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ABSTRACT

Young swine were subjected to repeated episodes of starvation and refeeding in which the starvation phases were terminated by short periods of pure nutrient feeding. A complete, natural diet was fed between experiments. Cardiovascular responses to the various dietary manipulations were followed daily throughout the 18-month study. These were measured in terms of heart and respiratory rates and systolic and diastolic blood pressures. Electrocardiograms were taken at various stages of experimentation. Post mortem examinations were performed after the animals had experienced eight starvation-refeeding experiments.

Tachycardia and apparent impairment in the blood pressure control mechanisms, as evidenced by extreme daily fluctuations upon refeeding, were immediately evident when the animals were refed with pure glucose, high glucose diets, or a complete, natural diet. Similar effects of lesser severity accompanied the refeeding with pure protein, but were not observed in conjunction with pure starch or corn oil refeeding.

Extreme hypertension and ventricular strain, as well as aortic placques and histological evidence of myocardial degeneration were observed, apparently as a consequence of the repeated refeeding stresses.

CARDIOVASCULAR EFFECTS OF REFEEDING STRESS FOLLOWING STARVATION[1]

Reports from the clinical field have revealed an increased incidence of hypertensive cardiovascular disease among populations rehabiliated following starvation or prolonged semistarvation (Harrison, 1946; Stapleton, 1946; Brozek, et al., 1946). Acute cardiovascular stress culminating in heart failure has been observed in man under conditions of unregulated realimentation following experimental starvation studies (Keys, et al., 1950). Studies with dogs (Wilhelmj, et al., 1951a and 1951b; 1953; 1956; 1957; and 1958) have demonstrated that the cardiovascular stresses which accompany refeeding after starvation are influenced in nature and extent by the composition of the refeeding diet; however, the full significance of these findings remains to be elucidated.

The present report concerns a study of cardiovascular responses to starvation and refeeding with varied diets. Attention is directed to the general effects of repeated starvation-refeeding experiments. Swine were selected as experimental subjects on the basis of their known susceptibility to heart failure (Sporri, 1954), as well as the peculiar resemblance to the human with respect to the problem of arteriosclerosis (Barnes, et al., 1959).

METHODS

Young swine were used in the study which extended over a period of approximately 18 months, and included eight starvation-refeeding experiments. A corn and soybean swine ration ("Diet 160")[2] was fed throughout the study except during the starvation periods and during short periods

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[1]Submitted for publication 26 August 1960

[2]"Diet 160" Swine Ration, University of Illinois Feed Storage Center, with a percentage composition of ingredients as follows: ground shell corn, 82.6; alfalfa meal, 2.4; soybean oil meal, 12.2; ground limestone, 1.0; bone meal, 1.0; trace mineral mixture, 0.5; and vitamin supplement, 0.3.

immediately following starvation when experimental diets were fed. Feed intake during the periods of natural diet feeding was generally regulated so as to provide for a slight increase in body weights without evidence of fattening. Water was available at all times throughout the study. When offered, feed was provided as single feedings in the early morning. Daily observations of cardiovascular responses were made in the late evening, usually 10 to 12 hours following feeding. This schedule minimized interferences due to traffic in the laboratory or to psychic stimulations associated with anticipation of feed, such as were found to occur when observations are made 20 to 24 hours postprandial.

Cardiovascular responses were measured in terms of heart and respiratory rates, systolic and diastolic blood pressures, and changes in the electrocardiographic patterns. Blood pressures were determined indirectly by the auscultatory procedure (Allen, 1923), with modifications and precautions as described by Wilhelmj and associates (1951a). Observations were made daily throughout the study, and daily values were obtained by averaging at least 10 separate observations for each animal. The animals were trained to lie down in a standard position on the right side and to submit voluntarily to procedures allowing the observations. All observations were made after at least 10 minutes of complete relaxation by the subject.

Three pigs of mixed breeding, two females and a castrate male, were obtained when approximately 5 months of age and weighing approximately 100 pounds. They were trained for submission to the experimental procedures with surprising ease in view of the difficulties sometimes encountered in the use of dogs (Wilhelmj, et al., 1951a), and appeared to be far less subject to disturbing influences of psychic and emotional origins than are dogs. Breed differences may exist among swine, however, as evidenced by difficulties encountered in this laboratory when individuals of the "Minnesota miniature strain"[3] of pigs were studied (B. C. Johnson and V. Fiorica, unpublished data). One such animal was observed in the present study, but the data are deleted from this report because of differences in responses obviously due to the genetic makeup and previous history of the animal.

Control Data

Prior to any other experimentation, control values for all observation criteria were obtained during a 30-day period of natural diet feeding at an

[3] A strain of small swine developed (by backcrossing on the wild pig) at the Hormel Institute.

intake level slightly in excess of the maintenance requirement. Subsequent "control" values were obtained at approximately the chronological midpoint of the study during the latter 25 days of a 70-day natural diet feeding period. In both instances, the observed criteria were generally stabilized throughout the "control" periods.

RESULTS

Initially, heart rates were uniformly in the range of 70 to 80 beats per minute. During the second "control period," heart rates had decreased to 65 or 70 beats per minute. Respiratory rates were initially in the range of 15 to 35 respirations per minute, and appeared to subside with age to a range of 10 to 20 respirations per minute. Daily variations in individual respiratory rates greatly exceeded the daily variations in individual heart rates; however, the two measures followed parallel trends during experimentation throughout the study.

Individual blood pressures during the initial 30-day control period ranged between 126 and 138 mm Hg systolic, and 88 to 114 mm Hg diastolic. Means of the 30 daily averages (with standard deviations) were 133 ± 6/96 ± 7 mm Hg. At the chronological midpoint of the study, individual observations ranged between 127 and 206 mm Hg systolic, and 69 to 127 mm Hg diastolic. Means of the 25 daily averages were 150 ± 8/104 ± 8 mm Hg. The over-all increase, as well as the increased range of daily variations, was magnified during subsequent periods and this trend is discussed below.

Electrocardiographic observations are considered only in brief in this report, since it is anticipated that the data will be presented in a detailed communication in conjunction with data from studies now in progress.

Experiment 1: Refeeding With Pure Corn Oil

A 29-day starvation period was terminated by feeding pure corn oil.[4] Subsequently Diet 160 was fed at a level supplying approximately one-half of the calculated caloric requirement for body weight maintenance. After 9

[4] "Mazola", refined corn oil, Corn Products Refining Co., Argo, Illinois

days, the intake of Diet 160 was increased to a level supplying approximately two times the requirement for maintenance.

Heart rate and blood pressure responses to this series of dietary regimens are indicated in Figure 1. The group means of daily responses are presented, with the ranges of control (prestarvation) values superimposed to facilitate comparisons.

All measurements (including respiratory rates which are not shown) diminished promptly at the onset of starvation; however, heart rates returned to the control range on the 6th day, fluctuated therein for several days, and then steadily declined to a state of definite bradycardia (for animals of this age) by the end of the starvation period. A trend toward gradual recovery from the initial decrease in blood pressures occurred during the first half of the starvation period; but this trend reversed abruptly at about the 20th day of starvation, and by the 26th day, the Korotkov sounds were inaudible. At the end of the 29-day starvation period, the pigs had lost approximately 20 percent of their initial body weights.

Pure corn oil was provided ad libitum for 5 days. Consumption amounted to approximately 1000 grams per pig at the first feeding, approximately 500 grams at the second, 300 grams at the third, and negligible amounts at the fourth and fifth feedings. Although heart rates exceeded slightly the control range on the third day of corn oil feeding, such effect was slight and transitory. The heart rates, respiratory rates, and blood pressure data showed no indication of refeeding cardiovascular stress.

Refeeding with Diet 160 at a low intake level (one-half maintenance) for 9 days failed to return the observed measurements to control ranges. When the intakes were increased, a transitory decrease in both heart rate and diastolic pressure was followed on the second day by elevated systolic pressure and a dramatic increase in heart rate which persisted throughout the 21 days that the regimen was continued. Return of systolic pressures to the control range without concomitant elevation of diastolic pressures gave rise to increased pulse pressures during this period. Daily variations in individual observations were greatly increased upon increasing the intake of Diet 160.

Experiment 2: Refeeding With Glucose

A 33-day starvation period was terminated by feeding pure glucose[5]

[5] "Cerelose 2001," refined corn glucose, Corn Products Co., New York, N. Y.

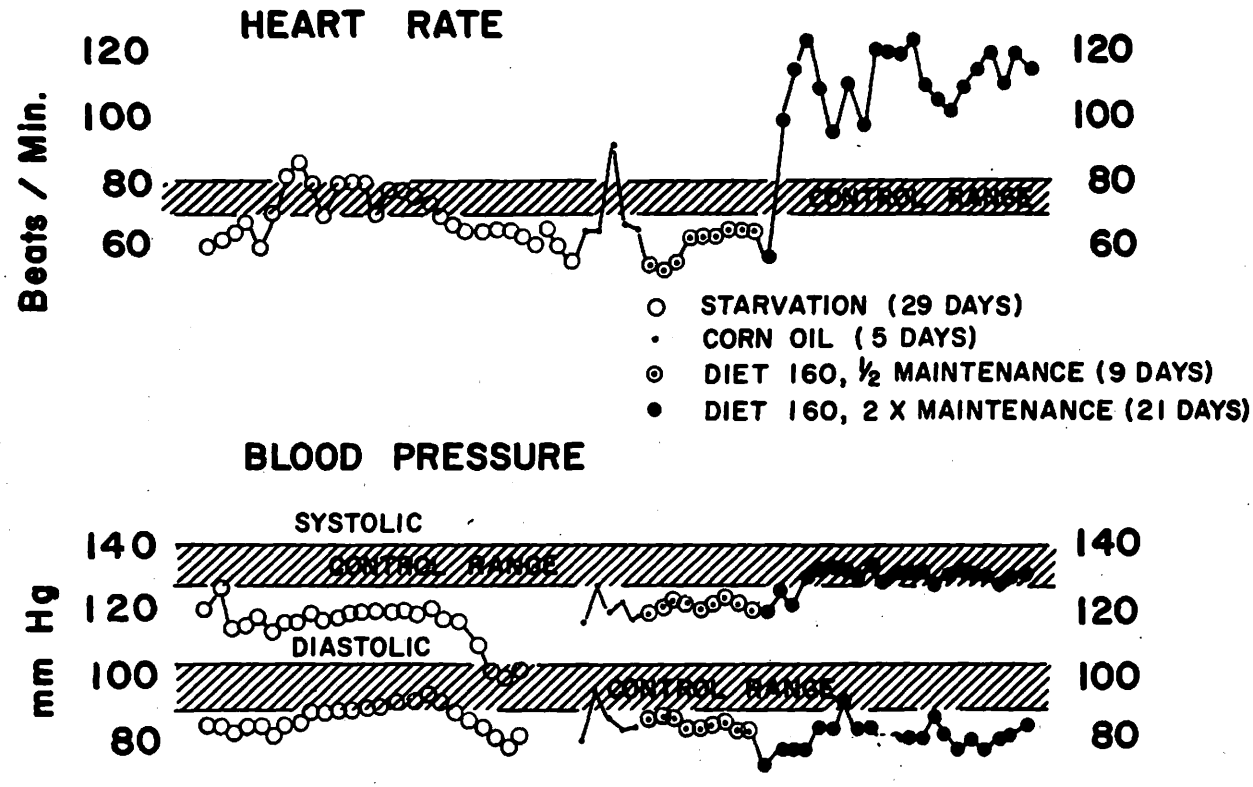

Figure 1. Heart rate and blood pressure responses to experimental diets.

for 5 consecutive days. During the next 3 days, a mixture containing glucose and NaCl (2 percent) was fed. Subsequently a balanced, semipurified diet, high in glucose content was fed for 15 days, and finally Diet 160 was fed at an intake level slightly above the calculated caloric requirement for body weight maintenance. The average body weight at the onset of this experiment was 120 pounds.

Heart rate and blood pressure responses to this series of dietary regimens are indicated in Figure 2. At the onset of starvation, heart rates and systolic pressures dropped immediately to levels slightly below the control range, and remained stable at the established lower levels throughout the starvation period. Diastolic pressures during the prestarvation period were already below the diastolic control range, having failed to return following the first experiment. A gradual rise in diastolic pressures occurred during the first 25 days of starvation, resulting in consistently decreased pulse pressures, since systolic pressures were unchanged. At the end of the starvation period, the average body weight loss represented approximately 25 percent of the prestarvation weights.

Pure glucose was provided ad libitum for 5 days. Consumption varied between 500 and 1000 grams per pig at the first feeding and, in contrast to corn oil consumption, did not diminish appreciably during subsequent feedings. The two pigs which consumed glucose most rapidly and in greatest quantity (800 to 1000 grams), exhibited tremors and nausea, with some vomiting, 4 to 6 hours following consumption. This condition was not observed after the first day of glucose feeding.

Heart rates were elevated abruptly to a state of slight tachycardia which immediately subsided and subsequently reached a level below the final starvation stage. Diastolic pressures were lowered promptly, and systolic pressures were elevated, giving rise to increased pulse pressures. Inclusion of NaCl in the diet (2 percent) increased the ad libitum feed intake (1000 to 2000 grams per pig), and elevated slightly the systolic pressures. The averages of systolic and diastolic pressures were not appreciably changed; however, daily variations in individual observations were markedly increased.

When a balanced diet[6] containing 82.7 percent of glucose was fed, ad libitum, consumption remained nearly the same in each pig as was obtained with the glucose and salt mixture. The over-all response was a gradual

[6] Composition was based on that of Diet 160 by replacing ground corn and soybean meal with appropriate amounts of glucose and purified soybean protein.

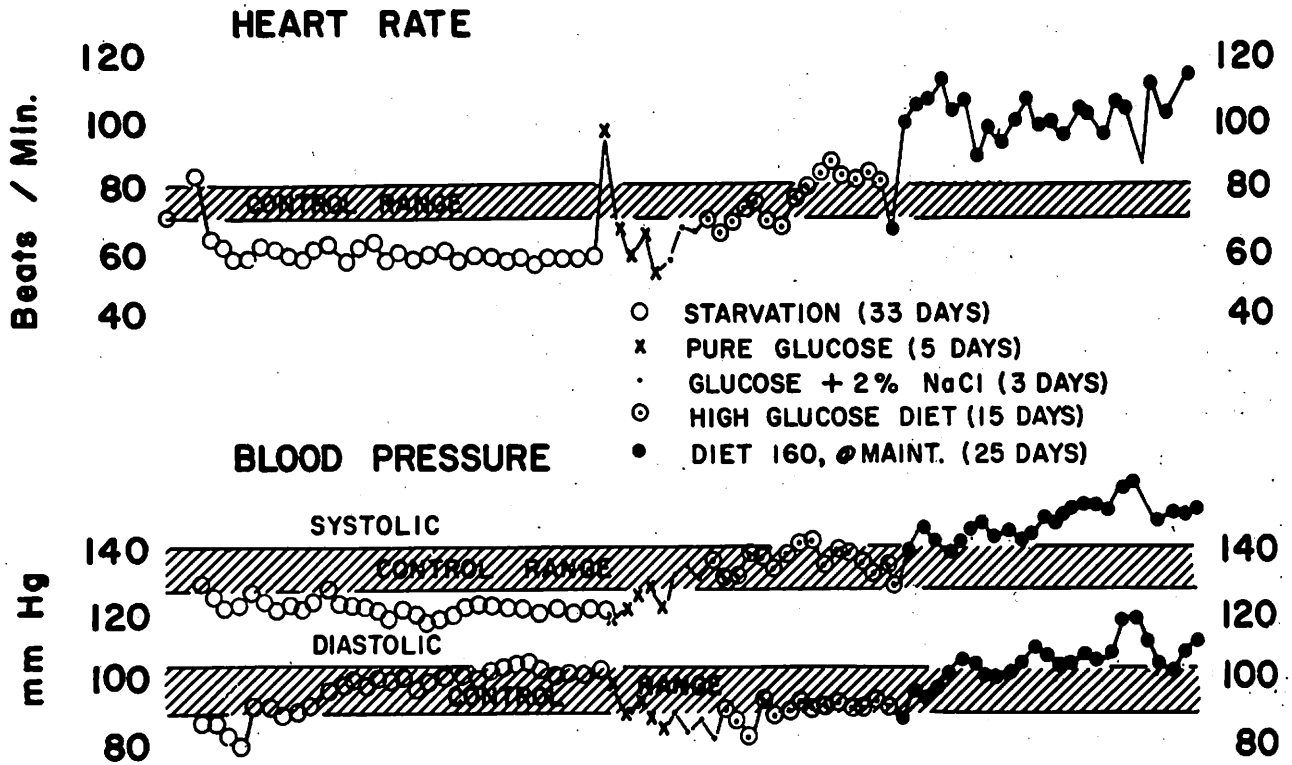

Figure 2. Heart rate and blood pressure responses to experimental diets.

rise in heart rates and both systolic and diastolic pressures.

The replacement of the semipurified ration with Diet 160 at an intake level slightly in excess of the maintenance requirement resulted in an initial decrease in all measurements. A similar response was noted upon increasing the intake of Diet 160 during Experiment 1. Subsequent to the initial drop, heart rates were dramatically increased to a state of mild tachycardia, and both systolic and diastolic pressures were abruptly elevated. Systolic pressures continued to rise throughout the remainder of the feeding period, reaching levels of 150 mm Hg and above. This entire period was marked by drastic fluctuations in the daily individual observations for heart rates and blood pressures as well. Heart rates gradually subsided to the control range after about 50 to 60 days of continuation of the Diet 160 regimen; however, systolic and diastolic pressures remained at a newly established level of approximately 150/110 mm Hg.

Experiments 3 - 6: Refeeding After Short-term Starvation

The immediate responses (1 to 2 days) to refeeding for short periods with approximately isocaloric amounts of either glucose, starch[7], purified soybean proteins[8], or corn oil following individual, short-term (6 to 8 days) starvation periods were studied. Diet 160 was fed for periods of 24 to 50 days' duration prior to each experiment. The responses are summarized in Figure 3. The control ranges indicated were obtained during the second "control period," which immediately preceded this series of experiments. Weight losses during starvation periods were negligible.

Glucose, starch, and protein intakes were approximately 1500 grams per feeding, and the corn oil intake was approximately 700 grams per feeding. As noted previously in Experiment 2, glucose was consumed rapidly, and elicited a condition of tremors and apparent nausea. A similar condition, with more pronounced nausea and vomiting, followed the single feeding of purified soybean protein.

Throughout the series of experiments, heart rates uniformly responded to starvation with a prompt drop to a stable level slightly below

[7]Refined corn starch, A. E. Staley Mfg. Co., Decatur, Illinois

[8]"ADM Assay Protein C-1," purified soybean protein, Archer-Daniels-Midland Company, Cincinnati, Ohio

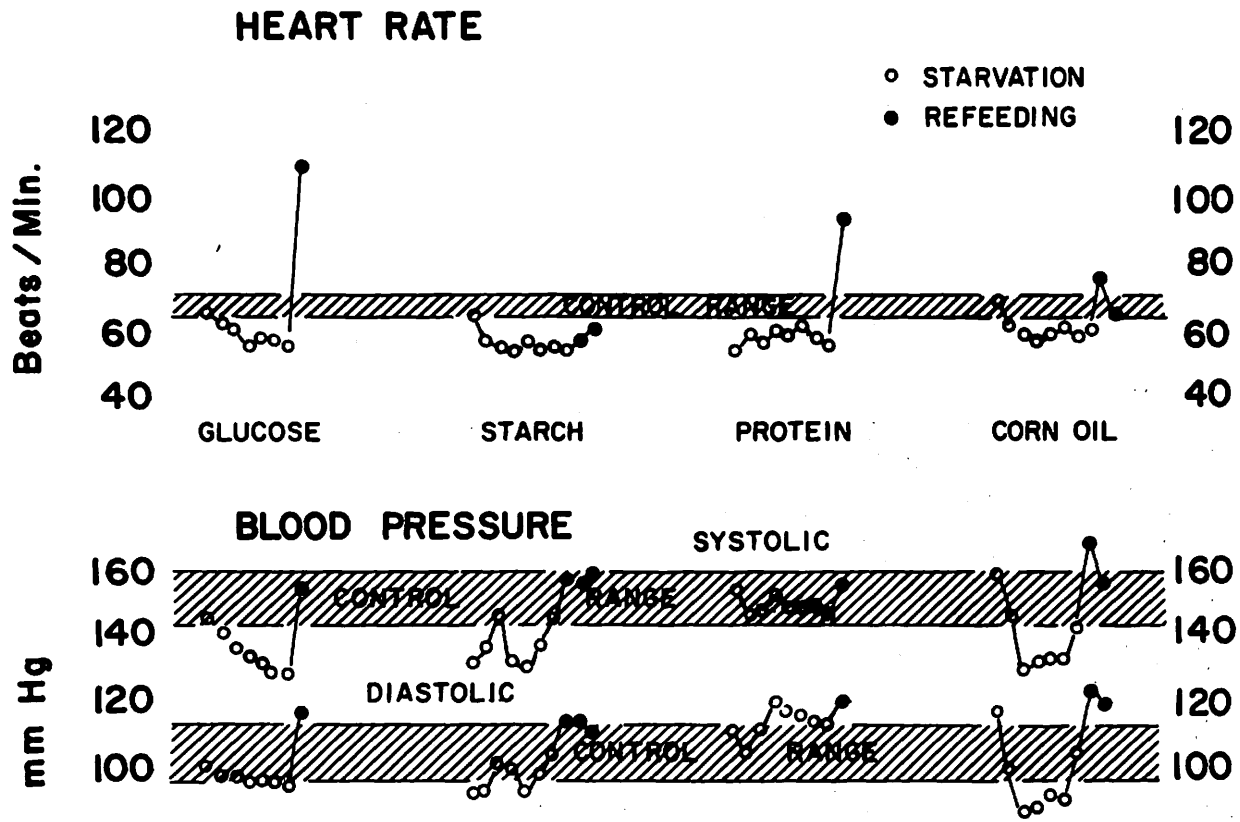

Figure 3. Summary of responses.

the initial, pre-starvation "control" level. Such was not the case with blood pressures, where the only consistent response was a trend toward elevated diastolic pressures in subsequent starvation periods.

Heart rates were increased promptly by glucose and protein, and to a lesser extent by corn oil. Both glucose and corn oil elicited prompt increases in systolic and diastolic pressures, with a lesser response in the case of protein. Refeeding with approximately isocaloric amounts of corn starch appeared to be without effect upon the cardiovascular system in terms of the observations made.

Experiment 7: Refeeding With Glucose and Sodium Chloride

As indicated previously, blood pressures during the initial control period were 133 ± 6/96 ± 7 mm Hg, and had risen dramatically to 150 ± 8/104 ± 8 mm Hg at the time of the subsequent control period following Experiment 2. A progressive increase was observed during the periods of Diet 160 feeding between Experiments 3 to 6, and following Experiment 6, a level of 168 ± 9/123 ± 6 mm Hg was reached during the period of Diet 160 feeding.

Experiment 7 was conducted to ascertain the response of the hypertensive pigs to a short-term starvation period followed by a 3-day period of feeding glucose plus NaCl (4 percent). Subsequently Diet 160 was fed.

During starvation, weight losses were negligible. Upon refeeding, the intakes of glucose and salt (4 percent) were controlled at 1500 grams per pig per feeding. All three feedings were readily consumed. Although no evidence of vomiting was noted, all pigs exhibited marked tremors within 1 to 2 hours after the first meal. These persisted to varying degrees throughout the period of feeding glucose plus salt. Marked irritability of the animals was noted during the first day, and this increased on the second day to the point of precluding pressure observations; however, the condition abated on the third day.

Individual responses to this experiment are indicated in Figure 4 as a means of emphasizing the daily fluctuations observed. Heart rates were not appreciably changed by feeding glucose plus salt, and were increased only slightly when Diet 160 was subsequently fed. However, systolic pressures were drastically elevated to extreme ranges by the glucose and salt diet; although diastolic pressures were likewise elevated, the change was not commensurate, resulting in increased pulse pressure. Apparently,

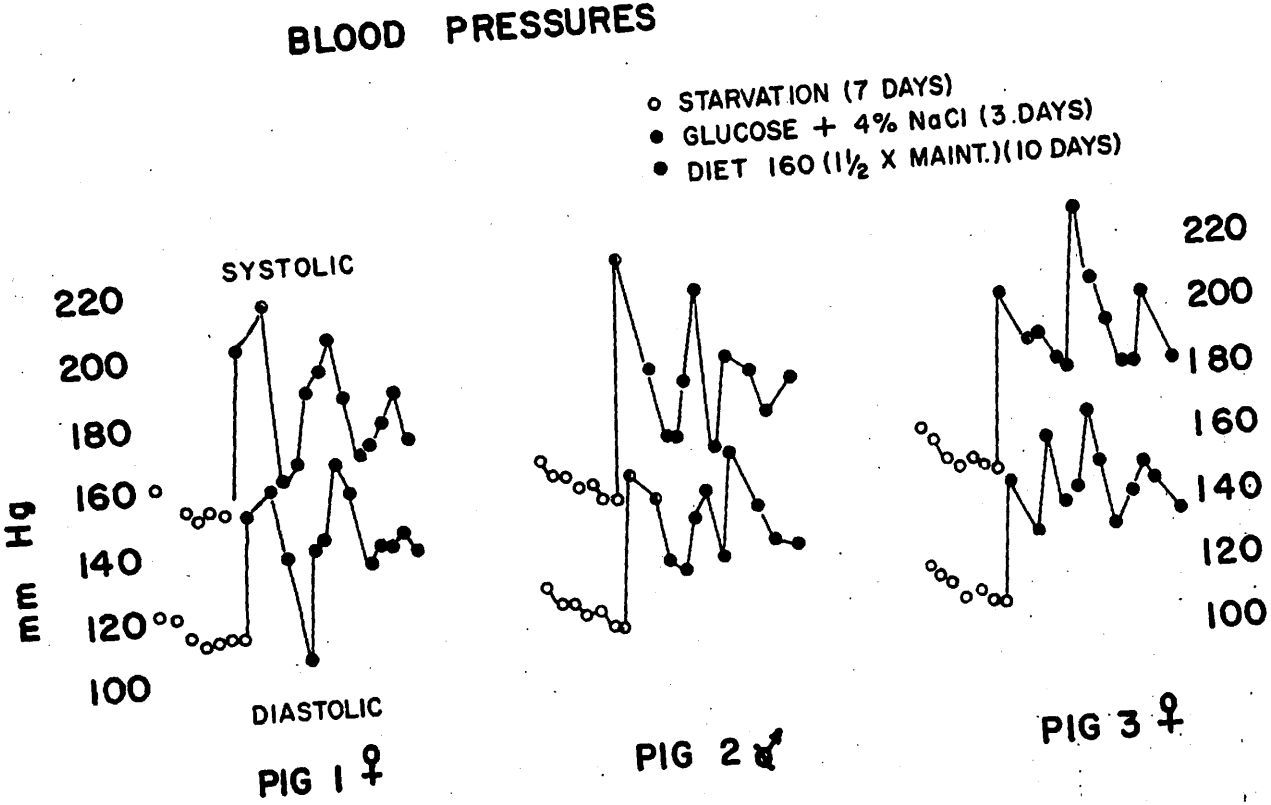

Figure 4. Individual responses.

the physiological mechanisms for control of blood pressure were completely disrupted as evidenced by the extreme ranges and daily fluctuations encountered during the subsequent period of feeding Diet 160.

Experiment 8: Refeeding With Control Ration

A 30-day starvation period was followed by feeding with Diet 160 at one and one-half times the caloric requirement for maintenance for 50 days, and then at three times the maintenance requirement during the next 20 days. Pre-starvation weights were approximately 265 pounds, and at the onset of starvation, all pigs were hypertensive. Body weight losses during starvation represented approximately 15 percent of the prestarvation weights.

Responses observed in Pig 3 (female) during this episode are presented in Figure 5, and are typical of the group responses. The individual data for a single pig are presented as a means of emphasizing the daily variations encountered upon refeeding.

Periods of apparent systolic "stress" occurred in all pigs on the 22nd and 29th days of starvation. Such occurrences had not been observed during previous experiments, and are without explanation at the present time. A condition of partial and recurring complete heart block, complicated by an apparent sinus arrhythmia, was noted in Pig 3 on the third day of starvation and gradually increased in severity during the starvation period. Occasional occurrence of a mild form of this condition had first been observed during the fourth starvation experiment. Refeeding with Diet 160 resulted in dramatic fluctuations in daily blood pressure values, suggesting serious imbalance in the blood pressure control mechanisms. In two of the three pigs (Pigs 2 and 3), drastic fluctuations were observed from hour to hour, as well as from day to day, and this effect was especially pronounced during the terminal phase of the experiment. During refeeding, a condition of recurring sinus tachycardia was observed in Pig 2, in which heart rate increased within a few seconds from 70 beats per minute to rates up to 140 beats per minute without noticeable increase in respiratory rate of body activity of any kind. Such tachycardias were of short duration (15 to 60 seconds), but recurred at intervals of 3 to 5 minutes during the periods of observation. Such periods were accompanied by very low pulse pressures. Electrocardiographic abnormalities were observed in the case of each of the pigs during the final period.

The animals were sacrificed at the termination of the last experiment. Post mortem examination (performed through the courtesy of Dr. E. I.

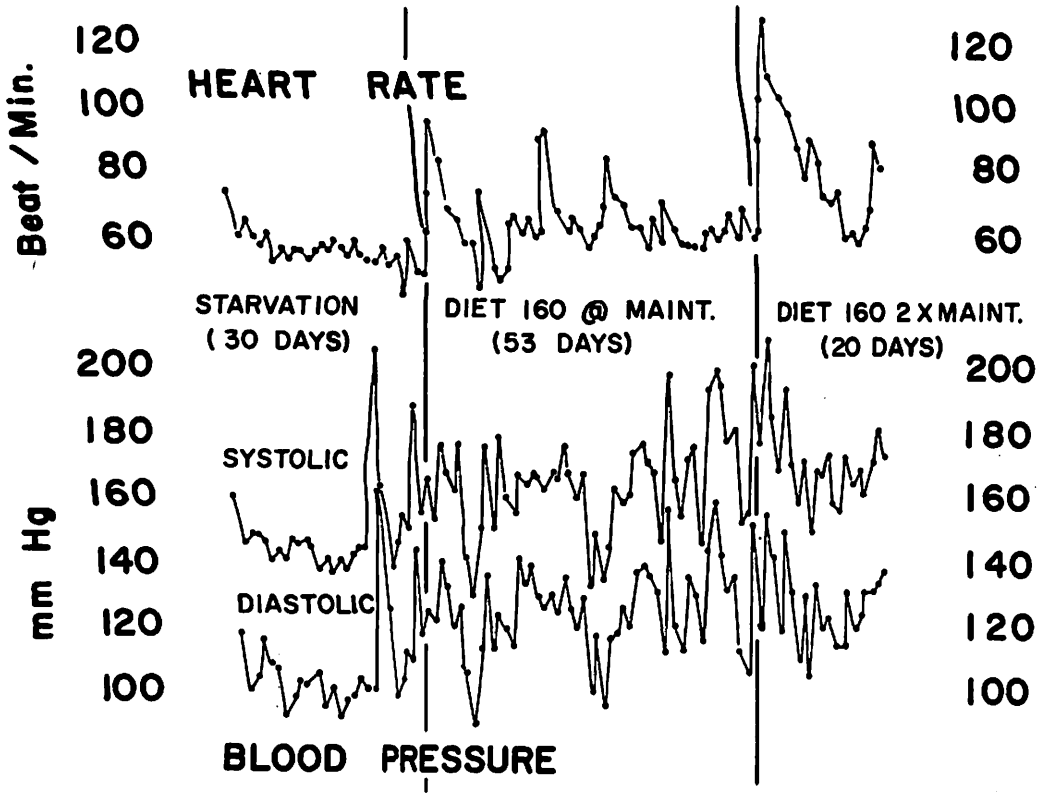

Figure 5. Responses in Pig 3.

Pilchard, Diagnostic Laboratory, University of Illinois College of Veterinary Medicine) revealed macroscopically apparent myocardial strain in each of the pigs, as indicated by abnormally firm or hardened ventricles. In the cases of two of the animals, the left ventricles were noticeably enlarged with excessively hardened and enlarged columnae carnae. Sclerotic placques were found in the aortas of all three pigs, being most evident in the case of Pig 3. Microscopically, the hearts showed suggestions of myocardial degenerative changes characterized by loss of striations in some areas, as well as some hemorrhages and atrophic fibers. The livers showed occasional inflammatory foci adjacent and within the connective tissue of the lobule, and the kidneys showed mild, subacute glomerulonephritis and occasional atrophic glomeruli. The adrenals uniformly showed medullary congestion with slight cortical degenerative changes.

DISCUSSION

This study, although somewhat preliminary in nature, has served to demonstrate the occurrence of refeeding tachycardia, hypertension, ventricular strain, and aortic placques in swine as a consequence of repeated episodes of starvation and refeeding. Moreover, the study serves to emphasize the suitability of swine as experimental subjects in studies of dietary stress and cardiovascular responses.

The elevation of blood pressures to long-standing hypertensive levels was evident after only two starvation-refeeding episodes, whereas, a similar effect in dogs (Wilhelmj, et al., 1956 and 1957) occurred only after six or more episodes, and only in dogs refed diets with a high content of animal fat. Species differences, such as those which enable the dog to resist the stresses of high-salt diets (Ladd and Raisz, 1949), and those which make the pig subject to heart failure (Sporri, 1954) might conceivably have served to accentuate this difference in blood pressure response to refeeding.

The period of time involved during refeeding with pure nutrients or mixtures of pure nutrients was too short to demonstrate any real differences between carbohydrate, fat, and protein upon blood pressure; however, the hypertensive effect of NaCl was well demonstrated. The elevated blood pressures and marked fluctuations in daily observations upon refeeding with

either the high-glucose, semipurified diet or with Diet 160 resembled effects previously noted in dogs (Wilhelmj, et al., 1953).

The occurrence and severity of refeeding tachycardia was dependent upon, or at least related to, both the composition and caloric intake level of the refeeding diet. However, factors other than the general source and the total amount of calories supplied were obviously involved, as evidenced by: (a) increased heart rate when glucose or glucose plus salt was replaced with a complete, high-glucose diet, and a subsequent increase when this diet was replaced with approximately isocaloric amounts of Diet 160; (b) increased heart rate when glucose was fed alone, but not when fed with salt; and (c) increased heart rate by glucose or soybean protein, but not by isocaloric amounts of either corn starch or corn oil. The differences resulting when glucose and corn starch were fed are particularly striking, and electrocardiographic pattern differences seen during these episodes further reflected important metabolic differences in the two episodes. Presumably such effects resulted from secondary metabolic differences, such as might accompany differences in electrolyte shifts, rather than from primary alterations in the metabolism of the absorbed glucose units, when glucose or starch was fed.

Data from studies with rats (Gillman, et al., 1958) indicate that hypertensive cardiovascular disease may simply be the late end result of single episodes of acute arterial injuries incurred traumatically or metabolically. The fluctuations in blood pressure upon refeeding in the initial episode, and in subsequent episodes as well, suggest that the primary impairment resulting in increased blood pressures in this study was in the hormonal or nervous control mechanisms rather than in physical damage to the elasticity of the vascular system. It is known, however, that the metabolic alterations which accompany starvation resemble in many ways the changes associated with diabetes (Winter, 1946); Wollenberger and Linton, 1947), and that these may eventually be reflected in vascular damage. Whether the severe hypertension seen in the latter part of the present study was dependent upon the subsequent series of short-term starvation episodes, or whether it was latent and could have been "triggered" by other metabolic, emotional or traumatic stresses is not known.

It should be emphasized that the initial refeeding stress in each experiment was registered perhaps more clearly in terms of the extreme daily fluctuations in blood pressure values than in terms of any over-all change in the mean of daily blood pressure values. The impairment reflected by such fluctuations appeared to accumulate from episode to episode, suggesting some damage of long-standing effect to the hormonal or nervous control mechanism.

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