prolonged exercise the changes were even more marked: the contribution of lipids was reduced from 58 to 2% and the contribution of carbohydrates increased from 30 to 67% (Table 4). Thus, nicotinic acid appeared to shift the metabolism of the heart in the fasting state, both at rest and during prolonged exercise, from the predominant utilization of blood lipid substrates to a predominant utilization of blood carbohydrate substrates.

Although the OERs in the control and nicotinic acid groups totaled 97 and 94%, respectively, at rest, they amounted to only 88 and 69% during prolonged exercise (Table 4). This suggests, particularly in the nicotinic acid group, that during prolonged exercise the heart is deriving energy from some source other than the blood substrates which we measured. Plasma ketone bodies can provide 5–7% of the heart's energy supply in the resting, fasting state (33, 43), but both after the administration of nicotinic acid and during exercise the arterial concentration of these substrates falls (7, 13). Although this fall could be due to increased peripheral utilization, it has been shown that the splanchnic production of ketone bodies is suppressed over 90% by nicotinic acid (9) and that during exercise myocardial extraction of ketone bodies decreases (33). Other blood metabolites such as amino acids do not appear to play a significant role in myocardial energy metabolism in the isolated perfused rat heart (17, 24) or in man either at rest or during exercise (14), although their role in myocardial metabolism during the administration of nicotinic acid has not been studied.

The fact that in the nicotinic acid group the total OER for the blood energy substrates which we measured is significantly less than 100%, and that the deficit can probably not be accounted for by other blood metabolites, suggests that during exercise in the presence of nicotinic acid there is a reduction in the total energy content of endogenous myocardial substrate pools. The principal endogenous myocardial energy stores are triglyceride fatty acids (18, 39) and glycogen (3, 28, 44). It is known that both exercise and nicotinic acid administration are accompanied by a decreased glycogen content in the rat heart (3, 42, 44) and that glycogenolysis is accelerated if the isolated perfused animal heart performs increased work (29, 38). It would seem possible, therefore, that in man during prolonged exercise combined with nicotinic acid administration there may also be increased utilization of myocardial glycogen stores.

Certain results in the present study suggest that there is also utilization of endogenous myocardial triglyceride stores in these circumstances. The average myocardial RQ of the nicotinic acid group was 0.91 both at rest and during prolonged exercise (Table 1). Although there are certain limitations in using the RQ of an organ to determine the percentage participation of carbohydrate and lipid in its oxygen consumption (47), an RQ of 0.91 would suggest that the heart is using approximately 70% carbohydrate and 30% lipid. It can be seen from Table 4 that at rest the total carbohydrate and lipid OERs are in reasonably good agreement with this predicted value. However, during exercise although the OER for total blood carbohydrates is 67 ± 6 (SEM)%, that for lipids is only 2 ± 10 (SEM)%. If the assumptions upon which the RQ and OER concepts

TABLE 4. *Relative contribution of blood lipid and carbohydrate substrates to myocardial energy metabolism at rest and during exercise as estimated from both oxygen extraction ratios and myocardial RQ: comparison between control and nicotinic acid groups*

| | Control | | Nicotinic Acid | |
|---|---|---|---|---|
| | OER | RQm | OER | RQm |
| Rest | | | | |
| Lipid | 64 ± 6% | 82% | 22 ± 7% | 31% |
| CHO | 33 ± 5% | 18% | 72 ± 5% | 69% |
| Total | 97 ± 8% | 100% | 94 ± 9% | 100% |
| Exercise | | | | |
| Lipid | 58 ± 4% | 65% | 2 ± 10% | 31% |
| CHO | 30 ± 5% | 35% | 67 ± 6% | 69% |
| Total | 88 ± 6% | 100% | 69 ± 12% | 100% |

OER = oxygen extraction ratio. RQm = myocardial respiratory quotient. Percentage contribution of lipid and carbohydrate to oxidative metabolism. (From Documenta Geigy, 6th ed., p. 628, Table 2). CHO = carbohydrate. Values are means ± SEM.

are based are valid, this would imply that the principal endogenous source of myocardial energy during prolonged exercise with nicotinic acid is in fact lipid, i.e., the myocardial triglyceride fatty acid pool. In this context it is of interest that in intact rats both exercise and the administration of nicotinic acid have been shown to reduce the triglyceride content of the heart (10, 19).

The radiopalmitate measurements also suggest that hydrolysis of glycerides is occurring across the heart in the nicotinic acid group, and they support the contention that it is endogenous myocardial glycerides rather than plasma triglycerides which are undergoing hydrolysis (31). At rest the specific activity of the coronary sinus FFA in the control group was almost always less than that of their arterial FFA, so that the ratio, $SA_{cs}SA_a$, was less than unity. However, during exercise this ratio approached unity. We have discussed these observations in earlier publications where we concluded that the low ratio at rest indicated the efflux into the coronary sinus of unlabeled or low specific activity FFA, and although these could arise from plasma triglycerides, the evidence suggested that endogenous myocardial glyceride stores were the most likely source (31, 34). Since this FFA efflux was not accompanied by free glycerol, we concluded that unless the fatty acids were derived from partial hydrolysis of glycerides, the rate of hydrolysis at rest must not exceed the myocardial capacity for reutilization of glycerol. Furthermore, we interpreted the findings that during prolonged exercise in these subjects the ratio approached unity, but that under this circumstance there was an efflux of free glycerol, as indicating accelerated myocardial glyceride hydrolysis with either *a*) a continuing efflux from this glyceride pool of fatty acids which now had a specific activity very close to that of the arterial FFA or *b*) increased intramyocardial oxidation of the fatty acids.

In the case of the nicotinic acid group in the present study, however, the ratio, $SA_{cs}SA_a$, was less than unity at rest, and although it rose during exercise, it still remained significantly less than unity. The fact that unlabeled fatty acids were entering the coronary sinus blood in this group

in which there was no evidence of significant hydrolysis of plasma triglycerides is support for the contention that the unlabeled fatty acids are derived from endogenous rather than plasma triglycerides (31). This argument will be valid unless formation of partial glycerides is an important fate of plasma triglycerides during passage across the heart.

However, neither at rest nor during exercise was there efflux of free glycerol into the coronary sinus blood. If the earlier interpretation of these phenomena is correct, then in the presence of nicotinic acid endogenous glyceride hydrolysis must occur at rest and must also continue during exercise, but not at a level which exceeds the myocardial capacity for metabolism of glycerol.

As discussed in the earlier publication, the rise in the ratio, $SA_{ss}SA_s$, which occurred with exercise in the absence of nicotinic acid, could be contributed to by one or more of three possible mechanisms: *a*) an increase in coronary blood flow, *b*) an increase in the specific activity of the FFA released into the coronary sinus relative to that of arterial FFA, *c*) a decrease in the rate at which FFA is released into the coronary sinus blood (31). In the present study, an increase with exercise in the coronary blood flow in the nicotinic acid group to only about 1.6 times the resting level could account for the entire rise observed in the ratio. With the heart rates which occurred during exercise in these subjects, coronary blood flow almost certainly increased by two to three times the resting level (26, 30). Since there was a fall in arterial FFA specific activity during exercise in the nicotinic acid group, this would also tend to reduce the difference between the specific activity of the arterial FFA pool and that of the endogenous pool from which fatty acids entering the coronary sinus were derived. It seems unlikely, therefore, that there was any reduction with exercise in the rate of entry of fatty acids into the coronary sinus blood. These results, and the apparent deficit between the relative contributions of lipid and carbohydrate indicated by the myocardial RQ and that actually provided by the blood substrates, suggest that endogenous myocardial glyceride hydrolysis occurs at rest in the presence of nicotinic acid and that during prolonged exercise it may even continue at increased levels.

The failure of glycerol to appear in the coronary sinus blood during exercise in the nicotinic acid group indicates that under these circumstances the myocardial capacity for glycerol metabolism has not been exceeded by glycerol production despite the fact that both the changes in the FFA, $SA_{cc}/SA_a$ ratio and the RQ and OER measurements discussed above suggest that there is increased utilization of endogenous lipid. This apparent paradox could arise *a*) if the actual magnitude of the exercise-induced increase in myocardial glyceride hydrolysis in the nicotinic acid group was not as great as that in the control group or *b*) if the myocardial capacity for glycerol reutilization was increased in the nicotinic acid group.

It is known that in adipose tissue nicotinic acid inhibits glyceride hydrolysis and blocks catecholamine stimulation of lipolysis (6). It is theoretically possible, therefore, that it has a similar effect on endogenous myocardial glyceride hydrolysis and suppresses the exercise-induced acceleration of hydrolysis which was thought to occur in the control group. In this case, if myocardial triglyceride content is reduced in exercising man after the administration of nicotinic acid, as it is in the rat (10), then the rate of triglyceride synthesis in the myocardium would have to be reduced to a proportionately greater extent than is triglyceride hydrolysis. Such a situation might occur with nicotinic acid since the very low arterial FFA concentration and myocardial FFA extraction would reduce the availability of fatty acids for incorporation into triglycerides. However, our data do not allow calculation of turnover or fractional turnover rates of endogenous lipid pools, and nothing appears to be known about the direct effect of nicotinic acid on glyceride metabolism in the heart. Similarly, although it is possible that the increased myocardial metabolism of carbohydrate substrate which occurs when nicotinic acid is administered could accelerate myocardial glycerol utilization, nothing definite seems to be known about the mechanisms controlling metabolism of glycerol within the heart.

### *Effect of Nicotinic Acid on Myocardial Extraction of Blood Substrates*

At rest the arterial concentrations of lactate and pyruvate were significantly higher in the nicotinic acid group, but the concentration of glucose, both at rest and during exercise, and the concentration of lactate and pyruvate during exercise did not differ significantly between the two groups (Table 2). Thus, in most cases, the increased myocardial extraction of these carbohydrate substrates by the subjects receiving nicotinic acid cannot be attributed to increased arterial concentrations of those substrates. Nor does it seem likely that the increased glucose extraction was due to an insulin effect, since the arterial insulin concentration did not differ between the two groups (unpublished observations). In previous studies (34, 35) we demonstrated a significant negative linear relationship between myocardial extraction of glucose, lactate, and pyruvate and arterial FFA concentration, which suggested that FFA might inhibit myocardial uptake of these carbohydrate substrates in a manner analogous to the inhibition of glucose uptake by FFA in the isolated perfused rat heart (41, 45). Since the arterial FFA concentrations in the present study were very much lower in the subjects receiving nicotinic acid than in the control subjects, reduced FFA inhibition could be one explanation for the increased extraction of glucose, lactate, and pyruvate in those subjects. It is also of interest that, particularly during exercise, there continued to be significant extraction of glucose by the heart even when the arterial concentration fell below the so-called myocardial glucose "threshold" of about 3,330 μmoles/liter (2, 20, 21) (Fig. 4).

The fact that the average arterial glucose concentration did not fall in the nicotinic acid group even after 2 hr of relatively strenuous exercise implies that there was either increased production of glucose from hepatic glycogen stores or gluconeogenesis, or that there was decreased peripheral utilization of glucose. The latter possibility seems unlikely, however, since myocardial glucose extraction was, in fact, increased in our subjects, and Bergström et al. (1)

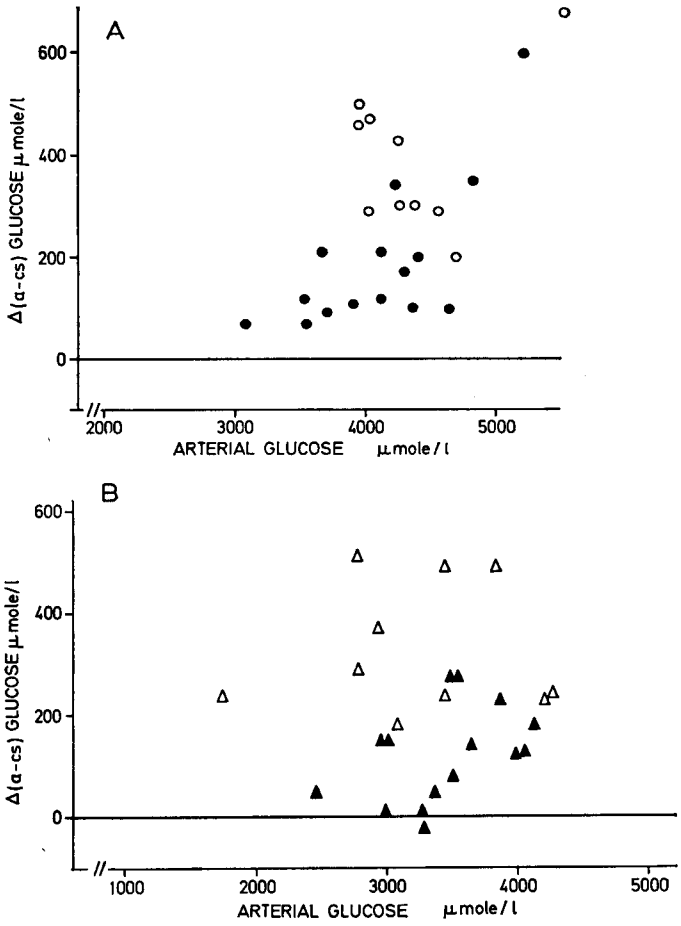


FIG. 4. Relationship between myocardial extraction of glucose (Δ(a-cs)glucose) and arterial glucose concentration, (*A*) at rest (circles) and (*B*) during prolonged exercise (triangles) in 15 control subjects (solid symbols) and 10 subjects receiving a constant intravenous infusion of nicotinic acid (open symbols).

found that after the administration of nicotinic acid glucose extraction by exercising skeletal muscle was either increased or unchanged. It seems more likely, therefore, that the arterial concentration is maintained by increased mobilization of glucose from the liver.

It has been claimed that in man there is an FFA "threshold" such that below an arterial concentration of about 350 μmoles/liter the heart does not extract this substrate (15, 40). In the present study a number of subjects receiving nicotinic acid had small but significant chemical (a-cs) differences in FFA concentration even at arterial concentrations of 200 μmoles/liter, but in others myocardial extraction was not evident at similar levels, and in a few subjects there were actually significant negative (a-cs) differences in FFA concentration. However, all subjects had significant myocardial extraction of radiopalmitate even when arterial FFA concentrations were as low as 140 μmoles/liter (Fig. 2). This suggests that the apparent FFA threshold which has been described in studies in which only chemical measurements of (a-cs) concentration differences were made is merely the level at which FFA uptake by the heart and FFA efflux from the heart are equal and, although there is no net uptake of the substrate at that concentration, fatty acids do continue to be extracted.

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## REFERENCES

1. BERGSTRÖM, J., E. HULTMAN, L. JORFELDT, B. PERNOW, AND J. WAHREN. Effect of nicotinic acid on physical working capacity and on metabolism of muscle glycogen in man. *J. Appl. Physiol.* 26: 170–176, 1969.
2. BING, R. J., A. SIEGEL, A. VITALE, F. BALBONI, E. SPARKS, M. TAESCHLER, M. KLAPPER, AND S. EDWARDS. Metabolic studies on the human heart in vivo. I. Studies on carbohydrate metabolism of the human heart. *Am. J. Med.* 15: 284–296, 1953.
3. BLOUNT, D. H., AND D. K. MEYER. Effects of cardiac work on glycogen fractions of the heart. *Am. J. Physiol.* 197: 1013–1016, 1959.
4. BOBERG, J. Separation of labelled plasma and tissue lipids by thin-layer chromatography. A quantitative methodological study. *Clin. Chim. Acta.* 14: 325–334, 1966.
5. BÜCHER, T., R. CZOK, W. LAMPRECHT, AND E. LATZKO. Pyruvat. In: *Metoden der enzymatischen Analyse.* Weinheim: Verlag Chemie, 1962, p. 253.
6. CARLSON, L. A. Studies on the effect of nicotinic acid on catecholamine stimulated lipolysis in adipose tissue in vitro. *Acta Med. Scand.* 173: 719–722, 1963.
7. CARLSON, L. A., L.-G. EKELUND, AND S. FRÖBERG. Concentration of triglycerides, phospholipids and glycogen in skeletal muscle and of free fatty acids and beta-hydroxybutyric acid in blood in man response to exercise. *European J. Clin. Invest.* 1: 248–254, 1971.
8. CARLSON, L. A., L.-G. EKELUND, AND L. ORÖ. Studies on blood lipids during exercise. IV. Arterial concentration of plasma free fatty acids and glycerol during and after prolonged exercise in normal men. *J. Lab. Clin. Med.* 61: 724–729, 1963.
9. CARLSON, L. A., U. FREYSCHUSS, J. KJELLBERG, AND J. ÖSTMAN. Suppression of splanchnic ketone body production in man by nicotinic acid. *Diabetologia* 3: 494–499, 1967.
10. CARLSON, L. A., S. O. FRÖBERG, AND E. R. NYE. Acute effects of nicotinic acid on plasma, liver, heart and muscle lipids. Nicotinic acid in the rat II. *Acta Med. Scand.* 180: 571–579, 1966.
11. CARLSON, L. A., R. J. HAVEL, L.-G. EKELUND, AND A. HOLMGREN. Effect of nicotinic acid on the turnover rate and oxidation of the free fatty acids of plasma in man during exercise. *Metabolism* 12: 837–845, 1963.
12. CARLSON, L. A., AND L. ORÖ. The effect of nicotinic acid on the plasma free fatty acids. Demonstration of a metabolic type of sympathicolysis. *Acta Med. Scand.* 172: 641–645, 1962.
13. CARLSON, L. A. AND J. ÖSTMAN. Plasma beta-hydroxybutyric acid response to nicotinic acid induced plasma free fatty acid dedecrease in man. *Diabetologia* 2: 127–129, 1966.
14. CARLSTEN, A., B. HALLGREN, R. JAGENBURG, A. SVANBORG, AND L. WERKÖ. Myocardial metabolism of glucose, lactic acid, amino acids and fatty acids in healthy human individuals at rest and at different work loads. *Scand. J. Clin. Lab. Invest.* 13: 418–428, 1961.
15. CARLSTEN, A., B. HALLGREN, R. JAGENBURG, A. SVANBORG, AND L. WERKÖ. Myocardial arteriovenous differences of individual free fatty acids in healthy human individuals. *Metabolism* 12: 1063–1071, 1963.

16. CHERNICK, S. S. Determination of glycerol in acyl glycerols. *Methods Enzymol.* 14: 627, 1969.
17. CLARKE, E. W. A simplified heart-oxygenator preparation suitable for isotope experiments: with some observations on the metabolism of acetate, pyruvate and four amino acids. *J. Physiol., London* 136: 380–392, 1957.
18. DENTON, R. M., AND P. J. RANDLE. Concentrations of glycerides and phospholipids in rat heart and gastrocnemius muscles. Effects of alloxan-diabetes and perfusion. *Biochem. J.* 104: 416–422, 1967.
19. FRÖBERG, S. Metabolism of lipids in blood and tissues during exercise. In: *Biochemistry of Exercise. Medicine and Sport.* New York: Karger-Basel, 1969, vol. 3, p. 100–113.
20. GOODALE, W. T., AND D. B. HACKEL. Myocardial carbohydrate metabolism in normal dogs with effects of hyperglycemia and starvation. *Circulation Res.* 1: 509–517, 1953.
21. GOODALE, W. T., R. E. OLSON, AND D. B. HACKEL. The effects of fasting and diabetes mellitus on myocardial metabolism in man. *Am. J. Med.* 27: 212–220, 1959.
22. HATCH, F. T., AND R. S. LEES. Practical methods for plasma lipoprotein analysis. *Advan. Lipid Res.* 6: 1–68, 1968.
23. HAVEL, R. J., A. NAIMARK, AND C. F. BORCHGREVINK. Turnover rate and oxidation of free fatty acids of blood plasma in man during exercise: studies during continuous infusion of palmitate-1-$C^{14}$. *J. Clin. Invest.* 42: 1054–1063, 1963.
24. HICKS, R. M., AND M. KERLY. Transaminase activity in the perfused rat heart. *J. Physiol., London* 150: 621–631, 1960.
25. HJELM M. Enzymatic determination of hexoses in blood and urine. *Scand. J. Clin. Lab. Invest. Suppl.* 192: 85–98, 1966.
26. HOLMBERG, S. Koronarcirkulation och myokardmetabolism vid angina pectoris. In: *Nordiskt Symposium Angina Pectoris*, edited by E. Varnauskas and L. Werkö. Göteborg: Lindgren, 1969, p. 20.
27. HOLMGREN, A., AND K.-H. MATTSSON. A new ergometer with constant work load at varying pedalling rate. *Scand. J. Clin. Lab. Invest.* 6: 137–140, 1954.
28. JEDEIKEN, L. A. Cardiac glycogen metabolism in vivo in fed and starved rats. *Biochem. J.* 99: 6P-7P, 1966.
29. JEDEIKEN, L. A., AND N. M. BUCKLEY. Glycogen concentration in working and non-working ventricles of isolated dog hearts. *Circulation Res.* 20: 463–472, 1967.
30. JORGENSEN, C. R., K. KITAMURA, F. L. GOBEL, H. L. TAYLOR, AND Y. WANG. Long-term precision of the $N_2O$ method for coronary flow during heavy upright exercise. *J. Appl. Physiol.* 30: 338–344, 1971.
31. KAIJSER, L., B. W. LASSERS, M. L. WAHLQVIST, AND L. A. CARLSON. Myocardial lipid and carbohydrate metabolism in fasting men during prolonged exercise. *J. Appl. Physiol.* 32: 847–858, 1972.
32. KESSLER, G., AND H. LEDERER. Fluorometric measurement of triglycerides. In: *Automation in Analytical Chemistry*, edited by L. T. Skegg, Jr. New York: Mediad, 1966, p. 341–344.
33. KEUL, J., E. DOLL, H. STEIM, U. FLEER, AND H. REINDELL. Über den Stoffwechsel des menschlichen Herzens. III. Der oxydative Stoffwechsel des menschlichen Herzens unter verschiedenen Arbeitsbedingungen. *Arch. Ges. Physiol.* 282: 43–53, 1965.
34. LASSERS, B. W. L. KAIJSER AND L. A. CARLSON: Myocardial lipid and carbohydrate metabolism in healthy, fasting men at rest. *European J. Clin. Invest.* In press.
35. LASSERS, B. W., M. L. WAHLQVIST, L. KAIJSER, AND L. A. CARLSON. The relationship in man between plasma free fatty acids and myocardial metabolism of carbohydrate substrates. *Lancet* 2: 448–450, 1971.
36. LUNDHOLM, L., E. MOHME-LUNDHOLM, AND N. VAMOS. Lactic acid assay with L(+) lactic acid dehydrogenase from rabbit muscle. *Acta Physiol. Scand.* 59: 243–249, 1963.
37. MOST, A. S., N. BRACHFELD, R. GORLIN, AND J. WAHREN. Free fatty acid metabolism of the human heart at rest. *J. Clin. Invest.* 48: 1177–1188, 1969.
38. NEELY, J. R., C. F. WHITFIELD, AND H. E. MORGAN. Regulation of glycogenolysis in hearts: effects of pressure development, glucose and FFA. *Am. J. Physiol.* 219: 1083–1088, 1970.
39. OLSON, R. E., AND R. J. HOESCHEN. Utilization of endogenous lipids by the isolated perfused rat heart. *Biochem. J.* 103: 796–801, 1967.
40. OPIE, L. H. Metabolism of the heart in health and disease. I. *Am. Heart J.* 76: 685–698, 1968.
41. RANDLE, P. J., P. B. GARLAND, C. N. HALES, AND E. A. NEWSHOLME. The glucose fatty acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1: 785–789, 1963.
42. ROOT, M. A., AND J. ASHMORE. The hypoglycemic activity of nicotinic acid in rats. *Arch. Exptl. Pathol. Pharmakol.* 248: 117–123, 1964.
43. RUDOLPH, W., D. MAAS, F. J. RICHTER, F. HASINGER, H. HOFMANN, AND P. DOHRN. Über die Beduetung von Acetacetat und β-Hydroxybutyrat im Stoffwechsel des menschlichen Herzens. *Klin. Wochschr.* 43: 445–451, 1965.
44. SCHEUER, J., L. KAPNER, C. A. STRINGFELLOW, C. L. ARMSTRONG, AND S. PENPARGKUL. Glycogen, lipid and high energy phosphate stores in hearts from conditioned rats. *J. Lab. Clin. Med.* 75: 924–929, 1970.
45. SHIPP, J. C., L. H. OPIE, AND D. CHALLONER. Fatty acid and glucose metabolism in the perfused heart. *Nature* 189: 1018–1019, 1961.
46. SJÖSTRAND, T. Changes in the respiratory organs of workmen at an ore smelting works. *Acta Med. Scand. Suppl.* 196: 687–699, 1961.
47. SOSKIN, S., AND R. LEVINE. *Carbohydrate Metabolism* (2nd ed.). Chicago, Ill.: Univ. of Chicago Press, 1952.
48. TROUT, D. L., E. H. ESTES, AND S. J. FRIEDBERG. Titration of free fatty acids of plasma: a study of current methods and a new modification. *J. Lipid Res.* 1: 199–202, 1960.
49. WAHLUND, H. Determination of the physical working capacity. A physiological and clinical study with special reference to standardization of cardio-pulmonary functional tests. *Acta Med. Scand. Suppl.* 215, 1948.