Pyruvate Metabolism in Obesity

By A. T. Miller, Jr., M.D.,* and Barbara M. Thomas, B.S.†

It is generally agreed that obesity is the result of excessive caloric intake in the sense that caloric restriction corrects the condition. Opinions differ, however, concerning the cause of the overeating. According to the "orthodox" view,[1] most obese persons are metabolically normal, and obesity results from failure to curb the appetite. This concept has, from time to time, been challenged by proponents of theories attributing obesity to metabolic abnormalities.[2-4] In recent years, Pennington has vigorously advocated a theory which makes obesity the necessary consequence of a defect in intermediary metabolism.[5-10]

Pennington's thesis is that obesity-prone persons are characterized by an enzymatic defect in carbohydrate metabolism which results in the accumulation of excessive amounts of pyruvate. The pyruvate in turn depresses the oxidation of fat and increases lipogenesis from carbohydrate, with the result that an abnormally large proportion of both carbohydrate and fat is diverted to fat storage instead of being oxidized for energy. Then the appetite, regulated to supply the energy needs of the body, dictates the intake of an increased amount of food to compensate for the amount diverted to storage. The inhibition of fat oxidation by pyruvate lowers the rate of mobilization of fat, but eventually the increased size of the adipose depots makes possible the release of enough fat to supply the energy needs of the body. "Thus obesity might be considered as a compensatory hypertrophy of the adipose tissues, providing for an increased use of fat by an organism that suffers an impairment in its ability to oxidize carbohydrate."[8] Pennington has suggested, on the basis of this theory, that the logical treatment of obesity is not caloric restriction, but rather restriction of the carbohydrate precursors of pyruvic acid in a calorically adequate diet.

The basic assumption on which Pennington's theory rests is that pyruvate accumulates in excessive amounts in the blood and tissues of obese persons when their metabolic mixture consists largely of carbohydrate. This assumption has not been tested directly in human obesity. Pennington bases his claim on the indirect evidence of a greater exercise-induced rise in blood lactate in obese subjects[11] and of blood pyruvate in diabetic subjects[12] than in normal subjects, and on the elevated blood pyruvate of the hereditarily obese-hyperglycemic mice.[13]

The experiments to be described were undertaken in an effort to obtain information of a more direct nature. They are based on the assumption that a metabolic defect of the type postulated by Pennington should be exaggerated by any condition which increases the demand for the metabolism of carbohydrate. Two such conditions are exercise of brief duration and the ingestion of glucose.

EXPERIMENTS

Basal Levels

The basal blood pyruvate level was measured in 16 normal-weight and 16 obese hospital patients (Table I). The obese patients averaged about 40 per cent overweight according to standard weight tables. The degree of obesity for each group is expressed in each table as: Relative weight = (actual weight)/(ideal weight), so that, for example, a relative weight of 1.3 would indicate 30 per cent overweight. In preliminary studies the basal blood pyruvate level was found to be variably elevated in patients with liver disease, congestive heart failure, collagen diseases, malignancy, and in healing fractures.[14] Accordingly, no

From the Department of Physiology, University of North Carolina Medical School, Chapel Hill, N. C.

* Professor of Physiology.

† Research Assistant in Physiology.

This work was supported by a grant from the Life Insurance Medical Research Fund.

TABLE I

Basal Blood Pyruvate Levels in Normal-Weight and Obese Patients

Normal-weight patients*					Obese patients†				
Diagnosis	Sex	Age	Relative wt.	Pyruvate *mg/100 ml*	Diagnosis	Sex	Age	Relative wt.	Pyruvate *mg/100 ml*
Functional uterine bleeding	F	29	0.7	0.95	Recurring right inguinal hernia	F	41	1.2	0.78
Glioblastoma multiforme	F	21	0.8	1.32	Spinal injury—quadriplegia	M	30	1.3	1.51
Ptosis, right kidney	M	23	0.8	0.90	Incisional hernia	F	44	1.3	0.92
Postpartum	F	26	0.8	0.63	Functional uterine bleeding	F	65	1.3	0.75
Eczema	F	17	0.8	0.75	Anxiety reaction	F	34	1.3	0.76
Postpartum	F	29	0.9	1.09	Cardiac enlargement	M	80	1.4	0.65
Patent ductus arteriosus, subacute bacterial endocarditis	M	19	0.9	1.30	Scar abscess of abdominal wall	F	40	1.4	0.8
Pyelitis, afebrile	F	22	0.9	1.23	Diabetes, hypertension	F	60	1.4	0.92
Pulmonary blastomycosis	M	23	0.9	1.29	Ruptured intervertebral disc	F	29	1.4	0.91
Postpartum	F	20	0.9	0.80	Fracture of right humerus 2 weeks previously	F	49	1.5	0.91
Bronchiectasis	F	61	1.0	1.11	Basilar artery thrombosis and essential hypertension	F	43	1.5	1.42
Sickle cell anemia	F	30	1.0	0.88	Chronic leg ulcers	F	50	1.5	1.10
Normal staff member	M	27	1.0	1.27	Multiple draining sinuses (staph. aureus)	M	34	1.6	0.65
Lung abscess	F	37	1.0	0.93	Dislocated elbow	F	25	1.8	1.19
Postpartum	F	33	1.0	1.35	Chronic leg ulcers	F	56	1.8	0.69
Postappendectomy	F	24	1.1	1.25	Postpartum	F	27	2.0	0.66

* Sex: males, 4; females, 12. Age: range, 17–61; average, 28. Relative weight: range, 0.7–1.1; average, 0.9. Blood pyruvate: range, 0.63–1.35; average, 1.07 mg/100 ml.

† Sex: males, 3; females, 13. Age: average, 44; range, 25–80. Relative weight: range, 1.2–2.0; average, 1.5. Blood pyruvate: range, 0.65–1.51; average, 0.91 mg/100 ml.

patients with these conditions, nor with fever, extensive drug therapy, or suspected vitamin deficiencies were included in the series.

Pyruvic acid,[15] lactic acid,[16] and glucose[17] concentrations were measured in blood obtained by venipuncture, without stasis and with rigid precautions for prevention of *in vitro* changes in these constituents. The average blood pyruvate levels were 1.07 ± 0.23 mg per 100 ml in the normal-weight patients, and 0.91 ± 0.25 mg per 100 ml in the obese patients. The difference between the two groups is not statistically significant. Most of the patients were in a state of "static" obesity, but there is no reason to believe that cessation of active weight gain would result in the disappearance of an abnormality of intermediary metabolism if one existed. It may therefore be concluded that there is no evidence that blood (and presumably tissue) pyruvate concentration is elevated in obese persons under basal conditions.

Pyruvate Levels after Glucose

It may, however, be argued that pyruvate would accumulate in obese persons only when the demand for metabolism of carbohydrate is increased. In order to test this possibility, blood pyruvate levels were compared in obese

TABLE II

Comparison of Blood Pyruvate Rise in Response to Glucose Administration in Normal-Weight* and Obese† Subjects

	Subjects	Time after glucose: Control	30 min	60 min	90 min	Maximum rise
Blood glucose, mg/100 ml	Normal	86 (60–99)	139 (104–164)	134 (75–164)	111 (62–170)	53 (24–98)
	Obese	74 (50–89)	109 (76–134)	114 (89–137)	97 (80–111)	40 (30–64)
Blood pyruvate, mg/100 ml	Normal	1.16 (0.75–1.60)	1.36 (1.10–1.70)	1.50 (1.23–2.03)	1.32 (0.90–1.80)	0.34 (0.11–0.76)
	Obese	1.12 (1.00–1.48)	1.30 (1.19–1.69)	1.39 (1.19–1.65)	1.27 (0.97–1.39)	0.27 (0.14–0.59)

* Relative weight: range, 0.9–1.1; average, 1.0.
† Relative weight: range, 1.2–1.9; average, 1.5.

TABLE III

Blood Glucose, Pyruvate, and Lactate Responses to Exercise in Normal-Weight* and Obese† Subjects

	Subjects	Time after exercise: Control	2 min	30 min	Maximum change
Blood glucose, mg/100 ml	Normal	81 (72–88)	62 (51–81)	76 (72–95)	−19 (+4 to −37)
	Obese	99 (86–109)	92 (68–112)	83 (58–119)	−16 (+14 to −40)
Blood pyruvate, mg/100 ml	Normal	1.20 (0.53–1.75)	3.02 (2.25–4.35)	1.75 (1.15–3.15)	1.82 (0.63–2.85)
	Obese	1.49 (0.93–2.07)	4.93 (3.59–6.23)	3.99 (2.58–5.87)	3.44 (1.78–4.91)
Blood lactate, mg/100 ml	Normal	12 (8–23)	58 (22–89)	19 (11–35)	46 (11–75)
	Obese	16 (10–24)	121 (92–172)	58 (35–85)	105 (79–148)

* Relative weight: range, 0.8–1.1; average, 1.0.
† Relative weight: range, 1.3–1.9; average, 1.6.

and normal subjects following (a) the ingestion of 50 grams of glucose, and (b) strenuous muscular exercise. The subjects used for the glucose tolerance and exercise studies were (with one exception) different from the hospital patients on whom basal blood pyruvate levels were measured.

It has long been known[18] that the ingestion of glucose is followed by a rise in the blood pyruvic acid concentration, presumably due to failure of the oxidation of pyruvate via the Krebs cycle to keep pace with the rate of its formation by glycolysis. If this failure is more marked in obese persons, as postulated by Pennington, the rise in blood pyruvate following glucose administration should be correspondingly exaggerated.

In preliminary tests in normal and obese subjects, it was found that the oral administration of 50, 100, and 150 grams of glucose caused about the same peak rise in blood pyruvate, although the pyruvate rise was more sustained with the larger doses of glucose. Accordingly, all subjects were given a standard dose of 50 grams of glucose as a 25 per cent solution in tea. The subjects were in a postabsorptive state and had rested in bed for one hour before the administration of glucose. Blood glucose and pyruvate concentrations were determined 30, 45, 60, and 90 minutes following glucose ingestion (Table II). The peak pyruvate rise usually occurred at 60 minutes, though occasionally at 30 or 45 minutes. In all cases, the blood pyruvate level was falling at 90 minutes. The average peak rise in blood pyruvate was 0.34 mg per 100 ml in eight normal subjects (range 0.11–0.76), and 0.27 mg per 100 ml in six obese subjects (range 0.14–0.59).

The time at which the peak rise in blood pyruvate occurred was not consistently different in the two groups of subjects.

Pyruvate Levels after Exercise

The blood pyruvate rise induced by the increased metabolism of endogenous carbohydrate during exercise was compared in normal and obese subjects. About one hour following the usual midday meal, the subjects rested in bed for 30 minutes and then ran at 7 miles per hour for 7 minutes on a motor-driven treadmill. Blood samples were obtained before the exercise, and 2 minutes and 30 minutes after exercise. Analyses were performed for glucose, pyruvic acid, and lactic acid (Table III). On another day, each subject was given a standard cardiovascular fitness test (the Harvard Step Test). The blood pyruvate concentration was always greater 2 minutes after exercise than it was 30 minutes after, and the former value was accordingly used for the peak response. The postexercise rise in blood pyruvate averaged 3.44 mg per 100 ml (range 1.78–4.91) in six obese subjects and 1.82 mg per 100 ml (range 0.63–2.85) in six normal subjects. The greater postexercise blood pyruvate rise in the obese subjects was proportional to their greater postexercise blood lactate rise (103 mg per 100 ml in the obese, and 44 mg per 100 ml in the normal subjects), and inversely proportional to their lower cardiovascular efficiency as measured by the Harvard Step Test scores (39 in the obese and 82 in the normal subjects), Figure 1.

It seems probable, therefore, that the greater postexercise rise in blood pyruvate (and of blood lactate in the experiments quoted by Pennington) in the obese subjects reflects their less efficient cardiovascular response to exercise rather than an abnormality in carbohydrate metabolism. In the normal subjects, the blood glucose values immediately after exercise were consistently about 20 mg per 100 ml lower than the resting values. In the obese subjects, the postexercise glucose changes were extremely variable, with a tendency toward a smaller decrease than in the normal subjects. Whether this represents a less efficient mobilization of glucose or a more rapid utilization cannot be decided on the basis of these data alone.

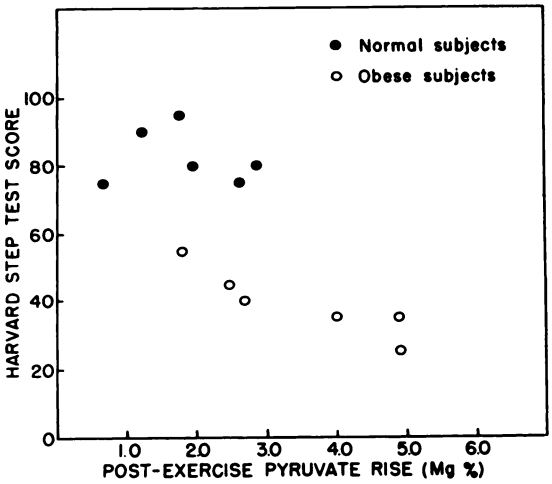

Fig. 1. The relation between postexercise blood pyruvate rise and cardiovascular fitness (Harvard Step Test score) in normal and obese subjects.

DISCUSSION

The administration of glucose increases its rate of utilization;[19] since blood pyruvate also increases, it would seem that the rate of glycolysis may readily exceed the rate of oxidative removal of pyruvate. The initial increase in the blood levels of pyruvate and lactate during moderate exercise is apparently due, at least in part, to an inadequate provision of oxygen for maintaining the oxidative removal of pyruvate, because the achievement of a steady state stops the further accumulation of pyruvate.

The fact that the blood pyruvate rise in response to glucose administration is of about the same magnitude in obese and normal subjects indicates that the oxidative removal of pyruvate is probably no less efficient in obese than in normal subjects. In addition, a reduced rate of oxidative decarboxylation, by decreasing the formation of acetate from pyruvate, would probably reduce the rate of lipogenesis from carbohydrate, instead of increasing it as claimed by Pennington.

If there is no impairment in the enzymatic reactions involved in the disposal of pyruvate in obese persons, it is probable that the greater

postexercise rise in blood pyruvate is due either to a higher rate of glycolysis because of the greater energy cost of exercise[20] or to a less adequate oxygen supply due to the less efficient cardiovascular adjustment to exercise. Prodger and Dennig[11] believed that the greater post exercise rise in blood lactate in their obese subjects was not due to circulatory inadequacy. Their point is not well taken, however, since their data indicate that exercise resulted in a greater oxygen debt and a greater increase in arteriovenous oxygen difference in the obese subjects. Both of these results indicate less adequate blood flow through the working muscles.

Pennington[21] has recently speculated on the most likely site at which a block in pyruvate metabolism might occur. Using the obese-hyperglycemic mice as the prototype of human obesity, he reasons that, since the obese mice are able to oxidize fat,[22] the pathway of fat breakdown and its entrance, by way of acetyl coenzyme A, into the Krebs cycle must be intact. "The metabolic fault in this form of obesity, therefore, must lie at a point above the level of acetyl CoA; it must be looked for somewhere between pyruvic acid and acetyl CoA."[21] The specific defect, according to Pennington, may involve the enzyme lipoic acid conjugase, which is essential for the formation of the coenzyme lipothiamide pyrophosphate (LTPP). There is evidence that LTPP is necessary for the transfer of the acetyl group (derived from pyruvate) to coenzyme A to form acetyl coenzyme A, the form in which metabolites enter the Krebs cycle.[23]

Pennington's speculations are open to serious question. Not only do the genetically obese mice differ from obese humans in important respects, but the claim that the obese mice have a defective capacity for oxidizing administered acetate[13] has not been confirmed.[24] Furthermore, Pennington's claim that the formation of the coenzyme LTPP is easily impaired is based on the fact that the enzyme lipoic acid conjugase is absent in a mutant strain of *E. coli*,[25] surely a far cry from the problems of human obesity.

Since the pyruvic oxidase system is almost selectively inhibited by very small amounts of arsenite,[26] it would seem that the concept of a block in pyruvate metabolism as the cause of obesity should be susceptible of experimental verification. Studies based on this idea are being undertaken in this laboratory. Another approach might be to test the effects on glucose oxidation of the addition of purified lipoic acid conjugase to tissue homogenates from obese and nonobese mice.

SUMMARY AND CONCLUSIONS

One explanation for the pathogenesis of obesity is Pennington's theory based on a postulated block in carbohydrate metabolism at the pyruvate level. Experiments to test this hypothesis were performed in 16 normal-weight and 16 obese subjects.

It was found that the basal blood pyruvate level is not elevated in obese subjects. The oral administration of 50 grams of glucose is followed by a similar rise in blood pyruvate concentration in both normal and obese subjects. Moderate exercise causes a greater rise in blood lactate and pyruvate in obese than in normal-weight subjects. Reasons are given for attributing this result to circulatory inadequacy rather than to metabolic abnormality.

The application of these results to Pennington's theory of obesity is discussed. It is concluded that no direct evidence exists in support of Pennington's basic postulate of a metabolic defect resulting in the accumulation of excessive amounts of pyruvate in the blood and tissues of obese persons.

REFERENCES

1. Newburgh, L. H., and Johnston, M. W.: The nature of obesity. *J. Clin. Investigation* 8: 197, 1930.
2. Bauer, J.: Obesity. Its pathogenesis, etiology and treatment. *Arch. Int. Med.* 67: 968, 1941.
3. Godlowski, Z.: Carbohydrate metabolism in obesity. *Edinburgh M. J.* 53: 574, 1946.
4. Goldzieher, M.: The treatment of obesity. *Am. J. Digest. Dis.* 15: 289, 1948.
5. Pennington, A. W.: Obesity and "the surface area law." *Indust. Med. & Surg.* 20: 69, 1951.
6. Pennington, A. W.: Caloric requirements of the obese. *Indust. Med & Surg.* 20: 267, 1951.

7. PENNINGTON, A. W.: An alternate approach to the problem of obesity. J. CLIN. NUTRITION 1: 100, 1953.
8. PENNINGTON, A. W.: A reorientation on obesity. *New England J. Med.* 248: 959, 1953.
9. PENNINGTON, A. W.: Obesity: overnutrition or disease of metabolism? *Am. J. Digest. Dis.* 20: 268, 1953.
10. PENNINGTON, A. W.: Pathophysiology of obesity. *Am. J. Digest. Dis.* 21: 69, 1954.
11. PRODGER, S. H., and DENNIG, H.: A study of the circulation in obesity. *J. Clin. Investigation* 11: 789, 1932.
12. HORWITT, M. K., HILLS, O. W., and KREISLER, O.: Lactic and pyruvic acids in the blood after glucose and exercise in diabetes mellitus. *Am. J. Physiol.* 156: 92, 1949.
13. GUGGENHEIM, K., and MAYER, J.: Studies of pyruvate and acetate metabolism in the hereditary obesity-diabetes syndrome of mice. *J. Biol. Chem.* 198: 259, 1952.
14. SESSIONS, J. T., JR.: Personal communication.
15. FRIEDEMANN, T. E., and HAUGEN, G. E.: The determination of keto acids in blood and urine. *J. Biol. Chem.* 147: 415, 1943.
16. BARKER, S. B., and SUMMERSON, W. H.: The colorimetric determination of lactic acid in biological materials. *J. Biol. Chem.* 138: 535, 1941.
17. NELSON, N.: A photometric adaptation of the Somogyi method for the determination of glucose. *J. Biol. Chem.* 153: 375, 1944.
18. BUEDING, E., STEIN, M. H., and WORTIS, H.: Blood pyruvate curves following glucose ingestion in normal and thiamine-deficient subjects. *J. Biol. Chem.* 140: 697, 1941.
19. WIERZUCHOWSKI, M.: Oxidation of glucose as function of its supply. *J. Physiol.* 90: 440, 1937.
20. MILLER, A. T., JR., and BLYTH, C. S.: Influence of body type and body fat content on the metabolic cost of work. *J. Applied Physiol.* 8: 139, 1955.
21. PENNINGTON, A. W.: Pyruvic acid metabolism in obesity. *Am. J. Digest. Dis.* 22: 33, 1955.
22. MAYER, J., RUSSELL, R. E., BATES, M. W., and DICKIE, M. M.: Metabolic, nutritional and endocrine studies of the hereditary obesity-diabetes syndrome of mice and mechanism of its development. *Metabolism* 2: 9, 1953.
23. REED, L. J.: Metabolic functions of thiamine and lipoic acid. *Physiol. Rev.* 33: 544, 1953.
24. PARSON, W., and CRISPELL, K. R.: Studies of acetate metabolism in the hereditary obesity-diabetes syndrome of mice utilizing C^{14} acetate. *Metabolism* 4: 227, 1955.
25. REED, L. J., and DEBUSK, B. G.: Lipoic acid conjugase. *J. Am. Chem. Soc.* 74: 4727, 1952.
26. PETERS, R. A.: The study of enzymes in relation to selective toxicity in animal tissues. *Symp. Soc. Exper. Biol.* 3: 36, 1949.