high-altitude which did not become frankly polycythemic.

Since adrenalectomy and hypophysectomy did not abolish the ulcerogenic effect of transfusion observed in our study, it seems unlikely that a non-specific stress reaction, usually thought to be mediated through the pituitary-adrenal axis(9,10), accounts for the results we observed.

It is possible that the relative circulatory stasis present in the distended vasculature of the polycythemic animals, similar to that discussed by Brooks(11) in studies on circulatory adjustments in human polycythemia rubra vera, may diminish tissue resistance sufficiently to allow ulceration even in the absence of frank thrombosis and mucosal infarction. Alternatively, by allowing CO_2 to accumulate in the gastric mucosa as a product of cellular metabolism, stasis may predispose to ulceration by increasing hydrochloric acid secretion via the carbonic anhydrase-dependent equilibrium: $CO_2 + H_2O \leftrightarrows H^+ + HCO_3^-$, which may be the basic mechanism of gastric acid secretion as recently demonstrated and emphasized by Davies(12) and Janowitz(13). The attractiveness of this latter speculation is enhanced by the observation that ulcers in patients with polycythemia rubra vera are largely (90%) duodenal(2,3), a location that has been most often associated with gastric hypersecretion of acid(14).

These findings suggest an interesting parallel between our experimental system and the patient with polycythemia rubra vera and its associated increased incidence of peptic ulcer. Additional studies are in progress to determine whether gastric hypersecretion of acid occurs secondary to the induced polycythemia, as we have postulated, or whether, in its absence, vascular factors alone may initiate ulcer formation.

Summary. Induction of polycythemia by repeated intravenous injections of homologous erythrocytes produced gastric ulceration in 26 of 29 rats, including normal, adrenalectomized, hypophysectomized, and sham-operated animals. An experimental system has therefore been developed for the study of etiologic factors which may parallel those leading to development of peptic ulcers in patients with polycythemia rubra vera.

1. Friedman, G. A., *Med. Rec.,* 1913, v84, 701.
2. Wilbur, D. L., Ochsner, H. C., *Ann. Int. Med.,* 1935, v8, 1667.
3. Lawrence, J. H., *Polycythemia* (Grune and Stratton, N. Y., p16, 1955).
4. Boyd, W., *Am. J. Med. Sci.,* 1934, v187, 589.
5. Norman, I. L., Allen, E. V., *Am. Heart J.,* 1937, v13, 257.
6. Anderson, W. A. D., *Pathology* (C. V. Mosby, St. Louis, p764, 1953).
7. Highman, B., Altland, P. D., *Arch. Path.,* 1949, v48, 511.
8. Reynolds, O., Phillips, N. E., *Am. J. Physiol.,* 1947, v151, 147.
9. Fletcher, D. G., Harkins, H. N., *Surgery,* 1954, v36, 212.
10. Zubiran, J. M., Kark, A. E., Montalbetti, A. J., Morel, C. J. L., Dragstedt, L. R., *A. M. A. Arch. Surg.,* 1952, v65, 89.
11. Brooks, W. D. W., *Roy. Soc. Med.,* 1936, v29, 1379.
12. Davies, R. E., *Biol. Revs.,* 1951, v26, 87.
13. Janowitz, H. D., *Lancet,* 1958, v1, 1353.
14. Kirsner, J. B., Palmer, W. L., *Am. J. Med.,* 1952, v13, 616.

Received February 13, 1959. P.S.E.B.M., 1959, v101.

Effect of Norepinephrine and Epinephrine on Nonesterified Fatty Acid Concentration in Plasma. (25039)

MICHAEL C. SCHOTZ AND IRVINE H. PAGE
Division of Research, Cleveland Clinic Fn., and Frank E. Bunts Educational Inst., Cleveland, O.

It has been suggested that the sympathetic nervous system has a role in regulation of fat transport(1). Fatty acids are transported in plasma, partially in nonesterified form(2,3). Their source in a fasting animal appears to be adipose tissue(4-6). Injection of epinephrine increases plasma nonesterified fatty acid (NEFA) concentration(2,3,7) by enhancing

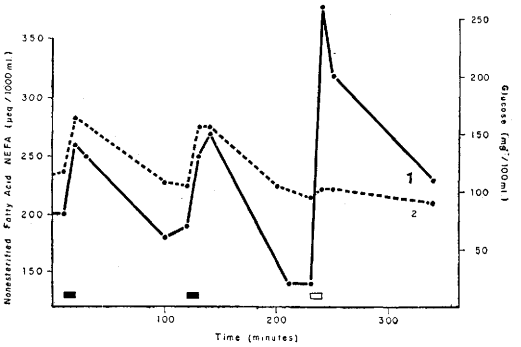

FIG. 1. Effect of epinephrine and norepinephrine on concentrations of plasma NEFA (Curve 1) and glucose (Curve 2). ■, infusion period of epinephrine; □, infusion period of norepinephrine.

hydrolysis of triglycerides to fatty acids in adipose tissue(8). Recently, it has been shown that addition of norepinephrine, a chemical mediator of sympathetic nerve endings, to flasks containing epididymal adipose tissue enhances hydrolysis of esterified fatty acids(9). The present report demonstrates that norepinephrine, as well as epinephrine, when infused into dogs, raises plasma NEFA concentration.

Method. Catheters were inserted in each femoral vein of 4 mongrel dogs, weighing 11 to 13 kg and fasted 24 hours and anesthetized with sodium pentobarbital. Solutions of epinephrine or norepinephrine bitartrate in 0.85% sodium chloride, adjusted to pH 5 with 0.1 N HCl, were made just before starting the infusion. A solution containing 10 μg base/ml was infused through one of the catheters at constant rate of 8.4 μg/min. for 10 minutes. Blood samples were withdrawn from opposite femoral vein 10 minutes before infusion was begun, at beginning, and 10, 20, and 90 minutes after infusion was started. Five ml of blood was immediately placed in a tube containing 0.5 ml of 3.8% sodium citrate, and the sample mixed and chilled in an ice bath. Plasma obtained by centrifugation was analyzed for NEFA(10) and glucose(11). The method of NEFA analysis excluded water-soluble organic acids.

Results. The data from one typical experiment are shown in Fig. 1. Infusion of epinephrine for 10 minutes increased initial plasma NEFA concentration by about 35%; followed by a slight decline 10 minutes after infusion was stopped. Repeating the infusion of epinephrine, in the same dog, gave essentially the same result. However, infusion of norepinephrine at the same concentration and rate increased the initial NEFA concentration almost 2-fold at the end of 10 minute infusion period; 10 minutes after infusion was stopped the concentration decreased slightly, and within 90 minutes it decreased considerably but remained higher than the initial NEFA concentration.

During infusion of epinephrine changes in the glucose concentration of plasma paralleled changes in NEFA concentration. In contrast, norepinephrine produced little change in plasma glucose concentrations although large changes in NEFA concentrations were noted.

Similar results were obtained in 3 other experiments. Reversal of the order of epinephrine and morepinephrine administration had no effect.

Discussion. White and Engel(9) have shown that both norepinephrine and epinephrine at same concentration stimulate hydrolysis of neutral fats to fatty acids to the same extent in adipose tissue incubated *in vitro*. Similar observations have been made by us. Therefore, it would be expected that infusion of epinephrine and norepinephrine into animals would have the same effect on plasma NEFA. However, in all 4 experiments, the increase in NEFA was greater when norepinephrine was infused. It is possible that the difference in response of plasma NEFA is due to faster destruction of epinephrine, or to an inhibitory effect of increased plasma glucose concentrations after infusion of epinephrine on release of NEFA from adipose tissue(5).

That infusion of norepinephrine and epinephrine produces an increase in plasma NEFA concentration suggests that these compounds may function as circulating hormones, acting directly on adipose tissue to regulate fatty acid mobilization. This suggestion is substantiated by the observation that adipose tissue from adrenalectomized rats, incubated *in vitro*, undergoes less hydrolysis of esterified fatty acids. The fact that norepinephrine is more effective than epinephrine is consistent with the hypothesis that sympathetic nervous

system is involved in regulation of fat transport due to release of norepinephrine at nerve endings in adipose tissue.

Summary. Concentrations of nonesterified fatty acids and of glucose in plasma were determined before and after infusion of epinephrine and norepinephrine into dogs. At the same concentration and rate of infusion, norepinephrine produced a greater increase in nonesterified fatty acids.

ADDENDUM: Since completion of this manuscript, we found that Laurell, S., Christensson, B., *Acta Physiol. Scand.*, 1958, v44, 248 reported increased plasma NEFA in human subjects following norepinephrine injection.

1. Ellis, S., *Pharmacol. Rev.*, 1956, v8, 485.
2. Dole, V. P., *J. Clin. Invest.*, 1956, v35, 150.
3. Gordon, R. S., Jr., Cherkes, A., *ibid.*, 1956, v35, 206.
4. Gordon, R. S., Jr., *ibid.*, 1957, v36, 810.
5. Gordon, R. S., Jr., Cherkes, A., PROC. SOC. EXP. BIOL. AND MED., 1958, v97, 150.
6. Reshef, L., Shafrir, E., Shapiro, B., *Metabolism*, 1958, v7, 723.
7. Grafnetter, D., Zemplényi, T., *Chem. Abstr.*, 1958, v52, no. 20549 g.
8. Wadström, L. B., *Nature, London*, 1957, v179, 259.
9. White, J. E., Engel, F. L., PROC. SOC. EXP. BIOL. AND MED., 1958, v99, 375.
10. Schotz, M. C., Masson, G. M. C., Page, I. H., *ibid.*, 1959, v101, 159.
11. Hoffman, W. S., *J. Biol. Chem.*, 1937, v120, 51.

Received April 13, 1959. P.S.E.B.M., 1959, v101.

Periarteritis in Rats Given Single Injection of 4′-Fluoro-10-methyl-1,2-benzanthracene.* (25040)

H. A. HARTMANN, E. C. MILLER AND J. A. MILLER
Dept. of Pathology and McArdle Memorial Lab. for Cancer Research, University of Wisconsin Medical School, Madison

Periarteritis nodosa has been recognized in patients for almost a century(1), and an etiology of hypersensitivity has been invoked (2-4). Thus, the disease sometimes appears to follow administration of foreign sera(4,5), and similar lesions can be induced in experimental animals by foreign proteins(6-11). A number of clinical cases of periarteritis nodosa have been ascribed to hypersensitivity reaction to various drugs (i.e., sulfonamides(12) and iodides(13)). Similar vascular lesions have been induced in experimental animals by a few compounds of low molecular weight. Periarteritis was observed in rats and monkeys stressed by unilateral nephrectomy and high salt diet and then given 9-fluoro- or 9-chloro-2-methylcortisol(14-16). Anemic infarction of lungs was found in rats treated with certain halogenated hydrocarbons such as hexachlorotetrafluorobutane(17). In a study on carcinogenicity of various fluorinated derivatives of 10-methyl-1,2-benzanthracene (10-Me-BA)† all rats injected subcutaneously with 2.14 mg of 4′-fluoro-10-Me-BA died within 8 weeks. A marked degree of vascular changes as found in lungs and kidneys, and pulmonary lesions appeared to cause death. Development of these lesions was followed in a second series of rats, and data for the latter experiment form the subject of this report.

Materials and Methods. Male adult albino rats of Holtzman stock‡ with average initial weight of 250 g were maintained in screen-bottom cages in groups of 2 to 4 and were fed Purina Laboratory Chow *ad lib.* Each rat received a single subcutaneous injection of 0.2 ml of tricaprylin (previously dissolved in petroleum ether and extracted with alkali to remove traces of free acid) or 0.2 ml of tri-

* This investigation was supported by grants from Nat. Inst. Health, U.S.P.H.S. and Alexander and Margaret Stewart Trust Fund. Assistance of Stanley Miczio is gratefully acknowledged.

† Carcinogenicity studies are being made in collaboration with Dr. Melvin Newman of Ohio State Univ., to whom we are indebted for hydrocarbons used.

‡ Holtzman Rat Co., Madison, Wis.