Exercise and Blood Glucose Concentration in Intact and Pancreatectomized Dogs

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SUMMARY

Exercise studies were performed on six intact and seven pancreatectomized, unanesthetized dogs to examine the conditions under which exercise decreases the concentration of glucose in blood.

No major change in blood glucose concentration was demonstrated during exercise experiments on normoglycemic intact dogs. In the pancreatectomized dogs, the blood glucose concentration curves during exercise followed either one of two patterns: Some rose with exercise and some fell. In dogs with baseline blood glucose concentrations less than 400 mg. per 100 ml., a sustained decline in blood glucose occurred with exercise, while in those dogs with an initial level greater than 400, a rise occurred.

No effect of exercise was evident in a pancreatectomized dog with blood glucose concentration near the normal range during continuous infusion of insulin. Exercise produced a decrease in blood glucose concentration in an intact dog with hyperglycemia induced by glucose infusion, but this dog's blood glucose level increased during rest periods following exercise.

Exercise, diet, and insulin constitute the accepted therapeutic triad for the treatment of diabetes mellitus. It has been known clinically for many years that intense muscular work increases the uptake of glucose from the blood, even in untreated diabetic patients.[1] This observation has formed the background for the emphasis that modern textbooks[1-3] place on the value of exercise and physical fitness in the treatment of diabetes mellitus. However, this clinical principle lacks extensive experimental support and, too, there has been evidence to the contrary[4-7] that suggests that the blood sugar is affected only if low enough initially.[8] Some of the studies on this problem have been done under distinctly unphysiologic circumstances,[9] and others have involved mainly nondiabetic subjects.[10,11]

Our study was prompted by the lack of precise data on (a) the nature and mechanism of the difference between nondiabetics and diabetics in the effect of exercise on blood glucose concentration; (b) the influence of the degree of metabolic compensation in diabetes mellitus on the hypoglycemic effect obtainable from a given amount of muscular work; and (c) the effect of the initial blood glucose concentration itself on the biochemical response to exercise.

To permit experimental inquiry on these points, unanesthetized intact and pancreatectomized dogs were studied while they were at rest and while they were running on a treadmill.

MATERIAL AND METHODS

Female mongrel dogs, ranging in weight from 10 to 18 kg., were used. They were trained to run on a treadmill and also to remain at rest for periods of thirty minutes. All dogs were maintained on a diet of canned dog food given as two meals daily. Water was allowed ad libitum.

Each dog was given a glucose tolerance test and, about a week later, an exercise experiment was performed. Total pancreatectomy then was performed, followed, usually at two-week intervals, by another glucose tolerance test and an exercise experiment. Pancreatectomized dogs were fed the regular diet supplemented with raw pancreas. Regular Insulin and, in some animals, Ultralente Insulin, was administered in two separate subcutaneous injections before the morning feeding and Regular Insulin was administered before the afternoon feeding.

Diabetic dogs were kept in metabolic cages* for at least one week before exercise tests. Urine was collected in twenty-four-hour samples and samples of blood were taken for glucose determinations. From these data, an appropriate insulin program was planned.

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*Dogs 2, 3, and 7 (first exercise test) were not kept in metabolic cages.

Each dog was fasted for approximately sixteen hours and weighed before each experiment. Pancreatectomized dogs received no insulin for sixteen hours before the experiments.

Tests of glucose tolerance were done uniformly by the slow, continuous infusion method.[12,13] The femoral vein of the dog was catheterized while the animal was at rest without sedation. Initial samples of blood were taken for baseline values and, thereafter, samples were taken at intervals of ten minutes for a period of two hours. A cephalic vein also was cannulated and a continuous infusion of 500 mg. of glucose per kg. per hour, in 10 per cent solution, was administered by a Harvard constant-infusion pump for a period of one hour. Urine collections were made, through an indwelling catheter, in three fractions (prior to, during, and one hour after the infusion).

The exercise test consisted of two thirty-minute periods of standardized running on a treadmill (3.45 miles per hour at an elevation of 12 degrees) alternated with three rest periods of similar duration. Blood samples were taken simultaneously, at the rate of ten per hour, from catheters introduced through the carotid artery to the aorta and through the jugular vein to the inferior vena cava. Urine samples were collected through an indwelling catheter before and at the end of each thirty-minute period.

Two pancreatectomized dogs (nos. 4 and 7) underwent two exercise studies each. In one, deliberately poor metabolic regulation due to suboptimal insulin dosage and, subsequently, the best possible control of diabetes preceded each test by a week. The reverse sequence of good and poor diabetic regulation was induced by manipulation of insulin dosage in the other dog.

One pancreatectomized dog underwent an exercise experiment during a continuous infusion of 0.05 units of Regular Insulin per kg. per hour, in physiologic saline, into a jugular vein.

An intact dog with glucose-induced hyperglycemia was studied during exercise. Two gm. of glucose per kg. per hour were infused through a catheter advanced into the right pulmonary artery via the right jugular vein. To allow attainment of a hyperglycemic condition, the exercise test was not begun until thirty minutes after infusion was started.

The concentration of glucose, both in blood and in urine, was measured by the AutoAnalyzer ferricyanide method.[6,14] The specimens were collected in tubes, containing oxalate and fluoride, which were stoppered and refrigerated to minimize glycolysis.

Samples of arterial blood for determination of total ketone concentration were obtained from one intact and three pancreatectomized dogs at the end of each part of the exercise test. These samples were centrifuged and then filtered by the method of Somogyi.[15] The protein-free filtrates were analyzed by the method of Bloom.[16]

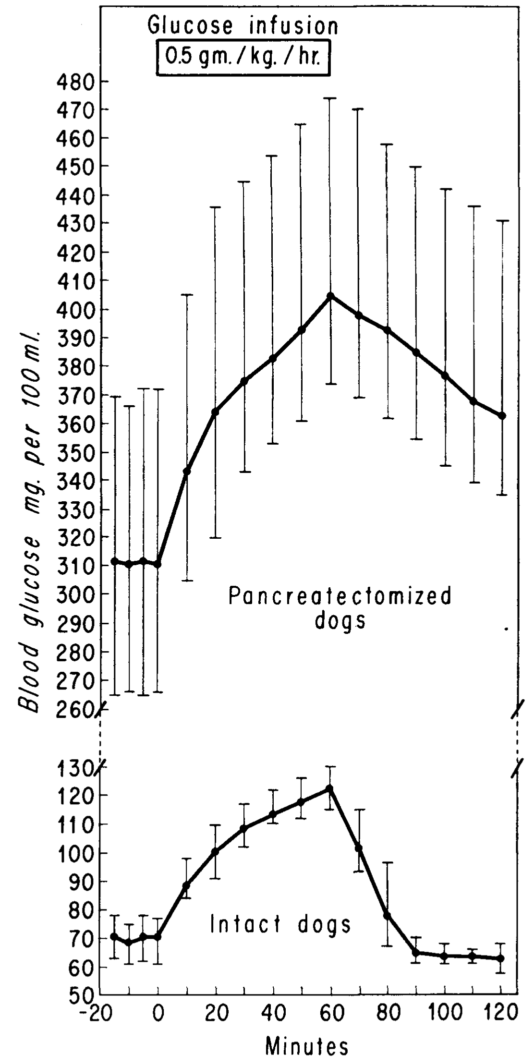

FIG. 1. Results of intravenous glucose tolerance tests. Means and ranges of blood glucose concentration for six intact and seven pancreatectomized dogs. Each solid circle indicates the mean and the vertical line through it extends to the highest and lowest observed values (range).

The slope-analysis technic[12] was used to measure the K values (specific rate constant of glucose disappearance) of the intravenous glucose tolerance test.

RESULTS

Glucose tolerance. The data are presented graphically in figure 1. Values for K in the pancreatectomized

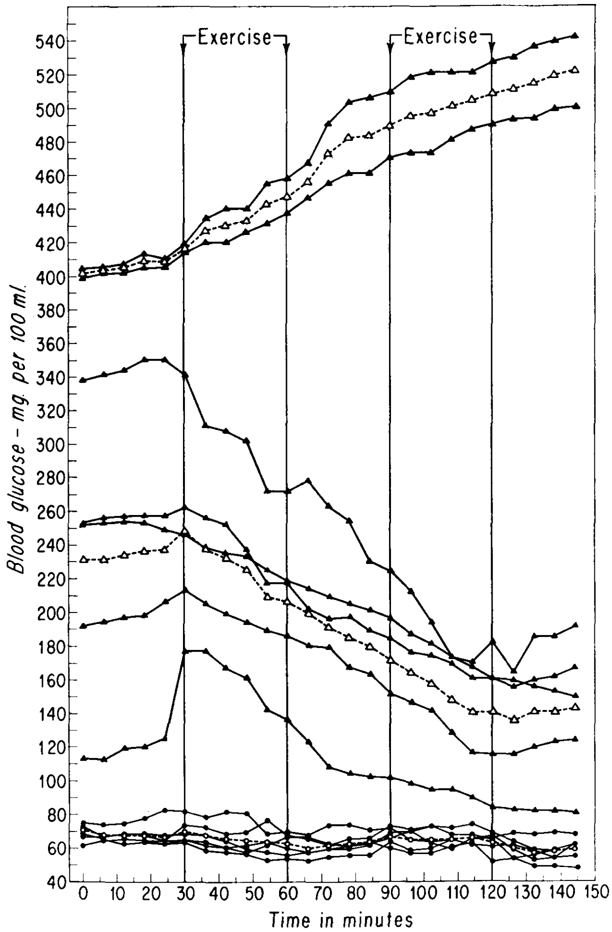

FIG. 2. Concentrations of glucose in venous blood during exercise experiments (see text for details). Vertical lines separate periods of rest and of exercise. Intact dogs are represented by circles and pancreatectomized dogs by triangles. The open circles and triangles represent the mean values for each group.

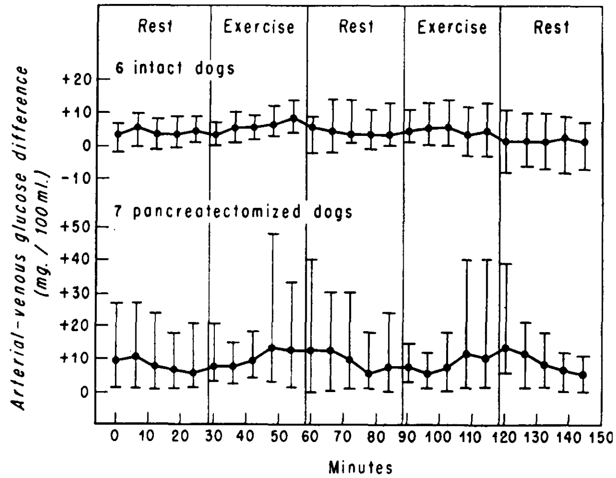

FIG. 3. Effect of exercise on arterial-venous (A-V) blood glucose differences (means and ranges) in six intact and seven pancreatectomized dogs. Each solid circle indicates the mean, and the vertical line through it extends to the highest and lowest observed values.

dogs were uniformly lower (mean $K = 0.016$) than those in the controls (mean $K = 0.039$).

Exercise. The effect of exercise on the concentration of glucose in venous blood is shown in figure 2. As expected, the mean concentration of glucose was uniformly lower in venous blood than in arterial blood (figure 3). The values discussed in the following paragraphs are those determined from the venous samples.

Intact dogs. No major change in the concentration of glucose in blood was demonstrated during any experiment (figure 2). The final values, however, uniformly were less than the initial concentrations.

Pancreatectomized dogs. The blood glucose curves are of two patterns (figure 2): In some dogs, concentration increased with exercise and in some it decreased. The distinction between dogs in the two categories appeared to depend upon whether the initial blood glucose concentration was more than or less than 400 mg. per 100 ml.

The pre-exercise resting values for blood glucose in the pancreatectomized dogs varied more than those of the intact dogs (figure 2). The increase seen in the majority of the pancreatectomized dogs may have been the result of increasing insulin deficiency or, possibly, the response to the stress of cannulation.

All dogs whose resting blood glucose concentrations were less than 400 mg. per 100 ml. had a progressive decrease in blood glucose concentration during the subsequent periods of exercise and during the intervening period of rest (figure 2). The mean decrease in blood glucose concentration during the first rest period was 30 mg. per 100 ml.; the mean decrease during the entire test was 91 mg. per 100 ml.

The two pancreatectomized dogs whose initial blood glucose concentrations were more than 400 mg. per 100 ml. showed a continuous increase in blood glucose concentration with exercise. The rest period which followed the first one-half hour of exercise showed the greatest increase, with a mean of 48 mg. per 100 ml. The mean total increase in blood glucose concentration for the two dogs was 117 mg. per 100 ml.

Arterial-Venous (A-V) differences in blood glucose. With few exceptions, values were positive in the intact dogs. In general the A-V differences were greater during exercise than at rest in both intact and pancreatectomized dogs. At rest, they were greater in the pancreatectomized than in the intact group. The mean

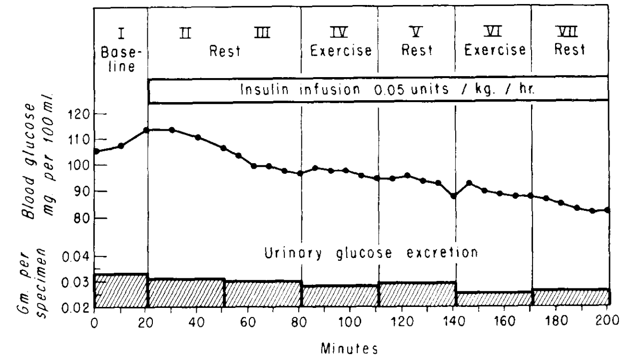

FIG. 4. Effect of exercise on venous blood glucose concentration and glycosuria in a pancreatectomized dog during a continuous infusion of insulin.

A-V difference during exercise for the intact dogs was 5.68 mg. per 100 ml., and during rest it was 3.87 mg. per 100 ml. The mean A-V difference during exercise in the pancreatectomized dogs was 9.77 mg. per 100 ml. and during rest it was 9.30 mg. per 100 ml.

Effects of optimal and poor control of diabetes on response to exercise in pancreatectomized dogs. Whether the exercise test was performed first during good or poor control of diabetes made no discernible difference on the effect, or apparent lack of effect, of exercise. The glucose curves at the top of figure 2 show the changes that occurred in the dogs with deliberate poor diabetic control. The results of exercise tests in the same two dogs during a perior of better diabetic control are in the middle group of curves of figure 2 (starting at 253 and 193 mg. per 100 ml., respectively).

Effect of continuous infusion of insulin on response to exercise in a pancreatectomized dog. The results are charted in figure 4. No definite effect on the blood glucose concentration clearly due to exercise was evident. This dog had a nearly normal blood glucose value at the start of the experiment.

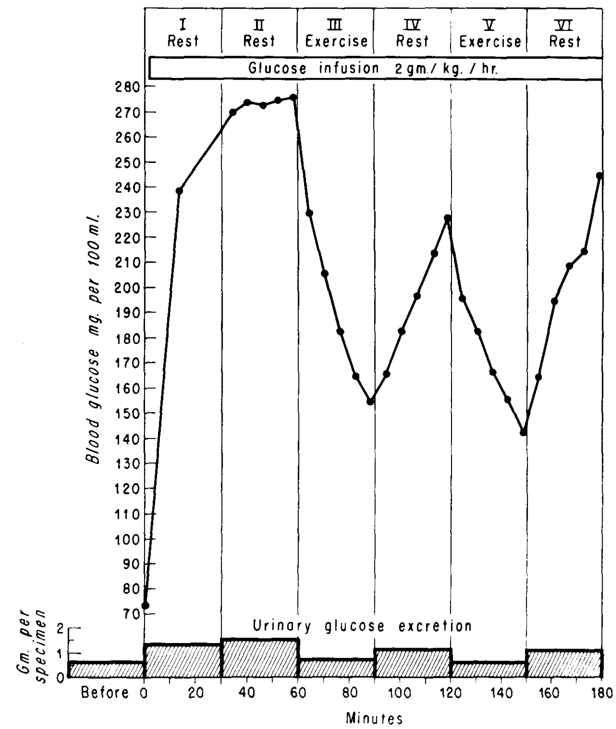

FIG. 5. Effect of exercise on venous blood glucose concentration and glycosuria in an intact dog with hyperglycemia produced by continuous infusion of glucose.

Effect of exercise on an intact dog with glucose-induced hyperglycemia. Exercise caused an abrupt decrease in blood glucose concentration (figure 5). In the first exercise period, the decrease was five times that found in the group of pancreatectomized dogs whose blood glucose concentrations were less than 400 mg. per 100 ml. This dog, in contrast to the diabetic dogs, showed a distinct increase in blood glucose concentration during each rest period after exercise. Urinary glucose excretion was less during exercise (figure 5) and, therefore, could not account for the decrease

TABLE 1

Effect of exercise on concentration of ketones in arterial blood

No.	Dog Condition	Arterial blood glucose (fasting) mg. per 100 ml.*	Arterial ketones, mcg./ml.† I Rest	II Exercise	III Rest	IV Exercise	V Rest
7	Normal‡	70	6.27	7.82	10.05	5.36	10.59
7	Pancreatectomized	200	17.82	15.35	16.35	8.91	11.39
7	Pancreatectomized§	408	23.06	24.75	27.22	33.75	37.12
4	Pancreatectomized	432	50.57	54.37	62.06	69.59	71.38
4	Pancreatectomized§	254	29.30	19.80	25.14	11.69	19.80
5	Pancreatectomized	123	16.67	13.41	28.40	12.56	20.49

*Mean of five determinations during initial phase of the exercise experiment.
†Mean of duplicate determinations.
‡Prior to pancreatectomy.
§Second exercise experiment.

in blood glucose concentration. Similar results were found in the pancreatectomized dogs.

Blood ketones during exercise. In one experiment on an intact dog and in three on pancreatectomized dogs with blood glucose concentrations less than 400 mg. per 100 ml., total arterial ketone concentration remained essentially unchanged or decreased during exercise but increased during postexercise rest periods (table 1). In two experiments on pancreatectomized dogs with initial blood glucose concentrations greater than 400 mg. per 100 ml., the blood ketone concentration increased progressively during both exercise and rest periods.

COMMENT

The slow, continuous infusion type of tolerance test was chosen because it was deemed to be a more physiologic procedure than the rapid intravenous test.[12] Glucose tolerance of pancreatectomized dogs was found to be impaired in contrast to intact animals, in agreement with the results of Hlad and Elrick[13] who demonstrated that the continuous infusion technic consistently yielded a decreased K value in diabetic subjects.

The correlation between the decrease in blood glucose concentration and the initial blood glucose level noted in our study confirms the work of Richardson,[8] who found that the effect of exercise on the diabetic patient depended on the initial level of the blood glucose concentration. Such findings are also in keeping with the clinical observation of the pre-insulin era that, while those patients with severe diabetes often were unable to exercise, patients with mild diabetes profited by it.[17]

The pancreatectomized dog with an almost normal blood glucose concentration reacted to exercise similarly to the diabetic patients described by Hetzel and Long.[18] These authors found that when insulin had been injected within the six hours prior to study and the blood glucose concentration was low to begin with, exercise had little or no observable effect. A lack of change in blood glucose concentration during exercise in normal human subjects also has been reported.[19]

A hypothesis that the influence of muscular work is mediated by a humoral factor elaborated by working muscles has been suggested by Goldstein and co-workers.[20] Goldstein[21] recently has demonstrated that cross-circulation of blood from working to resting dogs caused a depression of blood sugar in the resting recipient animals. Opposed to the humoral hypothesis are the data of Helmreich and Cori,[22] and Sacks and Smith,[23] which showed that a resting gastrocnemius muscle did not exhibit an increased uptake of pentoses when other muscles of the legs were stimulated. Dulin and Clark[24] investigated this problem by more direct means, including determination of the arterial-venous (A-V) glucose differences across resting and working legs of eviscerate dogs. Their experiments showed that exercise increased A-V glucose differences across working muscles and supported only the thesis that the effect of work on utilization of glucose is local.

The rate of flow of blood through tissues is variable, even in the resting state. It is obvious that changes in A-V differences, as measured in this study, do not completely reflect changes in the rate of peripheral glucose assimilation, especially if blood flow changes simultaneously. It has been estimated that, at the intensity of exercise used in this study, there was a two-and-one-half-fold increase in systemic blood flow during exercise.

The ketone concentrations found in the pancreatectomized dogs with blood glucose concentrations less than 400 mg. per 100 ml. were elevated but the fluctuations in the concentrations during the test were similar to those found in the intact dog. A decrease in ketone concentrations occurred during exercise with an increase in the following rest period (Courtice-Douglas[25] effect). These observations agree with those of others,[5,25] but again provide no explanation for the differences in blood glucose response to exercise in diabetic and intact dogs.

In the exercised intact dogs there was no major change in blood glucose concentration. It is well known[26] that active muscles metabolize a large amount of glucose; consequently, to prevent hypoglycemia, hepatic glycogenolysis must be accelerated. Thus the demand is met by the supply in the normal dog.

Both from the observed initial blood glucose concentrations and from the treatment the animals received, it is evident that the better regulated diabetic dogs must have had more insulin available to them (lower fasting blood glucose concentration, Ultralente insulin treatment). This available exogenous insulin may have had the effect of reducing hepatic glucose output[27] and thereby account for the differences observed in this group of animals. What effect the insulin-like "humoral hypoglycemic agent" from exercised muscles may have on hepatic glucose output is, at present, unknown.

In the pancreatectomized dog supplied with a continuous infusion of nearly physiologic amounts of exogenous insulin, a normal state appears to have been simulated. The implication of the results is that a "normal" state of production, utilization, and excretion of glucose existed.

Production of a sustained high blood glucose concentration in the intact dog by infusion of glucose creates a complex situation. It is possible that hepatic glucose output is suppressed, insulin secretion stimulated, and certain aspects of the diabetic state are reproduced. The similarity to the adequately (but not "perfectly") controlled diabetic animal is obvious.

The concentration of glucose in blood at the time of exercise appears to be a major determinant of subsequent changes in blood glucose concentration during moderately severe exercise both in pancreatectomized and in intact dogs.

SUMMARIO IN INTERLINGUA

Le Influentia de Exercito Super le Concentration Sanguinee de Glucosa in Intacte e Pancreatectomisate Canes

Studios de exercito esseva effectuate in sex intacte e septe pancreatectomisate canes sin le uso de anesthesia pro examinar le conditiones sub le quales exercitio reduce le concentration de glucosa in le sanguine.

Nulle major alteration del concentration sanguinee de glucosa esseva demonstrate in le curso de experimentos a exercito in intacte canes in stato normoglycemic. In le pancreatectomisate canes, le curvas de concentration del glucosa sanguinee sequeva sub le influentia de exercito un de duo configurationes: Certes del curvas montava con exercito, alteres declinava. In canes con concentrationes sanguinee de glucosa in stato de controlo amontante a minus que 400 mg per 100 ml, un continue declino del glucosa sanguinee occurreva durante le exercito. In canes con nivellos de base de plus que 400 mg per 100 ml, un augmento occurreva.

Nulle effecto de exercitio esseva evidente in un pancreatectomisate can con un concentration sanguinee de glucosa in le vicinitate del norma durante un continue infusion de insulina. Exercitio produceva un declino in le concentration sanguinee de glucosa in un intacte can con hyperglycemia inducite per infusion de glucosa, sed in iste can, le nivello sanguinee de glucosa montava durante periodos de reposo post exercitio.

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Dietary Fats and Atherosclerosis and Thrombosis in the Rat

Experimental evidence suggests that, along with other variables, unsaturated fats can be atherogenic and saturated fats thrombogenic in rats, rabbits, chicks, and human beings. High fat diets of butter, lard or hydrogenated fat plus cholesterol, cholic acid, and thiouracil produce myocardial infarcts and thrombosis in rats (W. S. Hartroft and W. A. Thomas, JAMA *164*: 1903, 1957). Bleeding, coagulation, and prothrombin times are shortened and platelet counts are elevated by adding saturated fat to rabbit diets (Nutrition Reviews *18*:246, 1960).

Feeding unsaturated fats and wheat germ to chicks, however, increases serum cholesterol deposits in the aorta (Nutrition Reviews *18*:146, 1960). C. J. P. Böttcher et al. (Lancet *1*:1378, 1960) found that human atherosclerotic plaques have a high content of an unsaturated fat, linoleic acid; the content increases with the severity of the disease.

Linoleic acid and saturated fats also behave differently in cholesterol metabolism. Linoleic acid increases the synthesis and breakdown of cholesterol while saturated fats have an opposite effect (Nutrition Reviews *18*: 91, 1960).

G. R. Gresham and A. N. Howard (Brit. J. Exp. Path. *41*:395, 1960) noted that atherosclerosis or thrombosis could be selectively produced by feeding rats diets containing different proportions of fat. Butter, cholesterol, cholic acid, and thiouracil produced thrombosis but substituting arachis oil for butter produced atherosclerosis. Since butter differs from arachis oil in containing large quantities of saturated fatty acids and small amounts of linoleic acid, the authors investigated the effects of diets containing different fatty acid compositions on the production of atherosclerosis or thrombosis and myocardial infarction in the rat (Ibid. *42*:166, 1961).

The animals were fed a diet of 40 per cent fat, 5 per cent cholesterol, 2 per cent cholic acid and 0.3 per cent thiouracil. The diet also contained 17 per cent sucrose, 20 per cent casein, vitamins, salts, cellophane flaked film, magnesium oxide, and inositol. The animals remained on the diet until death. The rats were divided into groups of five to ten and the fat content of the diet was varied in each group.

Rats fed butter, beef fat or hydrogenated arachis oil showed a 50 per cent incidence of thrombosis in the heart, aorta or coronary arteries. Myocardial infarctions occurred in eight of thirty-eight animals. Many lipoid filled macrophages were found but no atherosclerotic changes were seen in the aorta.

Rats fed arachis oil showed an 88 per cent incidence of atherosclerotic plaques in the proximal aorta and coronary arteries but no thrombi. Rats fed maize oil developed both atherosclerosis and thrombosis. Lipoid filled macrophages were rare in the arachis and maize fed animals.

A combination of atherosclerosis, thrombosis, and myocardial infarction was produced in groups fed mixtures of butter and arachis oil, butter and methyl linoleate or arachis oil followed by butter.

Atherosclerosis was not produced in rats fed synthetic glycerides of trilinoleate, mono-oleate distearate, dioleate monostearate or tri-oleate.

Thrombosis occurred in rats fed mono-oleate distearate and di-oleate monostearate. Rats fed trilinoleate or tri-oleate did not develop thrombi. Survival time was decreased in all rats fed synthetic glycerides.

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