5. Woods, J. W., *J. Clin. Invest.*, 1958, v37, 1686.
6. Shapiro, A. P., Braude, A. I., Siemienski, J., PROC. SOC. EXP. BIOL. AND MED., 1956, v91, 18.
7. Rocha, H., Guze, L. B., Freedman, L. R., Beeson, P. B., *Yale J. Biol. and Med.*, 1958, v30, 341.
8. Hollander, W., Jr., Winters, R. W., Williams, T. F., Bradley, J., Oliver, J., Welt, L. G., *Am. J. Physiol.*, 1957, v189, 557.

Received March 7, 1960. P.S.E.B.M., 1960, v104.

Response of Plasma NEFA Levels to Epinephrine Infusions in Normal and Obese Women.* (25748)

RODNEY D. ORTH, ROBERT H. WILLIAMS
Dept. of Medicine, University of Washington School of Medicine, Seattle, Wash.

The physiologic and pharmacologic behavior of adipose tissue within the human body may well be a major etiologic factor in human obesity. It has been demonstrated that epinephrine markedly enhances release of non-esterified fatty acids (NEFA) by adipose tissue both *in vitro*(1) and *in vivo*(2,3). There is much evidence that nor-epinephrine, secreted by post-ganglionic sympathetic fibers, and epinephrine derived from the adrenal medulla are important regulators of fatty acid release from tissue fat depots(4). The present study was undertaken to test the hypothesis that obese subjects might exhibit a gross quantitative difference from normal individuals in response of serum NEFA levels to infused epinephrine.

Methods. Ten obese and 9 control female subjects were selected from out-patient department or hospital staff. All were free from complicating disease, had no personal or family history of diabetes, and were normally active on an ambulatory basis. Each was instructed to eat freely on day prior to infusion, but no food was allowed after 7 p. m. At 8 a. m. the following morning (13 hr. fast) a control blood sample was drawn at time of insertion of the indwelling needle. Isotonic saline was infused for 30 minutes (control period), whereupon a second sample was obtained. After control period, epinephrine bitartrate was added to infusion bottle to produce an infusion rate of 0.01 μg/lb/min (as epinephrine equivalent) and the infusion continued 30 minutes. At termination of the infusion (while epinephrine was still being infused) a third sample was taken. All blood samples were added to pre-chilled oxalate tubes, put in packed ice, centrifuged at 4°C, and immediately extracted and titrated for NEFA by Dole's method(3). An occasional sample was frozen at −15° for 1-2 days before

TABLE I. Response of Plasma NEFA Levels to Epinephrine Infusion* in Normal and Obese Women.

		NEFA conc. (μEq/l)			Glucose conc. (mg %)		
Age	Wt	C_1†	C_2‡	Epin.§	C_1	C_2	Epin.
		Normal women					
23	110	392	507	1209	87	90	108
17	115	586	682	1045	91	86	99
23	123	739	721	1243		75	81
23	129	564	691	1061	89	89	106
28	130	605	722	913	80	83	90
37	130	485	376	664	83	80	84
22	133	603	588	1102	101	96	119
25	135	715	885	1875	89	80	91
23	140	374	456	900	97	96	109
‖ 26	127	562	625	1112	90	86	99
		Obese women					
22	144	694	900	1780	93	90	125
21	185	608	681	1108	100	94	125
40	188	555	748	1676			
30	190	429	424	755	85	86	106
20	198	366	466	805	90	90	119
20	210	391	355	753	96	96	134
25	215	590	648	1242			
31	235	535	583	1055	91	93	111
20	300	676	746	807	88	84	127
39	337	885	980	1173	94	92	117
‖ 27	220	573	653	1115	92	91	121

* Infusion rate = 0.01 μg epinephrine/lb/min., 30 min.
† Initial control value.
‡ 30 min. " " .
§ At end of epinephrine infusion.
‖ Mean value.

* This study carried out during tenure of traineeship. Supported by Grant by Nat. Inst. of Arthritis and Metabolic Diseases, U. S. Public Health Service.

analysis. Plasma glucose determinations were also done on all samples.

Results. Infusion of epinephrine at the rate of 0.01 μg lb min produced objective symptoms (restlessness and tachycardia) in only one patient, and most subjects were unable to note any subjective difference from the control period. Mean fasting values in normal and obese patients were nearly identical in this series of patients (Table I). It has previously been noted, however, that obese patients tend to have higher fasting NEFA levels than normals, although variable overlapping between the 2 groups has been present(3,5). Mean fasting value in normals in the present study is nearly identical with that reported by Munker in a series of 107 normal patients(5). The rise in plasma NEFA levels following epinephrine infusion ranged from 191-990 μeq l in normals, and from 61-1086 μeq l in overweight individuals. Mean rise and final level attained in each group was identical within the limits of the method. Plasma glucose levels tended to increase much more following epinephrine infusion in the obese group (avg. 30 mg %) than in normal controls (avg 13 mg %), a difference which has statistical significance ($p<0.001$).

Conclusion. These observations suggest, then, that there is no impairment in ability of fat stores in obese patients to release NEFA in response to epinephrine.

1. Gordon, R. S., Jr., Cherkes, A., PROC. SOC. EXP. BIOL. AND MED., 1958, v97, 150.
2. ———, *J. Clin. Invest.*, 1956, v35, 206.
3. Dole, V. P., *ibid.*, 1956, v35, 150.
4. Havel, R. J., Goldfein, A., *J. Lipid Res.*, 1959, v1, 102.
5. Munker, C., *Scand. J. Clin. Lab. Invest.*, 1959, v11, 388.

Received March 8, 1960. P.S.E.B.M., 1960, v104.

Mydriatic Half-Life of a New Anticholinergic as Affected by Dose, Route, Quaternization.* (25749)

F. M. STURTEVANT
Pharmacology Section, Smith Kline & French Labs., Philadelphia, Pa.

It has long been recognized that clearance of many drugs from the bloodstream approximates an exponential relationship with time (1-4), presumably because rate of clearance depends upon concentration of drug in blood. By extension, if degree of pharmacologic response and its rate of disappearance are determined by concentration of the drug on receptor sites, then disappearance of response should also approximate an exponential curve. The negative reciprocal of the slope of this semi-log curve would be the biologic half-life, a very useful index of drug performance (5). Recently, we determined the influence of dose, route, and quaternization on mydriatic half-life in mice of a new tertiary ammonium anticholinergic drug, SKF 5515(6).

Methods. Adult, male, Dierolf mice, in groups of 9-12, were given varying doses i.v., s.c., or p.o. of SKF 5515, 9-methyl-3-oxo-9-azabicyclo-(3,3,1)-nonan-7-yl benzilate maleate(6), or of SKF 5516, the methobromide quaternary derivative, and were observed at intervals for mydriasis. Pupillary diameter was measured in arbitrary units (5 units ≅ 1 mm) under constant illumination, using ocular micrometer. At each interval, the geometric mean increases in pupil size for each group were plotted on semi-log graph paper and least-squares lines fitted to a linear portion of the decay curve. The least-squares equations were in the form of $M = a\ e^{kt}$, where M = change in pupillary diameter in units, a = a constant determining the extrapolated ordinate intercept, t = time in hours, k = a velocity constant in hr^{-1}, and e is the Naperian base. Apparent half-lives ($t_{½}$) in hours were then calculated(5) from $t_{½} = 0.693/k$. The "total drug effectiveness," *i.e.*, areas under time-action curves (F), were cal-

* Presented at Fed. Meetings, Chicago, Ill., April 1960.