaged.

Effects of (0.5 U./kg. body weight) protamine zinc insulin on blood glucose concentration are summarized in Table 2. When the hormone was injected subcutaneously, the blood glucose concentration dropped from an average of 55.7 mg.% to 44.4 mg.%, or a difference of 20.3%. Two intramuscular injections lowered the concentration markedly from 55.7 to 13.6 and 10.1 mg.% or a difference of 75.6 and 81.9%, respectively.

Table 2. Effect of protamine zinc insulin on blood glucose concentration (mg.%).

Treatment	Insulin (0.5 U./kg. body wt.)
Control	58.6
Control	52.8
Subcutaneous	44.4
Intramuscular	13.6
Intramuscular	10.1

It is probable the subcutaneous injection had very little or no effect on the blood glucose concentration as there was a wide variation in the normal blood glucose values from one day to the next. Intramuscular injections produced a drastic drop in the blood glucose concentration. It was concluded that protamine zinc insulin increases the amount of glucose utilized by the animal.

Data presented in Tables 3 and 4 summarize the changes that occurred in the blood glucose concentrations when chloropropamide and acetohexamide were administered. Neither of these sulfonylureal oral hypoglycemic compounds had any marked effect even though there was a small decrease noticeable in the blood glucose concentration.

The average of the two control values of chloropropamide and acetohexamide was 52.3 and 45.7 mg.%, respectively. Graded levels of 25, 50, 100, and 200 mg. per lb. of feed of chloropropamide resulted in 36.0, 47.6, 42.1, and 52.4 mg.% of glucose in the blood, respectively, whereas the outcome of the increased levels of 100, 200,

Table 3. Effect of chloropropamide (Diabenese) on blood glucose concentration (mg.%).

Treatment	Chloropropamide (Diabenese)
Control	46.8
Control	57.8
25 mg./lb. of feed	36.0
50 mg./lb. of feed	47.6
100 mg./lb. of feed	42.1
200 mg./lb. of feed	52.4

Table 4. Effect of acetohexamide (Dymelor) on blood glucose concentration (mg.%).

Treatment	Acetohexamide (Dymelor)
Control	34.8
Control	56.7
100 mg./lb. of feed	39.1
200 mg./lb. of feed	49.6
400 mg./lb. of feed	40.2
800 mg./lb. of feed	40.8

400 and 800 mg. per lb. of feed of acetohexamide was, respectively, 39.1, 49.6, 40.2, and 40.8 mg.%. There appeared to be a slight decline of the blood sugar concentration, when the first three levels of chloropropamide were administered, while no change occurred when the highest level was administered.

Blood Urea Levels. The normal blood urea concentration for swine ranges from 8-24 mg.%. Each animal was within this range, both separately and when the two control values were averaged.

Results cited in Tables 5, 6, and 7, show that none of the treatments had any effect on the blood urea nitrogen concentrations. This indicates that none of the compounds used in this experiment had any effect on either protein anabolism or catabolism, and that the balance between the build-up and breakdown of protein remained status quo.

Table 5. Effect of protamine zinc insulin on blood urea concentration (mg.%).

Treatment	Insulin (0.5 U./kg. body wt.)
Control	13.1
Control	16.2
Subcutaneous	19.9
Intramuscular	17.2
Intramuscular	18.8

Table 6. Effect of chloropropamide (Diabenese) on blood urea concentration (mg.%).

Treatment	Chloropropamide (Diabenese)
Control	18.1
Control	20.1
25 mg./lb. of feed	20.1
50 mg./lb. of feed	17.5
100 mg./lb. of feed	18.0
200 mg./lb. of feed	18.5

Table 7. Effect of acetohexamide (Dymelor) on blood urea concentration (mg.%).

Treatment	Acetohexamide (Dymelor)
Control	18.0
Control	17.7
100 mg./lb. of feed	19.8
200 mg./lb. of feed	18.8
400 mg./lb. of feed	18.5
800 mg./lb. of feed	18.5

Experiment II

Visual Observations. The animals in all the lots of Trial 1 came through the fall in good uniform condition, although the weights of the animals within each lot were quite varied. It was difficult to distinguish animals in one group from those in another group by external appearances. They were all good quality pigs and were always in good health.

With the exception of 3 pigs, the animals in Trial 2 were quite uniform in size. However, they were apparently stunted prior to this experiment due to early weaning (20 days), prevalent scours, and low feed consumption (wheat). Tail biting occurred in the subcutaneous injected group of pigs midway through the experiment. This condition was corrected quickly by a 2% increase in the protein content of the diet for one week.

Results of Trial 1. Table 8 is a summary of the pertinent results obtained from Trial 1. It contains the average initial and final weight, average daily gain, average daily feed consumed, feed efficiency, and the backfat thickness for each lot.

Growth. The growth values were calculated from weights of the individual animals measured at weekly intervals. Table 9 is a summary of the lot weights measured at weekly intervals.

Comparison of the final average gains for each lot show that, at the end of the trial, the animals injected subcutaneously and intramuscularly with protamine zinc insulin gained, respectively, 3.6 and 4.1 kg. more than the untreated pigs. This amounted to a 10.7 and 12.3% increase, respectively.

Table 8. Summary of the average performance data of pigs for Experiment II (Trial 1).

Treatment	Control	Subcutaneous	Intramuscular
Insulin units/kg. body wt.	0	0.5	0.5
Lot number	1	2	3
Number of animals	5	5	5
Av. initial wt., kg.	63.2	65.0	65.0
Av. final wt., kg.	96.5	101.8	102.4
Av. daily gain, gm.	707.9	783.4	794.9
Av. daily feed consumed, kg.	3.1	3.5	3.3
Feed/kg. gain, kg.	4.4	4.4	4.1
Backfat thickness, cm.	3.6	4.3	3.8

Table 9. Summary of average lot weights measured at weekly intervals (kg.) Experiment II (Trial 1).

Week Number	Control	Subcutaneous	Intramuscular
0	63.7	65.2	65.2
1	72.5	72.6	75.2
2	77.6	79.5	79.7
3	81.1	84.4	83.6
4	84.6	89.0	89.2
5	92.0	97.2	95.6
6	95.7	99.6	101.4
7*	96.5	101.8	102.4

*Five day period

Coincidental with this increase in growth, was the increase in average daily gain. This parameter increased, about 75.5 and 87.0 gm., on the subcutaneous and intramuscular groups as compared to the control values.

The fact that the treated lots gained more weight indicates that some alteration or modification in the metabolism of the carbohydrates may have caused some change in the fat metabolism. It appears that more fat was deposited, as backfat, on these pigs.

No statistical differences could be shown for the increased growth rate. This was due to variations in the weights of the animals within each lot.

Feed consumed and feed efficiency. Table 8 shows the average daily feed consumed per kilogram of gain. The animals injected with protamine zinc insulin subcutaneously or intramuscularly consumed 0.40 and 0.20 kg. more daily feed, respectively, than did the control animals.

The animals injected with protamine zinc insulin intramuscularly consumed 0.24 less feed units/kg. gain as compared to the untreated animals. No differences were observed, however, in the comparison of efficiency between the subcutaneous lot and control animals.

Backfat thickness. Table 8 summarizes the backfat thickness of both the treated and untreated animals. The non-significant increase in the growth rate, or final weight of both the treated lots, was due, at least in part, to an increase in the backfat thickness. The subcutaneous and intramuscular treated pigs exhibited an increase of 0.7 and 0.2 cm., respectively, over the untreated animals.

Feed intake. Insulin seemed to stimulate the appetite of pigs receiving subcutaneous and intramuscular injections. It may be this hormone induced an alimentary peristalsis which, in turn, enticed the animal receiving this compound to consume more feed.

Results of Trial 2. Table 10 summarizes the results observed from Trial 2. As in Table 8, it contains the average initial and final weight, average daily gain, average daily feed consumed, feed efficiency, and backfat thickness for each lot.

Table 10. Summary of the average performance data of pigs for Experiment II (Trial 2).

Treatment	Control	Subcutaneous*	Intramuscular
Insulin units/kg/ body wt.	0	0.5	0.5
Lot Number	1	2	3
Number of animals	5	5	5
Av. initial wt., kg.	41.8	43.2	43.6
Av. final wt., kg.	98.9	90.6	100.3
Av. daily gain, gm.	554.3	460.8	549.8
Av. daily feed consumed, kg.	2.1	1.9	2.2
Feed/kg. gain, kg.	3.8	4.2	4.0
Backfat thickness, cm.	3.6	3.1	3.6

*Pigs set back from occurrences of tail biting.

Administration of protamine zinc insulin, both subcutaneously and intramuscularly, on the light weight fattening pigs appeared to have little or no effect on the criteria studied. No differences were noted when comparisons were made between the intramuscularly treated pigs and the controls. Pigs injected subcutaneously exhibited minor detrimental effects on the criteria studied when compared to the controls. These negligible factors were, in part, due to the occurrence of tail biting and can only be partially attributed to protamine zinc insulin.

GENERAL DISCUSSION

Experiment I

Effects of Protamine Zinc Insulin. A definite decline in the blood glucose concentration was observed when protamine zinc insulin was administered intramuscularly while very little decline was noted when the same level was injected subcutaneously. It is feasible to assume that the drastic drop of the blood glucose concentration observed in the intramuscularly treated lot was due to the readily available insulin and its ability to promote utilization of the glucose in the blood stream.

These results agreed with work done by Obdyke (1942). He found that a linear relationship existed between the hypoglycemic action of insulin and the dose of insulin administered. If this is true, it is a good assumption that the intramuscularly injected insulin corresponded to a larger dose than did the subcutaneous administration because it was

more readily available in a shorter period of time and at a greater concentration to react with the glucose in the blood stream.

It was theorized by Stadie (1957) that the adenosine triphosphate activity in the insulin binding tissues increases under the influence of insulin and that this hormone has an important role in the transport of glucose across the cell membrane. Oganesgan (1963) reported that the influence of insulin on membrane adenosine triphosphatase caused the adenosine triphosphate to break up, thus yielding its energy to the glucose carrier which, in turn, initiated the reaction of the insulin disulfide group of the receptor protein, probably adenosine triphosphatase.

It has been demonstrated by Pfizer Laboratories that chloropropamide is a potent and active oral hypoglycemic sulfonylureal compound, valuable in the treatment of diabetic patients. When repetitive doses of this compound are orally administered, no undue accumulation will exist in the blood stream due to the fact that the absorption and excretion rates become stabilized in about five to seven days after the initial therapy. Its biological half-life is approximately 24 hours.

Pfizer has found the effectiveness of chloropropamide may be the result of a slow excretion rate and an absence of significant deactivation. They have found, in humans, that the most effective dose for the stable diabetic is 250 mg. daily.

Eli Lilly and Company found that 3-18 mg/kg. body weight/animal (unknown) of acetohexamide gave no response to growth rate.

According to Ganong (1961) the sulfonylurea derivative such as

chloropropamide will lower the blood glucose level by stimulating the secretion of insulin from the pancreas.

Effects of Chloropropamide and Acetohexamide. As previously stated, Pfizer Laboratories found the level of 250 mg. daily of chloropropamide was effective for the normal, stable diabetic. In this experiment, orally administered levels of 25, 50, and 100 mg./lb. of feed, which was equivalent to approximately 131.25, 262.50 and 525.00 mg. daily, indicated there may be some decrease in the blood glucose concentration of 65.00 kg. finishing swine. However, when 200 mg./lb. of feed was administered, equivalent to 1050.00 mg. daily, the results showed that the blood glucose concentration remained stable and was higher than that found when the three lower levels were administered. This indicates that this compound had no effect on lowering the glucose concentration in the blood and that some other factor, such as environmental or eating habits, may have played a more important role in the lowering of the blood glucose level of these treatments as shown.

No effect was shown on blood glucose concentration when acetohexamide was orally administered at levels of 100 to 800 mg./lb. of feed.

Blood Urea Concentration. Lukens (1964) and Fritz et al. (1964) observed that the net formation of protein is accelerated by insulin. Under these circumstances, the urea nitrogen level of the blood would be expected to decrease and the protein anabolism rate would overshadow that of catabolism.

Blood urea nitrogen levels were determined to see if any of the treatments affected protein metabolism. The results indicated no change

in urea level of the blood. Thus, it appeared that all hypoglycemic compounds failed to alter the normal balance of protein anabolism and catabolism.

Experiment II

The success of a swine production operation is dependent upon (1) getting the finished product to market quickly; (2) using as little feed as possible per animal during this time; and (3) decreasing the backfat thickness of the carcass produced. This means that the animals must exhibit a fast growth rate, or more specifically, a high average daily gain, efficient feed consumption, and a small amount of backfat.

Of these three characteristics, finished weight, feed consumption, and backfat thickness, it is understood that for a given breed and under similar conditions, each aspect would respond, over a period of time, to the techniques of the nutritionist.

In this experiment, it was shown that the intramuscular and subcutaneous injections of protamine zinc insulin increased the growth rate of heavy fattening pigs although non-significantly. It was also observed non-significantly, that the average daily feed consumed, feed efficiency, and backfat thickness increased. All aspects of these results, with the exception of backfat thickness, are in agreement with those obtained by Anonymous (1961), Obydennov (1963), and Kosvolovskaja (1963).

Experimental work has shown that monthly injections of 0.3 U./kg. body weight to pigs 4 months of age increased the final weight at age

6½ months to an average of 8.9 kg. more than the controls (Anonymous, 1961). This worker also observed that the pigs receiving insulin gained 12.0% more daily than the controls. Treated pigs used 4.0 feed units/kg. gained against 4.4.

Obydennov (1963) reported that pigs injected with 0.5 to 1.0 U./kg. body weight every 10 days in the last month of fattening (varied from 5-9 months), daily gains averaged 620 gm. as compared to 422 gm. for the untreated controls. The feed consumption/kg. gain averaged 5.2 feed units for the experimental pigs and 6.9 feed units for the control, which amounts to 24.64% less feed per unit of gain.

Kosvalevskaja (1963) found that the injection of pigs (no weight given) with 0.1 to 0.3 units of insulin/kg. body weight, one to three times/month, increased body weight by 13-20%. The average daily gain was increased 83.5 to 85.0%. When the muscle and fat were analyzed, the quality of each was better in the pigs injected with insulin.

Although differences are evident when comparing the magnitude of average daily gain, (Kosvalevskaja, 1963), and feed consumed (Obydennov, 1963), it seems feasible that insulin may be of value in increasing the performance of fattening swine. It is doubtful, however, that this hormone will have any direct or indirect action in decreasing the back-fat thickness.

Brisby et al. (1951), Friatt et al. (1964), Beaton et al. (1965), and Stetton (1953), and other workers have shown that insulin, combined with a normal diet, will increase fatty acid synthesis. It is feasible that, on Trial 1 of Experiment II, an increase in fatty acid synthesis

may have increased the backfat thickness of both treated lots.

In an explanation, Lukens (1938) has reported that insulin has widespread effects on fat formation and mobilization. It promotes lipogenesis from glucose and acetate in the liver and many extra-hepatic tissues. It prevents the loss of depot fat and the accumulation of fatty deposits in the liver. It is probable that these different effects of insulin are closely interrelated and that they are all linked with its action on the oxidation of glucose.

It appears that the combination of a high carbohydrate diet coupled with the injection of insulin more than likely is the reason for the increase in the non-significant growth rate and backfat thickness as shown in Trial 1 of Experiment II.

Grossman and Stein (1948), and several other workers, have observed that sensations of hunger in the human are induced when insulin is administered. The gastric movements and contractions are increased and alimentary peristalsis is prevalent which, in turn, leads to an increased appetite. Apparently, this is the explanation for the cause of increased feed consumption in the subcutaneous and intramuscularly treated pigs in Experiment II, Trial 1.

The intramuscularly treated pigs of Trial 1 exhibited a greater feed efficiency than either the subcutaneous or control group. Theoretically, the insulin injected intramuscularly would have the ability to get into the blood stream and become bound to the binding tissues sooner than that of the subcutaneous injections, and thereby increase the efficiency of the feed consumed through more efficient carbohydrate or glucose utilization.

SUMMARY

Two experiments were conducted with fattening swine to determine if blood glucose level, blood urea level, growth rate, feed intake, feed efficiency, and backfat thickness could be altered by either oral or injected hypoglycemic compounds.

Experiment I was conducted to evaluate any changes that might occur in the blood glucose or urea concentrations when 0.5 U./kg. body weight of protamine zinc insulin was injected either intramuscularly or subcutaneously. Chloropropamide (Diabenese) and acetohexamide (Dymelor) were also thoroughly mixed in a high energy, well balanced ground ration and administered separately at levels of 25, 50, 100, 200, and 100, 200, 400, and 800 mg./lb. of feed, respectively. Intramuscular injections of protamine zinc insulin decreased the blood glucose concentration from 58.60 and 52.80 mg.% to 13.60 and 10.10 mg.%, respectively, however, no change was noted in the blood urea concentration. Subcutaneous injections failed to produce any changes in either the blood glucose or urea levels. Chloropropamide and acetohexamide also failed to alter these two criteria.

In Experiment II, two feedlot trials, involving 15 heavy and 15 light weight crossbred swine, were conducted to determine the effects of injected protamine zinc insulin (0.5 U./kg. body weight/week) on growth rate, feed efficiency, feed intake, and backfat thickness. Animals in each trial were allotted by weight and litter into three treatments: (1) control; (2) insulin subcutaneously; and (3) insulin intramuscularly. All animals were fed a diet of 89.8% sorghum grain (10% protein), 7.0%

soybean oil meal (44% solvent), 2.0% added minerals, and 1.0% supplemental vitamins A and D. Trial 1 lasted 47 days (initial weight 64.4 ± 12.9 kg.) and Trial 2 103 days (initial weight 42.9 ± 9.4 kg.). Average daily gain (gm./day), feed efficiency, and subsequent backfat thickness (cm.) for Trial 1 were, respectively, (1) 708, 4.4, 3.6; (2) 783, 4.4, 4.3; and (3) 795, 4.1, and 3.8. Results from Trial 2 were, respectively, (1) 554, 3.8, 3.6; (2) 461, 4.2, 3.1; and (3) 550, 4.0, and 3.6. Total feed consumption increased in both treated groups of Trial 1. Because the pigs in Trial 2 were stunted, prior to the experiment, from early weaning (20 days), prevalent scours, and low feed consumption (wheat), the data presented is not completely valid with respect to the treatments administered. No significant differences were obtained in either Trial 1 or 2 on the criteria studied.

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EFFECT OF HYPOGLYCEMIC COMPOUNDS UPON FATTENING SWINE

by

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Two experiments with fattening swine were conducted. The purpose of Experiment I was to study the effect of three hypoglycemic compounds on the blood glucose and urea concentrations. Protamine zinc insulin (PZI) was injected both intramuscularly and subcutaneously at a level of 0.5 U./kg. body weight. Two oral hypoglycemic compounds, chloropropamide and acetohexamide, were also administered in the feed at respective levels of 25, 50, 100, 200, and 100, 200, 400, and 800 mg.%. In Experiment II, PZI was injected intramuscularly and subcutaneously (0.5 U./kg. body weight) to both heavy (64.39 kg.) and light (42.88 kg.) weight fattening pigs. The criteria studied were growth rate, feed efficiency, feed intake, and backfat thickness. A high energy, well balanced ration was used for each experiment. In Experiment I, PZI injected intramuscularly decreased the blood glucose concentration from 55.70 mg.% to 11.85 mg.% but no change was observed on the blood urea level. Subcutaneous injections, chloropropamide, or acetohexamide did not alter blood glucose or urea levels. In Experiment II, PZI injected intramuscularly and subcutaneously, respectively, increased average daily gain from 708 gm. to 783 gm. and 795 gm. and backfat thickness from 3.6 cm. to 3.8 cm. and 4.3 cm. on the heavy weight pigs. Intramuscularly injected PZI increased feed efficiency from 4.37 to 4.13 on the heavier pigs, but the hormone administered subcutaneously showed little or no effect. Intramuscular and subcutaneous injections increased average daily feed consumption from 3.1 kg. to 3.3 kg. and 3.5 kg., respectively in the heavy pigs. No significant changes were observed in Trial 1 on the criteria studied. Changes observed were negligible on the criteria studied when the light weight pigs were treated with PZI.