ANAPHYLACTIC REACTIONS have been described frequently in the medical literature.\textsuperscript{1,2} It has been established, largely by studies with in vitro models, that anaphylaxis is caused by an IGE-mediated degranulation of tissue mast cells and basophils, with discharge of histamine, prostaglandins and other substances into the surrounding circulation. The profile of hemodynamic and biochemical change in such reactions, however, has not been fully documented in man, particularly as to whether catecholamines are released in response to increases in plasma histamine levels. A recent experience in which a patient sustained an anaphylactic reaction to the muscle relaxant succinylcholine provided an opportunity to correlate changes in hemodynamics with alterations in plasma histamine and catecholamine levels during anaphylaxis. Our findings suggest that, in addition to the direct effects of histamine on the cardiovascular system, the induced sympathoadrenal response may be an important component of the pathophysiology of anaphylaxis.

Case Report

The patient was a 28-year-old white female scheduled for a right total hip replacement. On the night before surgery, the primary anesthetist examined the patient and studied her past medical history. Although the records of a previous anesthetic 8 years before this admission were not available, the patient recalled that at that time she was told she was "allergic to anesthesia." The records were found subsequently, and these indicated that the patient sustained a "cardiac arrest" after induction of general anesthesia with 375 mg of sodium thiopental and 80 mg of succinylcholine. The patient was resuscitated and the operation was cancelled. Available records showed that 4 years before the current admission the patient had undergone a halothane general anesthetic without sequelae. One year before the current admission, the patient underwent another uneventful general anesthetic in which induction was carried out with intravenous diazepam and maintenance with enflurane. The patient had no current cardiorespiratory problems and was enrolled in an ongoing study of deliberate hypotension and vasoactive substances. On the morning of surgery, she was premedicated with morphine and scopolamine. On arrival in the induction room, central venous and arterial catheters were inserted. During the course of her anesthesia, heart rate, arterial and central venous pressures and cardiac output were monitored. Arterial blood samples were drawn and analyzed for plasma catecholamines, histamine, plasma renin activity, arterial blood gases and electrolytes. After induction with 300 mg of sodium thiopental, the patient was ventilated for 5 minutes with an oxygen–nitrous oxide mixture. Succinylcholine, 100 mg, was then administered to facilitate intubation. Immediately after administration of succinylcholine, the patient developed an intense red discoloration of her entire body and face and marked swelling of her eyelids. Within 3 minutes, her heart rate increased to 147 beats/min. Blood pressure decreased somewhat, but was maintained with rapid intravenous infusion of 1500 ml of lactated Ringer's solution to maintain a constant central venous pressure. One hundred percent oxygen was administered. The heart rate returned to normal over a 20-minute period. No bronchoconstriction was evident clinically. The skin redness and periorbital edema persisted for 36 hours. After cardiovascular stability was achieved, the hip replacement was undertaken and the rest of the procedure was uneventful. Postoperatively, intradermal skin tests of commonly used anesthetic drugs were applied to the patient in 0.1-ml applications (including 1:1000 dilutions of thiopental, decamethonium, curare, dimethyltubocurare, gallamine, pancuronium and succinylcholine). She reacted only to succinylcholine, with the
rapid appearance of an indurated area 2 cm in diameter.

Materials and Methods

Hemodynamics

Pressures in the radial artery and right atrium were measured by transducers (Hewlett-Packard type 267 BC) and were recorded continuously, together with lead 2 of the ECG, on a Sanborn four-channel pen recorder. Heart rate was calculated from the ECG tracing. Mean arterial (MAP) and right atrial (MRAP) pressures were obtained by electrical integration. Cardiac output (CO) was determined by dye-dilution technique, with injection of 5 mg of indocyanine green (Cardio-green) into the right atrium and withdrawal from the radial artery catheter through the cardiodensitometer (Lexington). All measurements were performed in duplicate. Stroke volume was derived from cardiac output divided by heart rate. Systemic vascular resistance (SVR) was calculated from the formula:

$$SVR = \frac{(MAP - MRAP) \times 80 \text{ dyn-sec-cm}^{-5}}{\text{CO}}$$

Hormone Measurements

Plasma histamine was measured using the double-isotope enzymatic method of Shaff and Beaven. All samples were assayed in duplicate. Plasma norepinephrine and epinephrine levels were measured by the sensitive radioenzymatic method of Da Prada and Zürcher in a chloroform-ethanol-ethanolamine solvent system. All samples were done in duplicate with internal standards. Inter- and intraassay variations were within 5%. Sensitivity of the assay in human plasma was greater than 25 pg/ml. Plasma renin activity was measured by radioimmunoassay.

Results

Preanesthetic plasma norepinephrine and epinephrine levels were 769 pg/ml and 359 pg/ml, respectively. These values were obtained after the insertion of venous and arterial catheters and may be slightly higher than those seen in normal resting man, but are compatible with preinduction values obtained in other patients. The elevated epinephrine levels may reflect psychological stress. Initially, plasma histamine was 2080 pg/ml, a value that is two to three times normal but not in the pathologic range. The patient had received morphine for premedication. Baseline hemodynamic function of this patient was similar to that of other preoperative patients undergoing similar procedures. Hemodynamic function did not change appreciably with the administration of thiopental, although there were slight decreases in heart rate, blood pressure, cardiac output, stroke volume and systemic vascular resistance (fig. 1).

Immediately after the administration of succinylcholine and concurrent with the appearance of
flushing, a substantial increase in cardiac output and stroke volume occurred. Although systemic vascular resistance fell precipitously from 1000 to 602 dyn-sec-cm⁻², arterial blood pressure declined slightly from 105/60 to 100/50 mm Hg. Massive release of histamine and catecholamines was indicated by large increases in their respective blood levels (fig. 1). These increases were evident within 1 minute. The high epinephrine levels at 1 minute suggested that the adrenal glands were the primary source of circulating catecholamines.

Three minutes after administration of succinylcholine, heart rate increased dramatically to 147 beats/min, but cardiac index and systemic vascular resistance remained unchanged. Stroke volume decreased sharply. Norepinephrine levels continued to rise to 2625 pg/ml, but epinephrine levels decreased from 1961 pg/ml at 1 minute to 1032 pg/ml at 3 minutes. As the major source of norepinephrine is the sympathetic nervous system, activation of the latter was probably responsible for the high level of circulating catecholamines at 3 minutes. Histamine levels remained elevated at 39,600 pg/ml.

Ten minutes after the administration of succinylcholine, there was both clinical and biochemical evidence of a decrement in the anaphylactic reaction (fig. 1). At 20 minutes, heart rate and plasma norepinephrine, epinephrine and histamine levels had all returned to preanesthetic values. The decreased cardiac output at 20 minutes was presumably secondary to the introduction of general anesthesia.

During the course of anaphylactic reaction, plasma norepinephrine levels correlated significantly with heart rate (analysis of data points by linear regression \( r = 0.857, p < 0.05 \). No correlation was found relating histamine to epinephrine or to any of the hemodynamic variables monitored, although rank-order analysis suggested a relationship between plasma histamine and systemic vascular resistance. Plasma renin activity, which initially was 4.05 units, increased to 19.97 units at 20 minutes.

**Discussion**

Our patient's previous episode of cardiac arrest under anesthesia was probably an anaphylactic reaction to succinylcholine. Anaphylactic reaction to succinylcholine and other relaxants has been widely reported, although most of these reports lack detailed information on the relationship between changes in hemodynamics and plasma levels of vasoactive amines. Reports of allergic reactions to propanidid suggested that increases in plasma histamine levels were largely responsible for the decrease in blood pressure and the increase in gastric acid secretion, an indicator of histamine release. It is thought that a plasma level greater than 10 ng/ml may cause serious cardiovascular sequelae; in our patient plasma histamine levels rose well above this level.

In isolated heart preparations, histamine has been shown to have a direct antidromic, inotropic and chronotropic action when administered directly into cardiac muscle or released by antigenic challenge. All of these actions were prevented by administration of \( H_1 \) and \( H_2 \) histamine receptor antagonists. Although studies of anaphylaxis in intact animals indicate that histamine release is responsible for many of the changes in cardiovascular function, it is not entirely clear if all hemodynamic changes are directly attributable to histamine. Release of other vasoactive amines, including catecholamines and histamine, may have secondary effects on cardiac function. There are abundant experimental data indicating that histamine releases catecholamines from adrenals, stimulates sympathetic ganglion cells and may release catecholamines from the myocardium. Our data suggest that anaphylaxis is associated with histamine release as well as sympathoadrenal stimulation. Catecholamine release appears temporally related to and the direct consequence of histamine liberation. Alternatively, reflex sympathoadrenal response to the decrease in blood pressure and systemic vascular resistance induced by histamine could induce the sympathoadrenal response. The exceptionally low systemic vascular resistance at 1 and 3 minutes suggests that even massive sympathoadrenal discharge could not fully compensate for histamine's vasodilatory effects.

In our patient the tachycardia appeared to correlate closely with changes in plasma norepinephrine concentration but not to the plasma histamine concentration. The observation that both the slowest and fastest heart rates occurred when plasma histamine was most markedly elevated suggests that histamine was not directly responsible for the tachycardia in this patient. In a companion series of seven patients (American Society of Anesthesiologists status 1) undergoing elective hip replacement, no increase in plasma epinephrine or norepinephrine was observed after the induction of general anesthesia with a similar protocol. Cardiac index decreased during the induction of general anesthesia in those patients.

In conclusion, we have described some of the hemodynamic sequelae of an anaphylactic reaction, which indicate that anaphylaxis is associated with both histamine release and sympathoadrenal discharge. Plasma histamine and epinephrine were markedly elevated despite only a modest decrease in blood pressure. It is likely that epinephrine release was a consequence of histamine's action on the adrenal glands, although a reflex action through the baroreceptors or by central nervous stimulation is possible. Further, the correlation between endogenous norepinephrine levels and heart rate suggests that this patient's tachycardia was a reflection of sympathetic stimulation rather than a direct chronotropic effect of histamine.

**Addendum**

Since the submission of our manuscript, confirmatory evidence of massive sympathoadrenal activation in anaphylactic reactions in experimental animals has been published. Hamberger et al. initiated dextran anaphylaxis in anesthetized and awake rats and showed a rapid increase in plasma epinephrine followed by a substantial in-
crease in plasma norepinephrine (Life Sci 26: 1465, 1980). The time course for their release into the circulation is similar to that in our patient.

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