The effect of CO_2 on renal perfusion was studied using a direct cannulation technique to measure renal blood flow. Pa_{CO_2} was varied from 20 to 120 torr. Measurements were made with Pa_{CO_2} maintained within narrow ranges. Renal vascular resistance, oxygen consumption, and filtration fraction were measured, as was creatinine and p-aminohippurate clearance, while excretion of sodium and potassium was monitored. No real change in renal perfusion occurred until Pa_{CO_2} exceeded 70 torr. A further increase in Pa_{CO_2} was associated with a progressive decrease in renal blood flow, accompanied by similar decreases in glomerular filtration rate, renal plasma flow, and electrolyte excretion. The depressed perfusion which resulted from hypercapnia was preventable by mannitol infusion and by renal nerve blockade. The authors suggest that CO_2 has no direct effect on the intrarenal vasculature, and that the vasoconstrictor effect of hypercapnia is secondary to the interaction between CO_2 and the sympathoadrenal system. (*Norman, J. N., and others: Effect of Carbon Dioxide on Renal Blood Flow, Amer. J. Physiol. 219: 672 (Sept.) 1970.*)

Respiration

2,3-DPG, *p*H AND HEMOGLOBIN–OXYGEN AFFINITY The influence of *p*H on hemoglobin affinity for oxygen (Bohr effect) is well known. On the other hand, we know now that an intermediate of glucose metabolism, 2,3-diphosphoglyceric acid (2,3-DPG) is present in high concentration in erythrocytes, and has been shown to reduce the affinity of hemoglobin for oxygen. In 1942, Guest showed that diabetic acidosis was associated with low erythrocyte 2,3-DPG. A reduction of the concentration of 2,3-DPG leads to a higher affinity of hemoglobin for oxygen, whereas the decrease in *p*H, mediated through the Bohr effect, leads to a shift of the dissociation curve to the right. The purpose of the present study was to investigate the adaptive response to systemic acidosis or alkalosis of oxyhemoglobin dissociation in normal man and to delineate mechanisms involved in this regulation.

Acidosis was induced acutely in four healthy volunteers with intravenous acetazolamide given in a one-week period. The acidosis was then rapidly corrected and alkalosis induced with sodium bicarbonate injected intravenously. Control values for hemoglobin–oxygen affinity, erythrocyte acid-soluble organic phosphates, plasma and erythrocyte *p*H, blood gases, plasma electrolytes, and hemoglobin were determined, and hematocrit readings were made. Serial values were obtained during acidosis and alkalosis. Arterial blood was obtained for all measurements.

Acute changes in plasma *p*H produced no alteration in erythrocyte 2,3-DPG content, but there were changes in hemoglobin–oxygen affinity, and these correlated with changes in mean corpuscular hemoglobin concentration (MCHC). When acidosis or alkalosis was maintained (usually for four hours) erythrocyte 2,3-DPG content was affected and correlated with the change in hemoglobin–oxygen affinity. An increase in *p*H was countered by an increase in 2,3-DPG; conversely, a decrease in *p*H was associated with diminution of erythrocytic 2,3-DPG. Provided the rate of *p*H change is not too rapid or too great, 2,3-DPG changes counteract the *p*H effect and hemoglobin-oxygen affinity *in vivo* remains unchanged. Approximately 35 per cent of the change in hemoglobin–oxygen affinity which occurs from alteration in erythrocytic 2,3-DPG, can be explained by the effect of 2,3-DPG on erythrocyte *p*H. (*Bellingham, A. J., Detter, J. C., and Lenfant, C.: Regulatory Mechanisms of Hemoglobin Oxygen Affinity in Acidosis and Alkalosis, J. Clin. Invest. 50: 700 (March) 1971.*)

Endocrine Function

THYROID ACTIVITY AND CATECHOLAMINE SENSITIVITY This paper reviews the state of our knowledge of thyroid hormone and its relationship to the action of catecholamines. According to the author, studies of the circulatory effects of hyperthyroidism in relation to catecholamine hypersensitivity published prior to 1960 are inconclusive, because they failed to utilize dose–response curves or their data were insufficient for statistical analysis.

Subsequent studies (1965–1967) found no difference between the responses of hyperthy-

roid and euthyroid animals to catecholamines; these experiments included studies of inotropism in ventricular muscle strips, changes in heart rate, and contractility of isolated atria and papillary muscle. Work in which reserpine was found not to alter the elevated capillary muscle contractility of hyperthyroid animals is cited. All the data obtained *in vitro* suggest that the effect of thyroid hormone on the contractile mechanism of the heart is not mediated via the adrenergic nervous system.

According to the author, clinical studies of sensitivity to catecholamines in hyperthyroidism are difficult to evaluate because the effects of hormone and those of catecholamine excess are similar; both may cause tachycardia, widen pulse pressure, lead to diaphoresis or cardiac arrhythmias, and increase oxygen consumption. In human subjects made "hyperthyroid" by the administration of triiodothyronine, no changes in responses to exogenous epinephrine and norepinephrine could be detected. It is also pertinent to note that beta-adrenergic blockers fail to lower heart rates to normal levels in hyperthyroid patients.

The chronotropic and inotropic effects of catecholamines on the heart are thought to be mediated by adenyl cyclase, which catalyzes the transformation of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cyclic AMP). No difference between the degree to which 1×10^{-4} M epinephrine increased cyclic AMP levels in hypothyroid and euthyroid cats was found. The author found no difference between the degrees of adenyl cyclase reactivity to norepinephrine of hyper- and hypothyroid left ventricles in terms of threshold response and half maximal activity, nor were there differences in contractility of papillary muscle among hypothyroid, euthyroid, and hyperthyroid cats during norepinephrine infusion. Certain thyroid hormones have a direct stimulating effect on the adenyl cyclase–cyclic AMP system—an effect not mediated via the catecholamines. Iodination of the 3′ position of the thyronine nucleus appears necessary for this action. Increased production of cyclic 3′,5′-AMP was shown for L-thyronine (135 ± 2.0 picomoles of cyclic AMP/3 min/mg of protein, $P < 0.001$), D-thyronine (133 picomoles/3 min/mg, $P < 0.02$), and 3,3′ diiodothyronine (118 picomoles/3 min/mg, $P < 0.02$), but was not seen with diiodotyrosine, monoiodotyrosine, or tyrosine. The control value was 92 ± 2.0 picomoles/3 min/mg. No direct inotropic or chronotropic effect of thyroid hormones has been demonstrated in isolated perfused hearts, although adrenergic blockers significantly reduce the circulatory effects of the hyperthyroid state. Although catecholamines must have an important role in the manifestation of hyperthyroidism, the hypothesis of increased myocardial sensitivity to catechols is no longer tenable. It is likely that binding of catecholamines in the myocardium is decreased in the presence of hyperthyroidism, resulting in a greater level of free catechols which interact with beta receptors. This appears to be the most acceptable explanation for the adrenergic effects of hyperthyroidism. (*Levey, G. S.: Catecholamine Sensitivity, Thyroid Hormone, and the Heart, Amer. J. Med. 50: 413 (April) 1971.*) ABSTRACTER'S COMMENT: A good review of current research into the mechanisms by which thyroid hormones affect the heart. This article also includes some of the author's original research on thyroid hormones and cyclic AMP. Although it brings us no closer to an answer, it does place the problem of catecholamine sensitivity and myocardial rhythmicity in better perspective.