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This study involved three separate research efforts in which some aspects of carbohydrate metabolism in gravid swine were examined.

In experiments I and II a modification of the glucose tolerance trial was used. Sows were given intravenously 0.15 gm of glucose per kg of body weight following a 24 hour fast. Plasma insulin and glucose concentrations were measured in plasma samples collected at 2, 4, 6, 8, 10, 20, 30, 40, 60, and 120 minutes post-infusion.

In experiment I glucose tolerance trials were performed on 16 sows of varying parity on day 21 post-breeding and the reproductive performance as a result of that breeding was recorded. The time for plasma glucose levels to return to fasting levels, the half-life of added glucose, and the glucose clearance rate were calculated from the regression of the logarithm of the plasma glucose concentrations against time. Tolerance time was positively correlated ($P<0.05$) with mean piglet birth weight while sow body weight was positively correlated ($P<0.05$) with number born and litter weight. No differences ($P<0.05$) were observed for glucose tolerance measurements for sows

conceiving and those failing to settle. A tendency for sows of increased parity to have a faster glucose clearance rate was noted but the measurements of glucose tolerance were not significantly affected by parity or body weight of the sow.

In experiment II, glucose tolerance tests were performed on six sows of varying parity on day 21, 84, and 110 of gestation. Insulin levels were measured by radioimmunoassay of the plasma samples. A quadratic equation of insulin levels as the dependent variable and time as the independent variable was found to describe a significant fit ($P<0.05$) of the insulin response post-glucose-infusion. The measurements of glucose tolerance, tolerance time, glucose half-life, and glucose clearance rate, showed a ($P<0.05$) tendency towards glucose intolerance as gestation progressed. The magnitude of insulin response decreased with increased day of gestation, while plasma insulin level remained above basal levels longer.

In experiment III, sows and gilts (116 total) were fed a daily energy intake of 6783 kcal D.E. or 10,583 kcal D.E. in combination with or without 1000 mg of dichlorvos daily for the last thirty days of gestation. High energy intake produced no effect on the reproductive characteristics of sows or gilts. At weaning, increased energy intake during gestation decreased ($P<0.05$) the number of pigs per litter, but increased ($P<0.05$) litter weights. Dichlorvos treatment during the last thirty days of gestation decreased stillbirths ($P<0.05$). The energy and parity interaction ($P<0.05$) showed that gilts fed high energy during gestation had fewer pigs at 21 days and at weaning and also had lower litter weights at these times.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDIX TABLES

GLUCOSE METABOLISM BY GRAVID SOWS

INTRODUCTION

Commercial production of livestock is dependent upon reproduction; all else -- capital, labor, and managerial talent -- is wasted if there are insufficient offspring to result in a profitable enterprise. The major areas of research in livestock reproduction have been (1) increasing ovulation and fertilization rates, and (2) decreasing embryonic mortality, in an effort to maximize the number of offspring produced and thus permit a profitable enterprise. For most commercial livestock industries, these types of research are indeed desirable. Swine, however, are unique among major livestock species in being multiparous. For the commercial swine producer, successful reproduction per maternal unit per gestation period is measured by the number born per unit. Thus, the fixed costs per pig at birth are inversely proportional to the litter size. Aside from the financial point, the larger the average litter size, the greater the base for selection of replacement parental stock.

The domestic sow has the capacity to ovulate from 12 - 24 ova per estrus and the domestic boar can fertilize 95 - 100% of those ova (Squiers et al., 1950, 1952; Robertson et al., 1951; Perry and Rowlands, 1962). Causes for embryonic mortality in early gestation, including intrauterine crowding (Rathnasabapathy et al., 1956; Bazer et al., 1968; Dzuik, 1968) and the dam's energy intake during early gestation (Self et al., 1955), have been identified and proper management practices have been offered to alleviate them.

A high ovulation and fertilization rate, together with a decreased embryonic mortality, insure a larger litter size and decreased fixed costs per piglet born. Unless piglets survive to market weight, however, the benefits of the increased litter size is lost along with the cost incurred by each piglet up until its death.

Pigs are born into a hostile environment in which they are ill-equipped to survive. Mortality from birth to weaning under common management practices is in the range of 20 -30% for all pigs born (Leman et al., 1972). Causes of this mortality are many. The piglet's heat-conserving ability is poor and efforts to maintain thermostability in cool or cold environments leave the piglet weak (Curtis, 1974). The neonate is dependent on carbohydrate stores, limited lipid stores, and dietary intake (Mersmann, 1974) to meet its energy requirements which, in stress conditions, prove to be survival limitations. These and other physiological limitations can leave the piglet weak and subject to the major direct causes of neonatal mortality--starvation, chilling, crushing by the sow, and infection.

Neonatal mortality can be substantially reduced or eliminated (England, 1974). The methods of reducing mortality are primarily postnatal prophylaxis and therapy; only limited research has been performed in the area of increasing piglet vigor prior to birth. The purpose of this dissertation is to (1) investigate the pattern of glucose clearance by gravid sows and (2) to test a method of increasing piglet weight and vigor by capitalizing on the diabetogenic condition produced in sows as gestation progresses by increasing carbohydrate intake.

REVIEW OF LITERATURE

DICHLORVOS

In the search for drugs to control internal parasites it is not unusual to develop a compound that is an effective anthelmintic and induces systemic changes in the host animal besides parasite removal. One such anthelmintic for swine that produces beneficial systemic effects is marketed under the tradename of ATGARD-C[1/].

The active ingredient in ATGARD-C is 2,2-dichlorovinyl 0,0-dimethyl phosphate, commonly known as dichlorvos, dichlorphos, and DDVP. Chemically it is a colorless or pale yellow liquid, slightly soluble in water (about 1%) and readily soluble in most organic solvents (Berg, 1970). As a swine anthelmintic, dichlorvos is formulated into plastic resin pellets with a relatively slow release rate (Hass, 1970). Dichlorvos inhibits acetylcholinesterases. It produces its anthelmintic effect by increasing or decreasing (depending on the effector organ) the frequency of spontaneous spike discharges of the cholinergic nerves of gastrointestinal nematodes; parasite death results from neural collapse (Hass, 1970). The anthelmintic efficacy of dichlorvos is reported to be 100% for most gastrointestinal parasites (Batte et al., 1965; Hass, 1970; Hass and Young, 1973; Young, Hass, and Brown, 1972).

[1/] Registered Tradename, Shell Chemical Company

The physiological action and metabolic fate of dichlorvos in the host animal have been explored. A large, single, oral dose of dichlorvos inhibits cholinesterase activities of the red blood cells and plasma; both red blood cell and plasma cholinesterase activities regenerate rapidly, and regain normal levels within five days (Ward and Glicksberg, 1971). The metabolic fate of dichlorvos is described in experiments with radioactively labelled dichlorvos, either ingested or inhaled by swine, which show no residues of dichlorvos, dichloroacetaldehyde, dimethyl dichlorvos, dichloroacetic acid or dichloroethanol in tissues samples from market hogs, gestating sows or their progeny (Loeffler et al., 1971; Page et al., 1971, 1972; Potter et al., 1973a, 1973b). The carbon- and chloride- labelled residues found in the tissues are believed to be due to degradation of the vinyl group in dichlorvos into chloride ions and the incorporation of the carbons into normal tissue constituents such as glycerine, serine, creatine, glucose, glycogen, fatty acids, cholesterol, choline, lecithin, and ribonucleic acids (Potter et al., 1973b).

Investigation has been made of the beneficial side effects observed when dichlorvos is administered to gravid sows and gilts. In a study on reproductive performance in sows, Bazer, Robison and Ulberg (1969) report that dichlorvos fed at a level of 800 mg per head per day to gilts for 21 days prior to breeding results in a significantly higher number of corpora lutea and a corresponding increase in the number of embryos. At farrowing, however, there were

no significant effects of dichlorvos treatment on the number born alive, number born dead, litter weight or individual piglet weight. Other workers (England et al., 1969; England and Day, 1970) report no indications of a beneficial effect of dichlorvos on ovulation rate or embryo numbers in the prebreeding or early gestation periods.

The major influence of dichlorvos feeding during gestation on sow productivity is through its favorable influence on both pre- and post-natal piglet survival. In a series of studies, England (1969a, 1969b) and England and Day (1970, 1971) report that late gestational feeding of dichlorvos to gravid swine increased average birth weights, decreased preweaning death losses and did not affect average weaning weight. Other workers (Batte et al., 1969; Batte, Robison and Moncol, 1969a, 1969b; Foster, 1968; Singh, Perkins and Schooley, 1968; Young, Hass and Brown, 1972) report increases in numbers of pigs born alive, birth weights, survival and growth rates to weaning. Findings by Bunding et al. (1972) indicate that gestational feeding of dichlorvos reduces the farrowing interval between piglets and decreases the incidence of stillbirths. Kennick et al. (1969) found no residual effects on carcass or meat characteristics at slaughter weight of progeny from dams fed dichlorvos during gestation.

In another study series (Anderson, 1970; Anderson and Wahlstrom, 1970a, 1970b) no main effect on farrowing performance due to dichlorvos feeding was found, but the interaction between dichlorvos and energy

intake was significant for the number of pigs born and the number born alive. Gilts receiving dichlorvos and a high energy intake farrowed more pigs per litter and had more pigs born alive per litter than the other groups.

The above reports establish that dichlorvos feeding in late gestation has a beneficial influence on farrowing and pre-weaning performance. The importance of those findings is more readily appreciated when it is understood that the benefits are beyond and apparently not dependent upon the mere removal of parasites (Young, Hass and Brown, 1972). The role of the interaction of dichlorvos and energy level intake during gestation needs further examination and clarification. The object of the present study is to investigate that interaction as a possible method for increasing sow productivity.

GRAVID SOW AND GILT NUTRITION

The nutritional requirements of pregnant swine and the effects of deprivation of various nutrients are covered extensively in published reports. Excellent reviews in the area of nutrition and reproduction in swine (Tassell, 1967) and in maternal nutrition and progeny performance of swine (Pond, 1973) are available.

The average age at puberty of gilts is about 200 days, but can vary markedly by breed and environment (George and England, 1974), including nutrition. Plane of nutrition has little effect on age at sexual maturity in native South African gilts (Holness, 1969). Fast growing gilts reach puberty earlier than slower growing gilts,

but no effect on puberty due to feeding level is found; although gilts fed ad libitum are heavier at first estrus (Robertson et al., 1951). Full-fed gilts are shown to be heavier at puberty, but limit-fed animals reached puberty slightly earlier in a study by Self, Grummer and Casida (1955).

Other workers have modified their nutrition trials on puberty to hold the other components of the ration constant while varying energy levels. Using two levels of productive energy, Gossett and Sorenson (1959) showed that on the lower energy diet, gilts reach puberty earlier; these results are similar to those of Self et al. (1951). Excessive reduction in energy intake has adverse effects, however, Haines, Warnick and Wallace (1959) reported that reducing energy intake by 50% of that of the full-fed group increased the age at puberty.

Much evidence exists which indicates that a high level of nutrition (flushing) results in a higher ovulation rate in gilts. Increases of two or more ovulations in the first or second estrus due to increased feed intake have been reported (Robertson et al., 1951; Self et al., 1955; Brooks et al., 1972). Attempts to "flush" sows are not successful (Brooks and Cole, 1971, 1972a, 1972b). A high plane of nutrition after conception, however, results in increased embryonic mortality (Robertson et al., 1951; Self et al., 1955; Dutt and Chaney, 1968). Starvation of the dam can produce death losses among embryos of the same magnitude as high energy intake (McGillivray et al., 1962).

Postulated explanations for the causes of increased embryonic mortality due to nutrient intake are endocrine differences (Rigor et al., 1963), uterine space limitations (Dzuik, 1968) and/or uterine secretions (Bazer et al., 1968; Bazer, 1970).

While the importance of nutritional factors affecting sow productivity cannot be diminished, the quality of sow productivity is the major concern of this literature review. Rippel (1970) in reviewing protein and amino acid nutrition during the gestation of sows states that the sow "effectively buffers her offspring, both before and after birth, against nutritional inadequacy." This statement comes after observing that reproductive criteria are not responsive to dietary protein level during the last trimester of pregnancy. The finding that the number of total and live piglets farrowed, birth weight and livability are not influenced by maternal protein intake is supported in works by Spriell, Hays and Cromwell, 1968; Meade et al., 1966; Hawton and Meade, 1971; Frobish, Speer and Hays, 1966; Bowland, 1964a, 1964b; and DeGeeter, 1971. However, severe protein restrictions during gestation and lactation significantly impairs subsequent reproductive efficiency (Svajger et al., 1972) and reduces the quantity or quality of milk produced by the dam with subsequent effects on growth of the progeny (DeGeeter et al., 1973).

Unlike protein intake, energy intake by the dam during gestation greatly affects the quality of piglets produced. Restriction in energy intake results in a reduction of individual pig birth weights. This phenomenon and its magnitude are demonstrated by several investigators.

Restricted feed and energy intake from conception to farrowing reduced average pig birth weight in sow and gilt litters in the following studies: Adam, 1972; Adam and Shearer, 1971; Clawson, 1964; Lodge, Elsley and MacPherson, 1966a; Frobish, 1970; Henson, Eason and Clawson, 1964; and Vermedahl et al., 1969. The number of piglets born and number stillborn were unaffected by energy level in these trials in which the highest energy level (approximately 7000 kcal/day D.E.) is approximately that recommended by the N.R.C. (1968) and the lowest energy level is approximately 50% of the higher level. No differences in survival or weaning weights between litters from dams fed restricted energy and litters from dams fed higher energy were detected at weaning. Other studies (Adam, 1972; Adam and Shearer, 1971; Frobish, 1970; Henson, Eason and Clawson, 1964; Lodge, Elsley and MacPherson, 1966a) indicated that limited feeding for the first half of gestation followed by heavier feeding to farrowing will give similar results to heavier feeding through gestation.

O'Grady (1967), Supnet and Eusebio (1970) and Arabian (1970) report data demonstrating high energy throughout gestation to either affect birth weights or to significantly reduce both birth weight and survival.

A high energy intake during gestation results in significantly increased maternal weight gain (Lodge, Elsley and MacPherson, 1966b; Adam and Hargreaves, 1970; Pike and Boaz, 1972). Building up sow body reserves during gestation is energetically inefficient if those reserves are utilized for lactation (Smith, 1960a, 1960b). Feeding for gain during lactation as suggested by Smith (1960b) does not

produce the effects on birth weight as high energy intake in gestation does (Hitchcock et al., 1971).

Several workers investigated some biochemical and physiological traits of piglets produced from sows fed different energy planes during gestation. Anderson and Wahlstrom (1970b) report lower total reducing sugars at birth in piglets from gilts with higher gestation weight gains. Buitrago et al. (1974) suggests that energy deficient diets during gestation might involve a reduction in all major nutritional elements (fats, glucose, and protein) for the fetus. A reduction in muscle fibers is also noted, indicating the possibility that energy restriction in gestation might cause hyperplastic growth of progeny skeletal muscles. Seerly and co-workers (1974) indicate increasing energy intake from the 109th day of gestation with corn oil rather than corn starch enhances survival of piglets under 1.0 kg birth weight, possibly from the increased carcass lipids.

The literature reveals that high energy intake during gestation improves piglet quality (e.g.--birth weight increased). "High" energy intake in most of these studies is approximately equal to the N.R.C. (1968) requirements for gestating swine, 6600 kcal D.E. per day. One of the questions explored in this dissertation will be the significance to piglet birth and weaning traits of energy intake during late gestation that is substantially more than the N.R.C. requirements.

CARBOHYDRATE METABOLISM IN PREGNANCY: MATERNAL AND PERINATAL COMPONENTS IN SWINE AND OTHER SPECIES

No review of the literature on carbohydrate metabolism is complete without reference to diabetes; yet diabetes mellitus has not been demonstrated to naturally occur in swine (Anderson, Elsley, McDonald and MacPherson, 1971). Surgically, diabetes can be induced but partial pancreatectomy in the pig doesn't result in as severe diabetes as in the case of other animals (Carlson and Drennan, 1912), although complete pancreatectomy does lead to fatal diabetes. Carlson and Drennan (1912) state that swine have a poor tolerance for glucose. Eveleth (1933) is in agreement with this statement as are Bunding, Davenport, and Schooley (1956). These early works indicate that the pig is a possible prediabetic or chemical diabetic.

Thus, selected works on diabetes mellitus do have a place in a literature review on carbohydrate metabolism in swine, prefaced with the understanding that normal and abnormal carbohydrate metabolism in the human being may not be parallel to that of swine. Several excellent reviews are available; basic carbohydrate metabolism is reviewed by Lehninger (1972); endrocrine function of the pancreas by Tepperman (1962), insulin and glucose homoeostasis by Catt (1970) and Carbohydrate Metabolism and its Disorders by Dickens, Randle and Whelan (1968).

Abnormal glucose metabolism is identified by a glucose tolerance test. The glucose tolerance test consists of an oral or intravenous

dose of glucose followed by blood glucose level measurements over an extended period of time (Dickens, Randle and Whelan, 1968). The pattern of blood glucose disappearance is the basis for determining abnormal carbohydrate metabolism. Diabetes mellitus causes an abnormally high fasting blood glucose level, an excessive rise after oral glucose, and a delayed return to normal levels. Smaller deviations from the normal pattern of blood glucose disappearance indicate the presence of "chemical diabetes", which may be a manifestation of early diabetes mellitus, or of a hormonal disorder other than insulin (Catt, 1970). The oral and intravenous glucose tolerance tests, as discussed by Anderson et al. (1971), are emperical tests designed to identify pathological abnormalities of carbohydrate metabolism.

Methods of quantitating the glucose tolerance test have been suggested. Fishberg (1930) showed that when foreign sugars such as xylose and galactose are injected intravenously into the rabbit, their rate of disappearance from the circulation is exponential with regard to time. Duncan (1956) computes a "total index" of glucose tolerance by plotting the logarithm of the total blood glucose concentration against time and an "increment index" which measures glucose tolerance as the fall of blood glucose per minute expressed as a percentage of the increment blood glucose value at that time. As the "increment index" is reproductible in an individual within a two-fold variation in the dose of glucose injected, it is the preferable measure of glucose tolerance. In Duncan's study (1956) the "increment index"

for normal individuals is 3.68 and for mildly diabetics is 1.83. However, Frankson and co-workers (1962) conclude that no one overall formula can be used to describe the whole glucose tolerance curve and that the rate of glucose disappearance after the diffusion of free glucose in its space of distribution is a simple exponential function.

Using the simple exponential function method, Taton et al. (1964) report a formula for determining the glucose clearance rate (K) in terms of the percent of glucose disappearing per minute. K values are reported for human subjects with diabetic parents, 1.65; subjects with a family history of diabetes, 1.71; and subjects with no family history of diabetes, 2.28. Sowers and workers (1969) report K values for Hormel miniature swine ranging from 0.92 to 3.64% per minute finding no statistically significant relationship found between the K value and fasting serum glucose, age, sex or body weight. While other workers report the results of glucose tolerance test in swine, the K value is not reported. Bunding, Davenport and Schooley (1956) observed changes in glucose tolerance patterns suggesting a diabetic response in stunted Yorkshire pigs, and a pattern change or decreased tolerance of glucose with age. The results of an intravenous glucose tolerance test when performed on the pig parallel the type of curve produced when the test is made on normal human subjects (Hanawalt, Link and Sampson, 1947). Some sow glucose tolerance patterns are reported in terms of the half-life of added glucose and the tolerance time (elapsed time for elevated blood glucose levels to drop to fasting levels); half-lives averaged 11.0 minutes and tolerance times ranged

from 17 to 47 minutes (Anderson and Elsley, 1970). Another report shows tolerance times in non-pregnant sows or sows in early gestation to average 28.8 minutes (Anderson et al., 1971).

Pregnancy as a diabetogenic event is the subject of reviews by Kyle (1963), and Wilkerson and Remein (1957). Kyle (1963) states:

> Pregnancy may be considered as a diabetogenic event which is nevertheless survived without apparent diabetes by the great majority of women. The mechanisms of this tendency towards diabetes is unknown although it is presumed to be the result of hormonal influences. Whether or not abnormalities of carbohydrate tolerance appear probably depends on the functional state of the islets of Langerhans prior to conception; normal islets meet the demand of pregnancy but functionally inadequate islets cannot, and hyperglycemia supervenes.

Wilkerson and Remein (1957) support this statement with an estimated incidence of 6.2% abnormal oral glucose tolerance tests in 17,000 unselected pregnancies and report a higher incidence with the progression of pregnancy: 1.5% of 134 negative glucose tolerance tests in the first trimester become positive in the second and 10% of 1253 negative glucose tolerance tests become positive in the third. Kyle (1963) concludes that while pregnancy is diabetogenic; the causes of this diabetogenic effect; which could be the result of insulin antagonists, the placental degradation of insulin, or both, are known.

Offspring born to mothers having an abnormal glucose tolerance test are heavier at birth than those newborn of mothers with normal glucose tolerance tests (Kyle, 1963; Wilkerson and Remein, 1957; Jackson, 1954; Francois et al., 1974; Kriss and Futcher, 1948). This phenomemon of large babies born to diabetic mothers is so closely correlated to diabetes that any human giving birth to a baby over 4.5 kg is con-

sidered to be a potential diabetic (Kriss and Futcher, 1948). In these women the development of clinical diabetes occurs in an average of 24 years, with a range of 1 to 46 years following the birth of the abnormally large child. Jackson (1954) suggests the "large baby production" is not entirely due to maternal factors but is a part of an inherited phenomenon linked to the genetic constitution of either parent.

Anderson et al. (1971) report data indicating that the glucose tolerance of the sow is associated with mean weight of the offspring ($r = +0.58$) but not with the number in a litter or with the total litter weight. Thus, the question of how the fetal components respond to blood glucose levels needs to be explained. Jack and Milner (1973) in a series of experiments with fetal decapitation with rabbits showed that plasma insulin concentrations of the decapitated fetuses were higher than those of the control with no differences noted in pancreatic insulin concentration. The pancreas of decapitated animals secrete more insulin than does that of the controls. The results of these experiments suggest that cephalic factors influence the development of pancreatic beta cell function in the fetal rabbit. Basset and others (1973) report that insulin release from the pancreas of the fetal lamb can be stimulated by glucose at the concentrations present in plasma and imply that glucose is a physiological regulator of insulin release in the lamb in utero.

Shelley (1973) suggests that the fetal lamb in the last third of gestation can regulate its plasma glucose level to some extent by

life, is lowest on the day of birth, and increases thereafter (Mersmann et al., 1972). Pyruvate kinase and phosphofructokinase activities are also low at birth in the pig while glucose-6-phosphatase activity increases during fetal life and the first days of neonatal life (Mersmann, 1971). Thus the potential to utilize gluconeogenesis is enhanced after birth.

Several workers (Sampson, Hester and Grahnm, 1942; Goodwin, 1957: Swiatek et al., 1968) report, however, that fasting neonatal piglets suffer from acute hypoglycemia as the result of an impairment of gluconeogenesis. Some work with human infants from diabetic mothers indicates a high incidence of hypoglycemia; this condition can be correlated with hyperinsulinism of the newborn (Francosis et al., 1974). Hypoglycemic underweight newborn children have significantly different plasma free fatty acid and blood lactate concentrations than normoglycemics following an intravenous glucose load; this suggests different hormonal responses, both quantitatively and qualitatively (Soltesz et al., 1972).

In the neonatal pig, plasma fructose decreases to zero and plasma glucose sharply increases from birth to two hours and declines by 32 hours of age (Pettigrew, Zimmerman and Ewan, 1971). Curtis, Heidenreich and Folley (1966) report similar patterns in the neonatal pig.

The role of insulin in glucose tolerance tests and carbohydrate metabolism can be reviewed in any of four references presented earlier in the review. Further explanation of insulin's mechanism(s) of action

and release is needed. Insulin response to glucose loading or an intravenous glucose tolerance test demonstrates individual differences often not associated with diabetes. In 15 out of 85 normal human subjects the plasma insulin response during a glucose tolerance trial is reported to be of the diabetic type although they had normal glucose tolerance (Cerasi and Luft, 1967c). This low response of insulin is shown to occur in a given individual under different stimuli, such as intravenous tolbutamide or oral glucose; thus the response is characteristic for a given individual (Cerasi and Luft, 1967b). Work with monozygotic twins, one diabetic, the other non-diabetic, demonstrates that the non-diabetic members have similar insulin response curves, and that the insulin response curve is both genetically determined and a prerequisite for the development of diabetes mellitus (Cerasi and Luft, 1967a). These findings are of low response of insulin; other workers (Bagdade, Bierman and Porte, 1967) report that elevated levels of insulin, both basal and in response to glucose, are related to obesity.

Kipnis (1968) suggests that measurements of circulating insulin responses to various insulinogenic stimuli indicate that the impairment of the secretion of insulin is a characteristic feature of the diabetic state.

Conn and Fajan (1961) state that "the high incidence of fetal complications of preganacy in women destined to become diabetics many years later supports the existence of an active metabolic abberation long before the insulogenic mechanism becomes overwhelmed."

Cunningham and Friend (1965) found that subcutaneous injection of epinephrine as well as norepinephrine increases plasma free fatty acids and glucose concentrations in the blood. Hertelendy et al. (1966) with infusions of epinephine in pigs, produced severe hyperglycemia with no rise in plasma insulin level until after the infusion was ceased. It appears that epinephine blocks the insulin release normally induced by high glucose levels.

In a series of papers (Porte, 1969; Porte and Robertson, 1973; Porte et al., 1973; Robertson and Porte, 1973) it is observed that:

(a) Catecholamines stimulate a pancreatic alpha-receptor blocking insulin release

(b) Catecholamines stimulate a pancreatic beta-receptor stimulating insulin release

(c) Intercellular cyclic AMP is decreased by alpha activity and increased by beta-receptor activity

(d) Glucose-stimulated insulin secretion can be blocked by activation of the sympathetic nervous system, but insulin output is maintained by simultaneous beta-receptor stimulation.

Thus, it is postulated that abnormal glucose-induced insulin secretion in diabetes is due to defects within specific pancreatic glucose receptors and not beta adrenegic receptors.

It is obvious from the literature review that the roles of insulin, the glucose tolerance test and pregnancy in carbohydrate metabolism are at best unclear. As illustrated in the literature review, the pig has an apparent tendency towards impaired carbohydrate metabolism. By following the sow through the course of gestation and monitoring her carbohydrate metabolism via the glucose tolerance test, the diabetogenic effect of pregnancy may be better understood.

STUDY I. CARBOHYDRATE METABOLISM AND REPRODUCTIVE PERFORMANCE OF SOWS

Introduction

The large neonatal piglet can survive, for nutrient availability, thermostability, and avoidance of trauma are adequate under common management practices, but not so for small pigs. Obviously the dam has some influence over the growth of the individual piglets in utero. The carbohydrate metabolism of the dam can influence the development of the fetus. Babies born to diabetic and "prediabetic" women have been reported to be heavier at birth than those born to non-diabetic women (Kyle, 1963). In addition, higher rates of fetal losses, stillbirths and congenital defects have been associated with impaired carbohydrate metabolism during gestation (Wilkerson and Remein, 1957).

Diabetes mellitus has not been demonstrated to occur naturally in swine; although it has been reported by several investigators that swine vary markedly in their response to a glucose load (Bunding, Davenport and Schooley, 1956; Anderson and Elsley, 1970). It has been demonstrated that the response of insulin to a glucose load is controlled genetically (Cerasi and Luft, 1967a). Thus, it is possible that certain relationships exist between production traits and carbohydrate metabolism. This paper reports the results of a study to determine the glucose clearance rate of individual sows at a specific time in early gestation and examines the relationship of glucose clearance rate to sow reproductive performance.

Materials and Methods

Sixteen Yorkshire x Berkshire crossbred sows, consisting of six second parity, four third parity, four fifth parity and two sixth parity animals, were utilized from the Oregon State University Experiment Station Swine Center sow herd. These had previously weaned a litter and had been bred on the first estrus following weaning. Through the course of gestation, they were housed in confinement in groups in pens with concrete slatted floors and were group fed 2.2 kg per head per day. The ration contained 14% crude protein and an energy content of 3230 kcal D.E. per kg (Appendix A).

On day 20 post-breeding each sow was removed from the group pens and a poly vinyl catheter, 1.52 meters long, was inserted 45.7 centimeters into the anterior vena cava via needle puncture. A 16 gauge needle was immediately attached to the access end of the catheter and was flushed with 3.5% sodium citrate. The catheter was then taped in place along the sow's neck or inserted subcutaneously along the neck of the sow. In either case the access end of the catheter was exposed at the top of the animal's shoulders, flushed with 3.5% sodium citrate, capped and taped into place.

Following a twenty-four hour fast during which the sow was confined to a farrowing crate, the access end of the catheter was freed; the excess length of the catheter permitted work without further restraint of the animal. The glucose tolerance trial was initiated by drawing 10 ml blood samples with a syringe via the indwelling catheter at -15 and 0 minutes pre-infusion. At 0 minutes 0.15 gm glucose per

kg body weight was infused rapidly via the indwelling catheter; 10 ml blood samples were then taken at 2, 4, 6, 8, 10, 20, 30, 40, 60, and 120 minutes post-infusion. Upon withdrawal, all blood samples were immediately placed in test tubes each containing 1.0 ml of 4% sodium fluoride and 4% potassium oxalate (dried prior to use). Following mixing of the blood in each tube, the plasma was separated by centrifugation and stored at -19°C until assayed.

Plasma glucose was determined by the enzymatic/colorimetric method described in Sigma Technical Bulletin #510 (Sigma Chemical Co., 3500 DeKalb Street, St. Louis, Missouri, 63118). Colorimetric determinations were made with a standard Bausch and Lomb Spectronic 20 Colorimeter. All glucose determinations were performed in duplicate and the mean value of the duplicates was used in all calculations.

Two measures of glucose tolerance used were T_o and T_i; both values were measured from the regression of the logarithm of plasma glucose concentration on time and represent the elapsed time for plasma glucose levels to return to fasting concentrations following glucose infusion. The T_o value represented the time in minutes for plasma glucose levels to return to the fasting level, measured from the end of infusion, and T_i values represent the elapsed time from the beginning of infusion. The half-life of the injected glucose was calculated by the equation, half-life = $\log_{10}2/b$; where b is the regression coefficient of the regression of the logarithm of the absolute plasma glucose concentration on time (Anderson and Elsley, 1970). The glucose clearance rate (K), % per minute, was determined by the method described by Taton et al.

(1964) in which K was calculated as the quotient of 69.4 (a constant) and the half-life of injected glucose. Data were collected on the number and weight of piglets born to each sow at normal parturition subsequent to the glucose tolerance trial.

Results and Discussion

Table 1 contains the results of the intravenous glucose tolerance trials performed at day 21 post-breeding. The difference between the times for plasma glucose levels to return to fasting levels from the end of infusion, T_o, and from the beginning of infusion, T_i, represent the mean infusion time period of 1.4 minutes. The mean values for the tolerance times, T_i and T_o, are not in close agreement with the results for sows and gilts in the study by Anderson and Elsley (1970), who report tolerance times from 19 to 47 minutes with the distribution significantly skewed to the higher tolerance times. The mean glucose clearance rate (K), 5.75% per minute, and the mean glucose half-life ($T_{1/2}$), 13.0 minutes, are in close agreement with Anderson and Elsley's (1970) reported values of 5.8% per minute and 11.9 minutes. However, the K values reported by Sowers et al., (1970) for miniature swine only range from 0.92 to 3.64% per minute. These discrepancies are apparently due to differences in the amount of glucose infused, the time length of infusion, and the length of the fasting period before the tolerance test was begun. In the study by Sowers et al. (1970) 1.0 gm glucose per kg of body weight was administered intravenously in three minutes following a 26-30 hour fast by minature swine. Andersen

TABLE 1. MEASUREMENTS OF GLUCOSE TOLERANCE OF 16 SOWS AT DAY 21 POST-BREEDING.

Item	Mean	±S.E.
T_o[1] (min)	19.4	1.2
T_i[1] (min)	20.8	1.3
K[1] (%/min)	5.75	0.47
$T_{1/2}$[1] (min)	13.0	0.9
Sow Weight (kg)	185.1	7.0

[1]See text for definition.

TABLE 2. GLUCOSE TOLERANCE CORRELATIONS WITH SOW BODY WEIGHT (n=16)

	T_o[1]	T_i[1]	K[1]	$T_{1/2}$[1]
Body Weight (kg)	-0.45	-0.44	0.29	-0.21

[1]See text for definition.

and Elsley (1970), however, using Large White sows, infused only 50 gm of glucose I.V., in four minutes after a 15 hour fast by sows weighing 110 to 240 kg. The glucose clearance rate (K) appears to be dependent upon the glucose load and more critically on the fasting time period.

The transformation of the plasma glucose concentrations to logarithmic values regressed against time produced a straight line from the end of infusion to the time at which plasma glucose concentrations reached fasting levels (Appendix B). This relationship agrees with the work of Taton et al. (1964) in calculating K values and supports the concept that the differences in K values are due to differences in glucose concentrations and fasting times.

The correlations of the body weight of the sows with their glucose tolerance test results reveals no significant correlations (table 2). This finding is confirmed with others (Sowers et al., 1969; Anderson and Elsley, 1970). It has been suggested that glucose tolerance decreases with age (Bunding, Davenport and Schooley, 1956). In the present study, glucose tolerance tends to become more efficient with increasing parity (table 3), although the trend was not significant ($P<0.05$)

Of the 16 sows that had glucose tolerance tests performed on day 21 post-breeding, seven failed to farrow as a result of that breeding. Comparisons of the glucose tolerance data failed to reveal any significant differences between those sows that conceived and those that failed. The results in table 4 report the mean values of the glucose tolerance trial and the reproductive performance of the nine sows that farrowed.

TABLE 3. MEASUREMENTS OF GLUCOSE TOLERANCE IN SWINE OF DIFFERENT PARITIES.

Item	Parity 2	3	5	6
T_o[1] (min)	21.7	19.1	17.8	16.7
T_i[1] (min)	23.0	20.7	18.8	18.1
K[1] (%/min)	5.2	6.3	5.0	8.0
$T_{1/2}$[1] (min)	15.9	11.7	14.3	10.3
n	6	4	4	2

[1]See text for definitions.

TABLE 4. MEASUREMENTS OF GLUCOSE TOLERANCE AT DAY 21 OF GESTATION AND SUBSEQUENT REPRODUCTIVE PERFORMANCE FOR 9 SOWS.

Item	Mean	±S.E.
T_o[1] (min)	19.4	2.1
T_i[1] (min)	20.8	2.2
K[1] (%/min)	5.62	0.77
$T_{1/2}$[1] (min)	13.7	1.4
Sow weight (kg)	187.9	7.7
Number born (#/litter)	9.1	1.3
Litter weight (kg)	12.8	1.5
Mean birthweight/piglet (kg)	1.45	0.08

[1]See text for definitions.

TABLE 5. MEASUREMENTS OF GLUCOSE TOLERANCE AND SOW BODY WEIGHT CORRELATED WITH REPRODUCTIVE PERFORMANCE (n=9).

	Number born	Litter Weight	Mean Birth Weight
T_o[1] (min)	-0.41	-0.25	0.70*
T_i[1] (min)	-0.41	-0.24	0.72*
K[1] (%/min)	0.03	0.03	-0.18
$T_{1/2}$[1] (min)	0.01	0.07	0.31
Sow body weight	0.73*	0.77*	-0.34

[1]See text for definitions.

*Significant at $P<0.05$.

TABLE 6. PREDICTION MODELS FOR MEAN PIGLET BIRTH WEIGHT (kg) BASED ON GLUCOSE TOLERANCE TIME OF DAMS.

a) Mean Birth Weight = 0.875 + 0.028Ti

$R^2 = .514$

b) Mean Birth Weight = 0.925 + 0.027To

$R^2 = .4897$

The similarity between the data in table 1 and table 4 illustrates the similarity between conceiving sows and those failing to settle.

Correlations (table 5) between glucose tolerance parameters, sow body weight, pigs per litter, litter weight, and mean piglet birth weight reveal some significant correlations. Mean piglet birth weight was correlated ($P<0.05$) with tolerance time from the end of glucose infusion, T_o, ($r=0.70$) and the tolerance time from the beginning of infusion, T_i, ($r=0.72$). The number born per litter and litter weight was correlated ($P<0.05$) with sow body weight; correlation values were 0.73 and 0.77 respectively. The correlation with body weight contains a reflection of parity effects as sows with increased parities were heavier. The correlation coefficients for tolerance times and mean birth weights are in agreement with a similar study by Anderson et al. (1971) who report a correlation coefficient of 0.58.

Two prediction models for the determination of mean piglet birth weight from glucose tolerance times account for 51 and 49 percent of the variation in weights (table 6). No significant improvement was made by the inclusion of parity or sow weight into the models.

This study only draws attention to the relationship of glucose tolerance times and mean birth weights of pigs. The results obtained, in reference to work cited for comparison of glucose tolerance measurements, are conflicting. The conflicts arise from the changes of the standard glucose tolerance trial dose of glucose from 0.5--1.0 gm per kg of body weight to 0.15 gm per kg body weight as used in this study.

Thus, in this study, elevated plasma glucose levels are only sustained for 10 to 30 minutes while in other studies (using 0.5 to 1.0 gm glucose per kg body weight) elevated plasma glucose levels persist for 2 to 3 hours. The modification presented here more closely approximates an actual physiological response to ingested glucose whereas the standard glucose tolerance trial is a qualitative test to monitor abnormal carbohydrate metabolism.

The question of the mechanism(s) by which dams with less efficient glucose tolerance produce larger offspring has not been clarified. Kyle (1963) reviewed the diabetogenic effect of gestation and concluded that impairment of carbohydrate metabolism is presumed to be the result of hormonal influences; the result of insulin antagonists, the placental degradation of insulin, or both. Perhaps the sows with less efficient glucose tolerance more closely approach the diabetic state, and the relationship of birthweight and tolerance in swine is essentially similar to the "large baby" phenomenon of the diabetic human.

Summary

Glucose tolerance trials were performed on sixteen sows of varying parity on day 21 post-breeding and the reproductive performance as result of that breeding was recorded. The time for plasma glucose levels to return to fasting levels, the half-life of added glucose, and the glucose clearance rate were calculated from the regression of the logarithm of the plasma glucose concentrations against time. Tolerance time was significantly correlated ($P<0.05$) with mean piglet

birth weight, while sow body weight was significantly correlated ($P<0.05$) with the number born and litter weight. No significant differences ($P<0.05$) were observed for glucose tolerance measurements of sows conceiving and those failing to settle. A tendency for sows of increased parity to have more efficient glucose clearance rates was noted but the measurements of glucose tolerance were not affected by parity or body weight of the sow.

STUDY II. MEASUREMENTS OF THE DIABETOGENIC EFFECTS OF PREGNANCY IN SOWS

Introduction

Human pregnancy is considered a diabetogenic event that is normally survived without apparent diabetes (Kyle, 1963). However, disturbances of pregnancy associated with diabetes occur with increasing frequency among prediabetic women (Wilkerson and Remein, 1957). While naturally occurring diabetes mellitus has not been observed in swine; Bunding, Davenport and Schooley (1956) suggest that upon reaching maturity, swine become poorer tolerators of glucose. The findings of Anderson et al. (1971) establish that, like the human diabetic or prediabetic, sows with decreased glucose clearance rates produce offspring with heavier birth weights. Thus, the concept of the sow as a potential prediabetic is a valid hypothesis.

This study examines the glucose clearance rate and insulin secretion pattern during the course of gestation as a monitor of carbohydrate metabolism and the possible prediabetic condition.

Materials and Methods

Six Yorkshire x Berkshire crossbred sows from the Oregon State University Experiment Station swine herd were studied through the course of one gestation. These were evenly divided into second, fifth, and sixth parity groups. All had been bred on the first estrus following weaning of their litters. They were housed in confinement in group pens with concrete slatted floors until the 84th day post-breeding at

which time they were housed in individual pens until removal to individual farrowing crates a few days prior to parturition. Throughout gestation each was fed 2.2 kg per head per day of a ration containing 14% crude protein and 3230 kcal D.E. per kg (Appendix A).

On day 20, 83, and 109 post-breeding each sow was removed from the pen and a polyvinyl catheter, 1.52 meters long, was inserted 45.7 centimeters into the anterior vena cava via needle puncture. A 16 gauge needle was immediately attached to the access end of the catheter, and the catheter was flushed with 3.5% sodium citrate. The catheter was then taped in place along the neck of the sow or inserted subcutaneously along the sow's neck. In either case, the access end of the catheter was exposed at the top of the animal's shoulders. The catheter was then flushed with 3.5% sodium citrate, capped and taped into position.

Following a 24 hour fast during which feed and water were withheld and the sow was confined to a farrowing crate, the access end of the catheter was freed and the excess length of the catheter permitted work without further restraint of the animal. The glucose tolerance trial was initiated by drawing 10 ml blood samples with a syringe via the indwelling catheter at -15 and 0 minutes pre-infusion. At 0 minutes 0.15 gm glucose per kg body weight was infused rapidly through the indwelling catheter; 10 ml blood samples were taken at 2, 4, 6, 8, 10, 20, 30, 40, 60, and 120 minutes post-infusion. Immediately upon withdrawal, all blood samples were placed in test tubes containing 1.0 ml of 4% sodium fluoride and 4% potassium oxalate (dried prior to use)

and mixed. The plasma was separated by centrifugation and stored at -19°C until assayed.

Plasma glucose was determined by the enzymatic/colorimetric method described in Sigma Technical Bulletin #510 (Sigma Chemical Co., 3500 DeKalb Street, St. Louis, Missouri, 63118). Colorimetric determinations were made with a standard Bausch and Lomb Spectronic 20 Colorimeter. Plasma insulin determinations were made by the radioimmunoassay method using the Phadebas Insulin Test (Pharmacia Laboratories Inc., 800 Centennial Ave., Piscataway, New Jersey, 08854). All glucose and insulin determinations were performed in duplicate and the mean of the duplicates was used in all calculations.

Two measures of glucose tolerance were T_o and T_i, both values were measured from the regression of the logarithm of glucose concentration on time and represent the elapse time for plasma glucose levels to return to fasting levels following a glucose infusion. The T_o value represented the time for plasma glucose levels to return to the fasting levels measured from the end of glucose infusion, and the T_i value represents the elapsed time from the beginning of infusion. The half-life of the injected glucose was calculated by the equation, half-life = $\log_{10} 2/b$; where b is the regression coefficient of the regression of the logarithm of the absolute plasma glucose concentration on time (Anderson and Elsley, 1970). The glucose clearance rate (K), percent per minute, was determined by the method described by Taton et al. (1964) in which K was calculated as the quotient of 69.4 (a constant) and the half life of injected glucose.

The data collected were analyzed by the two way analysis of variance (Steele and Torrie, 1960).

Results and Discussion

The results of repeated glucose tolerance tests on different days of gestation (table 7) indicate that in the sow, pregnancy is a diabetogenic event. The tolerance times, T_o and T_i, increased ($P<0.05$) as gestation progressed. Likewise, the glucose clearance rate, K, decreased and the half-life of added glucose, $T_{1/2}$, increased. These results show that as pregnancy proceeds the sow becomes a less efficient utilizor of glucose. These data agree with those of the study of Wilkerson and Remein (1957) in which a higher incidence of abnormal glucose tolerance tests occurred with the progression of human pregnancy. Kyle (1963) stated that the causes of the diabetogenic effect of pregnancy are possibly the results of insulin antagonists, the placental degradation of insulin, or both.

The resting plasma insulin levels of the sows after a 24 hour fast show no effect ($P<0.05$) due to day of gestation (table 8). These mean values for plasma insulin, ranging from 12.2 to 17.8 μU per ml, compared to the mean value of 5.8 μU per ml found by Machlin et al. (1968) for pigs weighing 20-24 kg are high. The mean insulin levels of 0.60 mμg or 15.0 μU for gilts weighing 67 to 84 kg in a study by Siers and Trenkle (1973) are in closer agreement with the values in this study. If, as Bunding, Davenport, and Schooley (1956) suggest, the tolerance to glucose of swine decreases with increasing age, then higher insulin

TABLE 7. MEASUREMENTS OF GLUCOSE TOLERANCE AS AFFECTED BY DAY OF GESTATION (n=6).

	Day of Gestation			
	21	84	110	±S.E.
T_o (min)	16.6[a]	20.7[b]	30.3[c]	1.4
T_i (min)	18.0[a]	22.3[b]	31.4[c]	1.4
K (%/min)	6.43[a]	5.37[b]	3.43[c]	0.41
$T_{1/2}$ (min)	11.7[a]	14.0[b]	20.9[c]	0.62

[abc]Values in the same horizontal plane with different superscripts differ significantly ($P<0.05$)

TABLE 8. PLASMA INSULIN FASTING LEVELS BY DAY OF GESTATION (n=6).

	Day of Gestation			
	21	84	110	±S.E.
Insulin (μU/ml)	17.8	17.3	12.2	3.7

levels in older (heavier) animals may represent a compensatory response.

Mean plasma insulin levels at the pre-designated time intervals by day of gestation indicate that high plateau levels of insulin remain longer as gestation progresses; especially in late pregnancy (table 9). On day 21 of gestation insulin levels are higher ($P<0.05$) at 8 minutes than at 10 minutes; by 20 minutes insulin levels have dropped to basal. The high values of insulin decline ($P<0.05$) after 10 minutes post-infusion on day 84, while on day 110 the insulin level at 20 minutes is not significantly different from prior levels but is greater ($P<0.05$) than at 30 minutes. The relative insulin levels at each time interval tend to be similar for days 21 and 84 but the magnitude of insulin response on day 110 appears to be lower than on day 21 or 84.

Catt (1970) states that insulin in the pancreatic beta cell forms two storage pools: a storage pool which responds by acute insulin release during stimulation and a pool that provides insulin secretion under basal conditions and during prolonged stimulation and replenishes the storage pool. Also, glucose stimulation results in peak insulin levels within two minutes followed by a further rise beginning sometime later. Table 9 shows this type of response; insulin levels have reached a plateau at 2 minutes post-infusion. Considering the half-life of porcine insulin to be six minutes (Stroll et al., 1971) then the results in table 3 also illustrate a secondary insulin release

TABLE 9. PLASMA INSULIN (μU/ml) IN RESPONSE TO INTRAVENOUS GLUCOSE BY DAY OF GESTATION.

Day of Gestation	Time Post-Infusion (minutes)									
	2	4	6	8	10	20	30	40	60	120
21	60.3[a]	63.8[a]	67.9[a]	77.5[a]	58.6[b]	15.2[c]	11.4[c]	14.9[c]	12.7[c]	13.2[c]
84	70.7[a]	83.0[a]	65.6[a]	83.8[a]	76.2[a]	34.7[b]	15.7[b]	15.8[b]	13.9[b]	16.3[b]
110	40.3[a]	39.6[a]	46.3[a]	43.9[a]	46.3[a]	57.1[a]	33.1[b]	27.8[b]	26.3[b]	19.9[b]

[abc]Values in the same horizontal plane with different superscripts differ significantly ($P<0.05$).

which accounts for the non-significant higher peak of insulin release at 8, 10, or 20 minutes on day 21, 84, or 110 of gestation.

It was noted that individual quadratic equations ($P<0.05$) describe the plasma insulin release and disappearance patterns for each sow (Appendix C); this is further indication that the pattern of insulin release differs as gestation progresses. In the quadratic equations used, plasma insulin levels are the dependent variable and time in minutes is the independent variable. Table 10 contains the means of the components of those equations and shows that the pattern of plasma insulin response post-intervenous-glucose is different ($P<0.05$) at day 110 of gestation from days 21 or 84.

The quadratic equations were differentiated and integrated to obtain the minima and area described by each curve. Table 11 shows the mean minima and area by day of gestation. Again the response of insulin differs by day of gestation. Minima values occur significantly later ($P<0.05$) as gestation proceeds. The area was calculated from 2 minutes post-infusion to the minima value to give an estimation of the amount of plasma insulin available. The area on day 21 is smaller ($P<0.05$) than the area on day 84, which is greater ($P<0.05$) than the area on day 110.

Correlations between insulin response and the glucose tolerance measurements are shown in table 12. The area under the insulin curve is not significantly correlated to any of the glucose tolerance parameters or to the insulin curve minima. The insulin curve minima are

TABLE 10. MEANS OF THE GENERAL MEAN AND SLOPES OF THE QUADRATIC EQUATIONS DESCRIBING INSULIN LEVELS IN RESPONSE TO INTRAVENOUS GLUCOSE.

Day of Gestation	μ	b_1	b_2	b_3
21	79.96^a	-3.58^a	0.056^a	-0.00026^a
84	92.71^a	-3.52^a	0.048^a	-0.00022^a
110	41.75^b	0.69^b	-0.022^b	0.00014^b

^{ab}Values in the same vertical plane with different superscripts differ significantly ($P<0.05$).

TABLE 11. MEAN MINIMA AND AREA DESCRIBED BY THE QUADRATIC EQUATIONS OF INSULIN RESPONSE TO INTRAVENOUS GLUCOSE.

	Day of Gestation		
	21	84	110
Minima (minutes)	48.2^a	62.3^b	84.7^c
Area	1232.3^a	2099.3^b	1679.5^c

^{abc}Values in the same horizontal plane with different superscripts differ significantly ($P<0.05$)

TABLE 12. CORRELATIONS OF MEASUREMENTS OF GLUCOSE TOLERANCE AND INSULIN RESPONSE (n=18).

Item	T_i[1]	K[1]	$T_{1/2}$[1]	Minima	Area
T_o[1]	.621*	-.814**	.912**	.648**	.340
T_i[1]	---	-.528*	.586*	.728*	.330
K[1]	---	---	-.895**	-.482*	-.135
$T_{1/2}$[1]	---	---	---	.618**	.271
Minima	---	---	---	---	.423

*P<0.05
**P<0.01
[1]See text for description.

positively correlated ($P<0.01$) to the tolerance times T_o and T_i; and to the half-life of added glucose. The minima are negatively correlated ($P<0.05$) to the glucose clearance rate, K. Based on these correlations it would appear that the minima described by the plasma insulin curve are realistic values, while the area is not a representation of total insulin release.

The results indicate that plasma insulin levels are affected by the course of pregnancy. Based on the data in table 9 it appears that the storage pool of insulin as described by Catt (1970) is exhausted as gestation progresses, and that by day 110 of gestation the insulin response at 2 minutes post-infusion is of reduced magnitude. Thus, the minima values reflect the longer period of synthesis and mobilization of insulin from the second pool. If the areas described by the plasma insulin curves are accepted as valid, which they may not be (table 12), then the greater ($P<0.05$) area on day 84 together with a greater ($P<0.05$) tolerance time suggest an insulin anatagonist as postulated by Kyle (1963) and other workers. The end result, regardless of what mechanism(s) increase tolerance times and decrease glucose clearance rate, is prolonged fetal exposure to elevated plasma glucose.

Summary

Glucose tolerance tests were performed on six sows of varying parity on day 21, 84, and 110 of gestation. The time for plasma glucose levels to return to fasting levels, the half-life of added glucose, and the glucose clearance rate were calculated from the

regression of the logarithm of plasma glucose concentrations against time. Insulin levels were measured by radioimmunoassay of the plasma samples. A quadratic equation of insulin levels as the dependent variable and time as the independent variables was found to describe a significant fit ($P<0.05$) of the insulin response post-glucose-infusion. The measures of glucose tolerance, tolerance time, glucose half-life and glucose clearance rate, showed a significant ($P<0.05$) tendency to glucose intolerance as gestation progressed. The magnitude of insulin response decreased with increased day of gestation, while plasma insulin level remained above basal levels longer.

STUDY III. EFFECTS OF DICHLORVOS AND INCREASED LATE GESTATIONAL ENERGY INTAKE BY SOWS AND GILTS ON REPRODUCTIVE PERFORMANCE AND PROGENY PERFORMANCE TO WEANING.

Introduction

Conflicting findings on the effects of energy intake by gestating swine exist in the literature. Forbish (1968) reported that increasing energy intake during gestation can increase the number of pigs born and reduce stillbirths. Other workers (Clawson et al., 1963; Lodge, Elsley and MacPherson, 1966; O'Grady, 1967; Baker et al., 1969) showed no influence of increased energy intake in the number of piglets farrowed, live or stillborn. Vermedahl's et al., (1969) findings showed that increased energy intake increased total number of piglets farrowed but had no effect on stillbirths.

Birth weights have been reported to increase with increased maternal energy intake by gravid gilts (Clawson et al., 1963; Lodge, Elsley and MacPherson, 1966; Vermedahl et al., 1969; Baker et al., 1969). Other workers show no effect of maternal energy intake on piglet birth weight (Forbish, Speer and Hays, 1966; Meade et al., 1966). No differences in survival or weaning weight between litters from dams fed restricted energy levels and litters from dams fed higher energy levels were detected.

Investigations have been made of the beneficial effects observed when dichlorvos was administered to gravid sows and gilts. In a series of studies, England (1969a, 1969b) and England and Day (1970, 1971) report that late gestational feeding of dichlorvos to gravid swine

significantly increased average birth weights, decreased preweaning death losses, and did not affect average weaning weight. Other workers (Batte et al., 1969; Batte, Robison and Moncol, 1969a, 1969b; Foster, 1968; Singh, Perkins and Schooley, 1968; Young, Hass, and Brown, 1972) report significant increases in numbers of pigs born alive, birth weights, survival, and growth rates to weaning.

This study was conducted to ascertain the effects of added energy and dichlorvos during late gestation on the reproductive performance of sows and gilts. In addition, the subsequent performance of the progeny was monitored to weaning to observe the residual effects of maternal energy intake and dichlorvos treatment.

Materials and Methods

One hundred sixteen bred Yorkshire and Yorkshire-Berkshire cross-bred sows and gilts from the Oregon State University Experiment Station swine herd were utilized in a feeding trial. They were housed in groups in confinement pens with concrete slatted floors until the 84th day post-breeding, at which time they were housed in individual pens prior to removal to the farrowing unit. At 84 days they were randomly assigned to one of four gestation rations for the remainder of gestation. One group was fed 2.2 kg per head per day of a ration with a caculated energy content of 3230 kcal D.E. per kg (Appendix A) to provide a daily energy intake of 6783 kcal D.E. Another group was fed identically but with 1000 mg of dichlorvos (DDVP) added to the diet daily. The other two groups received the same rations, respectively,

plus 1.0 kg of wheat starch to raise the energy intake to 10,583 kcal D.E. daily. After farrowing all dams were full-fed and handled alike. Weight gain from 84 days to removal for farrowing was recorded.

The number of pigs born, alive and dead, and litter and piglet birth weights were recorded at farrowing. At 21 days post-farrowing and weaning at approximately 42 days, the number alive and litter and piglet weights were recorded. These data were analyzed by least-squares regression analysis (Steele and Torre, 1960) for parity, energy level, drug level, and interaction effects.

Results and Discussion

Two models were used to analyze the data. The first model (table 13) was called the simple model as it included only treatment and interaction variables. The second model (table 13) was called the metabolic weight model as it included all the variables of the simple model plus a regression for sow metabolic weight ($W^{0.75}$). For all farrowing data, except total born, both models included a regression for total born to correct to a uniform litter size. The 21 day performance traits[1] were corrected in a similar manner for the total born alive and the weaning performance traits[1] were corrected for total born alive and days to weaning.

Table 14 contains the general means of the farrowing parameters uncorrected for treatment effects, parity effects or on test sow metabolic weight. The significant effects on these parameters are shown in table 15. In the simple model parity is shown to have a

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1/ See Appendix D for general means.

TABLE 13. LEAST SQUARES REGRESSION MODELS.

Simple

$$Y_{ijk} = \mu + E_i + P_j + D_k + (EP)_{ij} + (DE)_{ik} + (DP)kj + \Sigma_{ijk}$$

$W^{0.75}$

$$Y_{ijk} = \mu + E_i + P_j + D_k + (EP)_{ij} + (DE)_{ik} + (DP)_{kj} + \Sigma_{ijk} + (W^{0.75})$$

E = Energy Level.
P = Parity.
D = Dichlorvos.
Y = Total born, no. born alive, litter wt., mean piglet wt., no. at 21 days, mean piglet wt. at 21 days, no. weaned., weaned litter wt., and ave. weaned piglet wt.

TABLE 14. UNCORRECTED SIMPLE MEANS OF FARROWING PERFORMANCE IN SWINE.

Item	Number of Litters	$\bar{x}$	±S.E.
Total born/litter	116	10.12	.25
Total born alive/litter	116	9.92	.25
Litter wt. (kg)	112	13.17	.31
Ave. birth weight/pig (kg)	112	1.32	.02

significant effect on the total born, litter weight and average piglet birth weight. Sows farrowed more ($P<0.05$) piglets per litter (1.3 piglets), heavier ($P<0.05$) litter weights (1.21 kg), and heavier ($P<0.01$) piglets at birth (0.15 kg) than gilts. When metabolic weight is held constant, however, parity effects are no longer significant; the regression of metabolic body weight has a significant effect ($P<0.05$) on the total born (increase of 0.1 piglet per 1 unit increase in metabolic weight) and total born alive (decrease of 0.02 piglets per 1 unit increase in sow metabolic weight). Litter weight and average piglet birth weight are also affected ($P<0.01$) by sow metabolic body weight; each one unit increase in sow metabolic body weight increases litter weight by 0.10 kg and decreases average piglet birth weight by 0.01 kg. Thus, parity effects appear to be in part a reflection of increased sow body size. Intrauterine crowding has been postulated as a possible cause of reduced litter size (Rathnasabapathy et al., 1956; Bazer et al., 1968; Dzuik, 1968). If increased body size is indicative of increased uterine capacity, then the increase in total born and litter weight can be due to a reduction in uterine crowding.

In both models, the dichlorvos (DDVP) treatment increased the number born alive by 0.20 piglets ($P<0.05$) per litter. This finding is consistent with reports of Batte et al., 1969, Batte, Robison and Moncol (1969a, 1969b), Foster (1968), Singh, Perkins, and Schooley (1968) and Young, Hass and Brown (1972). No effects due to energy or its interactions were noted on any of the farrowing traits. This finding

is in opposition to the increased birth weights due to increased energy intake by gravid gilts reported by Clawson et al. (1963), Lodge, Elsley and MacPherson (1966), Vermedahl et al. (1969) and Baker et al. 1969). However, it is supported by similar studies showing no energy effect on birth weight (Frobish, Speer and Hays, 1966; Meade et al., 1966).

Anderson and Wahlstrom (1970b) found the interaction between gestation gain and dichlorvos to be significant; gilts receiving dichlorvos farrowed more total and live pigs when fed for higher gestation gains than those fed for lower gains. While sows and gilts on the higher energy in the present study gained more ($P<0.01$) weight per head per day (0.26 kg), no significant interaction between energy level and dichlorvos was found for any of the farrowing traits.

No main effects due to treatment are significant ($P<0.05$) for the 21 day litter performance traits except that parity increases ($P<0.01$) average piglet 21 day weight (table 16). Piglets average 0.47 kg more weight at 21 days when born to sows rather than gilts. This parity effect is removed when metabolic weight is held constant (table 16). The simple model was used to determine interaction differences. Inspection of the metabolic weight model showed no marked changes in any of the slopes of the variables except the main effect of parity. While use of metabolic weight in the model with parity represents a partial confounding error, it does explain a part of the parity effects.

The number alive per litter and litter weight at 21 days are affected ($P<0.05$) by the interaction of energy and parity in both the

TABLE 15. SIGNIFICANT EFFECTS FOR NATAL TRAITS IN SWINE USING TWO STATISTICAL MODELS.[1]

	Significant Effects	
Farrowing Performance	Simple Model	Metabolic Wt. Model
Total born	Parity*	$W^{0.75}$*
Total born alive	DDVP*	$W^{0.75}$* DDVP*
Litter weight	Parity**	$W^{0.75}$**
Piglet birth weight	Parity**	$W^{0.75}$**

*P<0.05
**P<0.01
[1]Models defined in text.

TABLE 16. SIGNIFICANT EFFECTS FOR 21 DAY LITTER PERFORMANCE TRAITS USING TWO STATISTICAL MODELS[1].

	Significant Effects	
21 Day Performance	Simple Model	Metabolic Wt. Model
Number alive	Energy x parity*	Energy x parity*
Litter weight	Energy x parity*	Energy x parity*
	Drug x parity*	Drug x parity*
Ave. piglet weight	Parity**	

*P<0.05
**P<0.01
[1]Models defined in text.

simple and metabolic weight models. As total born alive per litter is held constant only differences are reported (table 17).

Gilts receiving the lower energy ration have a greater piglet survival to 21 days than any other group. The difference between the number of pigs at 21 days is 1.12 piglets more for the lower energy fed gilts than higher energy fed gilts. High energy intake during the last thirty days of gestation appears to be detrimental to piglet survival to 21 days and to weaning (table 19). Likewise, litter weight is reduced in the gilts fed high energy. However, litter weight is improved in the sows fed high energy indicating that added energy probably resulted in added body reserves for the lactation period. But as Smith (1970a, 1970b) reported, increased gains in gestation for utilization in lactation is energetically inefficient.

The significant parity x dichlorvos interaction ($P<0.05$) for litter weight at 21 days indicates that dichlorvos feeding in gestation is not beneficial to the progeny of gilts, but is beneficial to sow progeny (table 17). As this effect is not present at weaning (table 18), the significance of a dichlorvos x parity interaction is questionable and may represent an artificat of the data.

The significant treatment effects on weaning parameters, holding litter size and days to weaning constant, are shown in table 18. Average piglet weaning weight was reduced ($P<0.05$) in gilt litters by 1.33 kg per pig compared to sow litters. Also, litter weight at weaning was less ($P<0.05$) in gilt litters by 10.22 kg per litter. Once again, introducing metabolic weight into the model removed the

TABLE 17. MEAN DIFFERENCES FOR SIGNIFICANT INTERACTIONS FOR LITTER 21 DAY PERFORMANCE TRAITS

Interaction Term	Differences from Mean	
	Number Alive	Litter Weight (kg)
Gilts x Low Energy	+.65	1.11
Gilts x High Energy	-.47	-3.87
Sows x Low Energy	-.27	-0.20
Sows x High Energy	+.09	2.96
Gilts x No Dichlorvos	---	.78
Gilts x Dichlorvos	---	-3.55
Sows x No Dichlorvos	---	- .04
Sows x Dichlorvos	---	2.82

TABLE 18. SIGNIFICANT EFFECTS FOR LITTER WEANING PERFORMANCE TRAITS USING TWO STATISTICAL MODELS[1].

Weaning Performance	Significant Effects	
	Simple Model	Metabolic Wt. Model
Number weaned	Energy*	Energy*
	Energy x parity*	Energy x parity*
Litter weight	Energy*	Energy*
	Parity*	
	Energy x parity*	Energy x parity*
Ave. piglet wt.	Parity*	

*P<0.05

[1]Models defined in text.

TABLE 19. MEAN DIFFERENCES FOR SIGNIFICANT INTERACTIONS FOR LITTER WEANING PERFORMANCE TRAITS.

Interaction Term	Differences from Mean	
	Number Weaned	Litter Weight (kg)
Gilts x Low Energy	+0.79	7.99
Gilts x High Energy	-0.81	-17.76
Sows x Low Energy	-0.09	1.26
Sows x High Energy	+0.11	8.51

the significance of the parity effects. A significant main effect of of energy ($P<0.05$) on the number weaned (0.74 more pigs for low energy dams) and the litter weaning weight (9.95 kg more for high energy dams) was found. Significant energy x parity effects ($P<0.05$) on the number weaned and litter weight at weaning were found.

In conclusion, high energy intake during the last thirty days of gestation produces no advantage over conventionally fed sows. Farrowing performance was unaffected by increased energy feeding. Weight increases in progeny from high energy fed dams were offset by reduced survival to weaning. Dichlorvos feeding in late gestation did increase the number born alive in gilts as well as sows.

Summary

High energy intake during the last 30 days of gestation produced no effect on the reproductive characteristics of sows or gilts. At weaning increased energy intake during gestation decreased ($P<0.05$) the number of piglets per litter, but increased ($P<0.05$) litter weaning weights.

Parity effects on total born, litter weight and average piglet birth weight were found not to be significant when metabolic weight was held constant. The number born and born alive, litter weight, and average birth weight of piglets increased ($P<0.05$) as metabolic weight increased.

Dichlorvos treatment during the last thirty days of gestation decreased stillbirths ($P<0.05$). No other significant effect of dichlorvos or its interactions was observed.

The interaction of energy and parity showed that gilts fed high energy during gestation had fewer pigs at 21 days and at weaning and had lower litter weights at these times.

SUMMARY

The glucose tolerance test was used to correlate the results of that test with subsequent reproductive performance of sows. A regression of the logarithm of plasma glucose concentrations against time was used to calculate the time for glucose levels to return to fasting levels (the tolerance time), the half-life of added glucose, and the glucose clearance rate (percent glucose disappearance per minute). Tolerance time was positively correlated ($P<0.05$) with mean piglet birth weight, while sow body weight was positively correlated ($P<0.05$) with the number born and litter weight. The finding of a positive correlation with tolerance time and mean birth weight is supported by Anderson et al. (1971). The positive correlation of number born and litter weight is probably a reflection of parity effects. From the tolerance times a prediction model for mean piglet birth weight was generated, which accounted for 51% of the variation. No improvement in the model was made by the inclusion of parity or sow weight.

No significant differences in the measurements of the glucose tolerance test were noted for sows conceiving and those not settling.

In a second study the diabetogenic effects of pregnancy were examined using the glucose tolerance test and measuring plasma insulin levels post-infusion of glucose in sows. The tolerance times increased with the progression of gestation as did the half-life of added glucose. The clearance rate of glucose decreased as pregnancy advanced. Fasting plasma insulin levels did not differ as pregnancy proceeded.

However, the response pattern of insulin to an intravenous glucose load, as described by quadratic equations, did differ as pregnancy advanced, especially in late gestation. The length of time that high plasma insulin plateaus remained increased with advanced gestation, while the magnitude of plasma insulin levels decreased. This finding supports a postulated depletion of the primary pool of insulin in the pancreatic Beta cell and reflects the probable longer period of mobilization and secretion of insulin from storage pools as gestation progresses.

Calculations of the area and minima described by the quadratic curves showed that the period of time until the minima of plasma insulin levels was reached was significantly correlated with the glucose tolerance parameters. The minima increased with advanced gestation suggesting a prolonged release of insulin. However, the area was not significantly correlated with glucose tolerance. Thus, the area described by the curve was not a valid indicator of total insulin release.

A third study was conducted to assess the benefit of increased carbohydrate energy intake and dichlorvos in late gestation on reproductive performance and progeny performance to weaning. High carbohydrate energy intake (50% higher than N.R.C. requirements) produced no significant effect on the reproductive characteristics of sows or gilts. At weaning increased energy intake during gestation decreased ($P<0.05$) the number of piglet weaned per litter, but increased litter weights ($P<0.05$).

Dichlorvos treatment during the last thirty days of gestation decreased stillbirths ($P<0.05$). No other significant effects of dichlorvos or its interaction were observed.

The interaction of energy and parity showed that gilts fed high energy during gestation had fewer pigs at 21 days and weaning and had lower litter weights at these times.

In conclusion, the glucose tolerance tests and insulin response to glucose by the gravid sow present an excellent model for the study of carbohydrate metabolism. Pregnancy was demonstrated to be a measurable diabetogenic effect in the sows. Attempts to exploit this diabetogenic condition by increasing carbohydrate energy intake during pregnancy failed to increase piglet birth weights or survival to weaning.

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APPENDIX

APPENDIX TABLE A

Ingredient composition and calculated analysis of experimental swine gestation ration.

Item	Percent
Yellow Corn	63.75
Meat Meal (50%)	5.00
Cottonsed Meal (41%)	2.50
Soybean Meal (44%)	2.50
Wheat Mill Run	15.00
Dehydrated Alfalfa Meal (20%)	2.50
Sun Cured Alfalfa Meal	7.50
Ground Limestone	.75
Trace Mineralized Salt	.50
Also Added	
Zinc Sulphate	.34 kg
Vitamin D	320,000 IU
Vitamin B_{12} Supplement (1320 mg/kg)	10.00 gm
Niacin	10.00 gm
Riboflavin	2.00 gm
Pantantoic Acid (dl-Ca) Supplement	13.00 gm
Minium Calculated Analysis[a]	
Crude Protein %	14.00
Calcium %	.83
Phosphorus %	.63
Digestible Energy kcal/kg	3230

[a]Air-dry Basis

APPENDIX TABLE B

The regression of the logarithm of plasma glucose concentration on time post-infusion at 21 days post-breeding.

Sow	Regression Equations	R^2
1231-8	Y = 2.35 - .049X	.969
1303-11	Y = 2.21 - .022X	.995
1519-9	Y = 2.27 - .028X	.937
1319-11	Y = 2.32 - .027X	.998
1663-5	Y = 2.37 - .022X	.993
1517-5	Y = 2.36 - .020X	.978
1301-14	Y = 2.23 - .016X	.945
1613-10	Y = 2.24 - .019X	.925
1459-8	Y = 2.35 - .029X	.944
1200-13	Y = 2.36 - .021X	.947
1303-10	Y = 2.41 - .024X	.996
1591-7	Y = 2.41 - .028X	.948
1517-7	Y = 2.33 - .023X	.866
1663-4	Y = 2.39 - .022X	.801
1470-11	Y = 2.48 - .037X	.969
1591-10	Y = 2.41 - .015X	.963

APPENDIX TABLE C

Quadratic equations describing insulin response post-infusion of glucose.

Sow	Day	Equation	R^2
1231-8	21	$Y = 85.39 - 3.45X + 0.049X^2 - 0.0002X^3$	.863
	84	$Y = 176.68 - 7.22X + 0.095X^2 - 0.0004X^3$	.662
	110	$Y = 64.55 + 0.12X - 0.034X^2 + 0.0002X^3$	.868
1303-11	21	$Y = 87.61 - 4.30X + 0.082X^2 - 0.0004X^3$	.883
	84	$Y = 92.39 - 3.29X + 0.041X^2 - 0.0002X^3$	.927
	110	$Y = 29.28 + 1.44X - 0.046X^2 + 0.0003X^3$	.776
1591-9	21	$Y = 76.68 - 3.79X + 0.066X^2 - 0.0003X^3$	.964
	84	$Y = 93.75 - 5.14X + 0.094X^2 - 0.0005X^3$	.955
	110	$Y = 79.73 - 2.94X + 0.046X^2 - 0.0002X^3$	.936
1319-11	21	$Y = 39.82 - 1.56X + 0.022X^2 - 0.0001X^3$	.698
	84	$Y = 42.67 - 2.43X + 0.045X^2 - 0.0002X^3$	.939
	110	$Y = 6.77 + 1.88X - 0.046X^2 + 0.0003X^3$	.512
1663-5	21	$Y = 110.34 - 4.78X + 0.066X^2 - 0.0003X^3$	.639
	84	$Y = 69.36 - 1.14X - 0.003X^2 - 0.0001X^3$	.613
	110	$Y = 28.42 + 2.49X - 0.070X^2 + 0.0004X^3$	.257
1517-5	21	$Y = 79.92 - 3.58X + 0.053X^2 - 0.0002X^3$	.833
	84	$Y = 81.40 - 1.90X + 0.014X^2 - 0.0000X^3$	.916
	110	$Y = 41.77 + 1.13X + 0.017X^2 - 0.0001X^3$	.860

APPENDIX TABLE D

Simple means of farrowing, litter 21 day, and weaning performance of sows and gilts.

Item	Number of Litters	Mean	±S.E.
Farrowing Performance			
Total born/litter	116	10.12	.25
Total born alive/litter	116	9.92	.25
Litter weight (kg)	112	13.17	.31
Litter weight (kg) (alive only)	116	12.94	.32
Average piglet birth weight (kg)	112	1.32	.02
Average piglet birth weight (kg) (alive only)	116	1.33	..02
21 Day Performance Litter Traits			
Number alive	98	8.66	.22
Litter weight (kg)	97	38.50	1.13
Average piglet weight (kg)	97	4.46	.08
Weaning Performance Traits			
Number weaned	91	8.23	.24
Litter weight (kg)	91	80.36	3.33
Average piglet weight (kg)	91	9.90	.33
Pre-farrowing Sow Data			
Sow body weight (kg)	116	449.69	8.64
Sow metabolic body weight ($kg^{0.75}$)	116	24.48	.35
Sow average daily gain (kg/day)	110	.40	.03