Anesthetic considerations for pheochromocytoma

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Pheochromocytoma is an uncommon disease. An understanding of the pathophysiology of this disease and the drugs and anesthetics that influence it can remove the enigma of anesthetic management of the patient with pheochromocytoma. This article reviews the pathophysiology of pheochromocytoma and discusses the drugs, anesthetic agents, and techniques which affect this pathology.

Twenty-three million Americans, or 10% of the United States population, suffer from essential hypertension. About 20,000 persons, or 0.1 to 0.5% of hypertensive individuals, also have pheochromocytoma. This catecholamine-producing tumor arises from the chromaffin cells of the sympathetic-adrenal system. It is a tumor which has no age or sex predilection, but seems to occur more often during the second and sixth decades of life. About 20% of the reported tumors have occurred in children, 39% of whom have had bilateral adrenal medulla tumors or multiple tumors occurring along the sympathetic axis. There seems to be a familial tendency in 5% of the cases and a somewhat greater incidence (from 5 to 20%) in patients with von Recklinghausen's neurofibromatosis, a cutaneous disease frequently involving bone, the central nervous system, and chromaffin tissue.

The tumor was described as early as 1886, but it was not until 1912 that it was named pheochromocytoma, or "black celled tumor." During the 1920's Cesar Roux and Charles Mayo first successfully removed a pheochromocytoma. The clinical symptoms of this tumor were believed to be due to epinephrine. However, in 1949 and 1950 with the demonstration of the presence of norepinephrine in pheochromocytoma, it became apparent that the clinical manifestations were related at times to the secretion of norepinephrine as well as epinephrine.

Pheochromocytoma may appear where any sympathetic nervous tissue exists, from the base of the brain to the pelvis. One just has to consider the preponderance of sympathetic ganglia to conceptualize the potential invasiveness of this disease. The sympathetic ganglia are arranged in three major groups. The first group is the paravertebral ganglia consisting of a chain of 22 ganglia on each side of the spinal cord connected to spinal nerves by white and grey rami. These ganglia are connected together, forming a sympathetic chain which extends from the base of the skull to the front of the coccyx. The second group is the prevertebral or collateral ganglia. These lie in the thorax, abdomen, and pelvis in relation to the aorta and its branches. The terminal (peripheral) ganglia, the third group, lie close to the organs innervated. These ganglia are associated with the bladder and rectum.

The majority of pheochromocytoma tumors are found within the abdominal cavity, and there is an 80-90% proclivity for tumor growth in or near the adrenal gland, with the right adrenal
gland more commonly affected. Tumors have been located in intracranial areas, in the paraganglia (paragangliomas) of the cervical and thoracic regions, in the aortic bodies, in the organs of Zuckerkandl located at the aortic bifurcation, and in the urinary bladder.²³⁵ Pheochromocytoma is usually benign and in 20% of the cases more than one tumor is present. Only when there is evidence of direct invasion of surrounding structures and distant metastasis can the diagnosis of malignancy be made. The incidence of malignant tumors in both children and adults ranges in the area of 2.3%.²³⁴ The majority of extra-adrenal tumors are pure norepinephrine producers, while tumors of the adrenal medulla produce epinephrine and norepinephrine in a ratio of 15% to 85%, respectively. Interestingly, this ratio is reversed in the normal gland. Pure epinephrine tumors are rare.

The physiological manifestations of pheochromocytoma are due to the actions of the catecholamines, norepinephrine, and epinephrine on the cardiovascular and metabolic functions of the body.

Hypertension is usually the cardinal sign of cardiovascular involvement and is usually manifested in one of three patterns. Paroxysmal hypertension is the most characteristic, with periods of hypertension (200/100) which may last for a few minutes or for up to a week. These episodes of hypertension may occur spontaneously or be precipitated by exercise, postural changes, emotion, or hypoglycemia, or they may be due to abdominal palpation during a physical examination. Weakness, exhaustion, and hypotension may follow an attack. The second manifestation of hypertension is the sustained pattern without paroxysms. The elevated blood pressure resembles the hypertensive pattern seen in essential hypertension. The third pattern of hypertension associated with pheochromocytoma is the most severe. It is characterized as sustained hypertension with superimposed paroxysms of hypertension.²³⁵

The metabolic manifestations of pheochromocytoma frequently resemble the physiological manifestations of other diseases, and for this reason pheochromocytoma has been called the great mimic.²³ It may imitate certain hypermetabolic states such as hyperthyroidism, in which the individual exhibits tremor, tachycardia, and elevated basic metabolic rate. Because of epinephrine's anti-insulin effect and its effect on triglycerides and proteins (catecholamines stimulate gluconeogenesis), elevated blood glucose found concomitantly with glycosuria, the typical picture seen with diabetes mellitus. Weight loss commonly occurs in the patient with pheochromocytoma because of the increase in lipolysis and in the breakdown of protein from the muscles. Furthermore, the increase in vasoconstriction of the mesenteric arteries results in decreasing mesenteric blood flow and inactivation of the gastrointestinal tract with closure of the sphincters, ultimately producing nausea and vomiting.²³⁴ There is prominent vasoconstriction of the renal vessels, resulting in a functional slowing of all portions of the urinary system. The catecholamines cause contraction of the spleen, thereby increasing the circulating red-cell mass.

Other symptoms frequently seen, especially during hypertensive episodes, are sweating, dilated pupils, and fever. The patient often complains of headache and may be described as anxious, apprehensive, or even psychotic. These latter symptoms are due to the alpha receptor stimulation in the central nervous system. There is evidence that psychotic patients have elevated catecholamines in both serum and in cerebral spinal fluid.²³⁴ The mechanism for sweating is not really known except that it is mediated through sympathetic cholinergic fibers. Headache results from the increase in intracranial pressure due to massive vasodilation of the vessels of the brain. Pupil dilation is due to alpha stimulation of the radial muscles of the iris and beta receptor stimulation of the ciliary muscles.²³⁴ The fever that is frequently seen results from the large quantities of adenosine triphosphate (ATP) that are produced from the oxidative processes of the Krebs cycle.

Marked pallor and coldness of the extremities in conjunction with the apprehension that frequently occurs during a hypertensive crisis can be misdiagnosed as hypovolemic shock. This misdiagnosis can easily be promoted by the fact that the severe peripheral vasoconstriction of the muscle and skin which is producing the pallor can cause ablation of the blood pressure when it is taken by the Riva-Rocci method. The preoperative placement of an intra-arterial line through which the arterial pressure can be ascertained may obviate this misdiagnosis during surgery.²³

During hypertensive episodes, the heart is stressed excessively. Fortunately, the lactic acid accumulation resulting from glycogen metabolism in the muscles can be converted to glucose in the heart and used for energy. In addition, the rate of resynthesis of phosphofructokinase, which is essential for the conversion of glycogen to glucose-6-phosphate and ultimately to glucose, is stimulated by epinephrine. Thus, the increase in lactic acid and in the resynthesis of phosphofructokinase improves the resistance of the heart to fatigue.
Diagnosis of pheochromocytoma

There are many laboratory and pharmacological tests that can be used in determining the presence of pheochromocytoma. These tests, of course, cannot be indiscriminantly employed on every patient who manifests certain signs and symptoms which may be indicative of pheochromocytoma. However, there are four general classes of patients on whom these tests may be appropriate. They are: (1) patients under the age of 30 with hypertension; (2) patients with hypertension who also have evidence of hypermetabolism, such as heat intolerance, sweating, or weight loss; (3) patients who evidence hypermetabolism in the absence of hyperthyroidism; and, (4) patients with hypertension who also have diabetes mellitus.

A tentative diagnosis of pheochromocytoma can be made in many cases on the basis of a history of typical hypertensive attacks palpable mass, blood pressure rise with position changes or direct pressure over the tumor. Tumors that appear in the neck are usually palpable, and those in the thorax are visible roentgenographically. CAT scans and/or contrast angiography may also be employed to help locate the tumor, but caution must be utilized when using these techniques since radio-contrast media can cause release of catecholamines and a subsequent hazardous rise in blood pressure.

Pharmacological tests. There are certain pharmacological agents that can be used in ascertaining the presence of pheochromocytoma. The one agent that is primarily employed is histamine, which has a direct stimulatory effect on the chromaffin cells of the tumor. Other agents that can be used are tyramine tetraethylammonium (TEA), and methacholine. These latter agents have different mechanisms of action, but their end response is an abnormal pressor action. Tyramine displaces norepinephrine from the cytoplasm of the axonal terminal. Tetraethylammonium is a curious drug in that it has anticholinergic effects on postganglionic membranes but enhances the release of acetylcholine from presynaptic endings, thus causing the stimulation of the adrenal medulla.

Methacholine is a parasympathomimetic drug that, when given to an individual suspected of having pheochromocytoma, will cause a marked rise in systolic and diastolic pressure which is just the opposite of its usual vasodepressor response. This response is not understood, but it is believed by some investigators to be a more reliable and specific test for pheochromocytoma.

There are other pharmacological agents which precipitate a fall in blood pressure when given to the patient with pheochromocytoma. Piperoxan, a benzodioxan, is a competitive blocking agent which inhibits the responses of circulating catecholamines. It is no longer available for clinical use and has been replaced by less toxic agents such as phentolamine hydrochloride (Regitine®) which is an alpha blocker. Administering 5 mg of this drug during a hypertensive period would cause a drop in blood pressure if the hypertension was due to tumor-secreting catecholamines. On the other hand, if the cause of the elevated blood pressure was essential hypertension, then there would be no drop in the blood pressure.

Clinical tests. Diagnosis of pheochromocytoma is heavily dependent on urinary catecholamines and metabolic products. Patients are placed on a vanillylmandelic acid (VMA)-free diet (that is, no bananas or vanilla) and urine is collected for 24 hours in hydrochloric acid. Fluorometric or biological assay of the catecholamines and their metabolites is conducted on the sample. Normal 24-hour urinary excretion of the catecholamines and metabolites is shown in Table I.

The normal metabolic pathway of the catecholamines is illustrated in Figure 1. When pheochromocytoma exists, the amount of VMA, epinephrine, and norepinephrine excreted usually depends on the size of the tumor. Small tumors (those weighing 30 grams or less) have a small amount of

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*See references 6, 11 and 13.
enzymes necessary for the breakdown of catecholamines. As a result, urinary excretion of VMA is reduced while the parent molecules, norepinephrine, and epinephrine are excreted in quantitatively larger amounts. Large tumors (those weighing 250 grams or more) on the other hand usually have large quantities of VMA produced in relation to the parent molecules.\textsuperscript{1,14}

Dopamine (Figure 2) and its metabolite, homovanillic acid, may also appear in the urine, but fortunately their appearance is rare. Mature pheochromocytomas do not ordinarily secrete a great deal of dopamine; however, malignant degenerate tumors can release large quantities of it. Therefore, the appearance of this catecholamine and its metabolite may be indicative of the presence of malignant pheochromocytoma.

Determining the ratio of catecholamine metabolites to free catecholamines in the urine may be helpful in determining the location of the tumor. For example, if the urine contains increased amounts of norepinephrine and epinephrine, as it does in 40\% of the cases, the tumor is almost always located in one of the adrenal areas or in the organs of Zuckerkandl. On the other hand, if the catecholamine excretion is limited to norepinephrine, the tumor may still lie in or near one of the suprarenal areas as it does in two-thirds of the cases. In the remaining one-third of these cases, all the other sites must be considered.\textsuperscript{2}

**Treatment**

Surgical excision of the tumor(s) is the treatment of choice. In the majority of cases, once the tumor is removed, complete remission of symptoms results. This remission may not be apparent in those patients where one or more tumors were not removed or in cases of prolonged hypertension resulting in renal damage. In this latter instance, hypertension persists even after removal of the tumor.

The operative mortality rate for patients with pheochromocytoma has greatly decreased over the last 50 years. In the 1940s, the mortality rate ranged from 25-50\%, and in the last six years the mortality rate has declined to less than 3\%. This decline is ultimately due to a better appreciation of the effects of prolonged elevated catecholamines on the cardiovascular system and on various metabolic processes, as well as a better understanding of the sympathetic nervous system and the drugs that influence it.

**Preoperative preparation.** Adequate preoperative preparation is an important phase of treatment, for it can reduce surgical mortality. In the past, the patient undergoing removal of a tumor experienced a precipitous reduction in blood pressure following the excision of the tumor. It was determined that much of the fall in blood pressure was a consequence of volume depletion resulting from preoperative hypertension. The restoration of circulating blood volume can be accomplished by two methods. The first method requires the blocking of the production of catecholamines, achieved by administration of alpha-methylparatyrosine which blocks the hydroxylation of tyrosine (Figure 2) by inhibiting the enzyme tyrosine hydroxylase. This drug is administered in doses of 2-5 mg daily for a period of two to four weeks prior to surgery.

The second method involves the administration of alpha and beta adrenergic blockers, which block the effects of catecholamines. Two main groups of alpha blockers are currently being employed for the control of hypertension in patients with pheochromocytoma. Phentolamine and tolazoline are examples of the imidazoline group. Phentolamine is primarily used. It exerts true competitive blockade of alpha receptors in doses of 5 mg intramuscularly at intervals of every six hours for a period of two days. Because its effects last only six to eight hours, it can be given on the day of surgery.

Phenoxybenzamine (Dibenzyline\textsuperscript{\textregistered}) represents the second group of alpha blockers, the chlorethylamines, which are chemically related to the nitrogen mustards. Phenoxybenzamine is a haloalkyla-
mine which produces an extremely long-acting...
blockade of alpha receptors and is given in 10 mg increments every six hours for approximately 14 days prior to surgery or until the recumbent diastolic pressure is 90 to 100 mmHg, and there is no disabling postural hypotension. Because the drug has a duration of action of 14 hours or more, it is recommended that it be discontinued two days before surgery. \( ^{6,7,12,15,16} \) This allows vascular receptors to remain active during the operative exploration for catecholamine-producing tumor.

Phenoxybenzamine seems to be an important drug in helping to restore preoperative fluid volumes. It must be remembered that the patient with pheochromocytoma has a deficiency not only in plasma volume, but also in red-cell volume. Phenoxybenzamine, by way of its vasodilatory effect, allows for the re-expansion of the plasma volume while at the same time stimulating reticulocyte formation. \(^{12} \) The restoration of plasma volume occurs at a faster rate than the restoration of red cells, and as a consequence, the hematocrit may fall after three to four days of treatment with phenoxybenzamine. From a prognostic viewpoint, this is advantageous for it indicates a restoration of plasma volume. The anemia can be treated with packed red-blood cells. \(^{11,13} \) Another salutary effect of phenoxybenzamine is its ability to ameliorate ventricular extrasystoles which result from the increased myocardial irritability and shifting of the pacemaker away from the SA node caused by both epinephrine and norepinephrine.

In addition to its cardiovascular effects, phenoxybenzamine allows fasting-blood glucose levels to return to normal levels. \(^{11} \)

Prazosin is a relatively new alpha adrenergic-blocking agent. It is absorbed after oral administration, with peak plasma levels occurring in two to three hours. It seems to have a greater effect in lowering plasma norepinephrine levels than phenoxybenzamine, presumably because it allows the accumulation of norepinephrine to negatively feed back on itself and thus inhibit the enzyme necessary for the hydroxylation of tyrosine, with the ultimate effect of decreasing norepinephrine production (Figure 2).

In comparison, phenoxybenzamine and phenolamine not only block alpha receptors, but they also block this inhibitory effect of norepinephrine, thus allowing for the continued production of norepinephrine within the osmophilic granules. Prazosin reduces vascular tone in both resistance (arterioles) and capacitance (veins) vessels, increases baroreceptor sensitivity and, unlike phenoxybenzamine and phenolamine, does not cause a compensatory tachycardia or increase renin release. Thus, it appears that it may be the agent of choice in treating the severe hypertension associated with pheochromocytoma. \(^{6} \)

Beta blockers have limited use in treating hypertension produced by excessive catecholamine production. They should be used only when adequate alpha blockade has been established since exaggerated hypertension might occur. \(^{6} \) Propranolol (Inderal\(^{\textregistered} \)) has been advocated at oral doses of 20-40 mg at eight-hour intervals for 14 days including the day of surgery. It has been recommended that the use of propranolol be restricted to treating a resting tachycardia of greater than 120 beats per minute or when there is evidence of premature ventricular contractions after adequate phenoxybenzamine therapy has been instituted. \(^{14} \) Propranolol may produce bronchospasm and therefore should be used with caution in asthmatics.

Practolol is another beta adrenergic blocking agent which seems to be more cardio-selective in its action and is therefore less likely to produce bronchospasm. It differs from propranolol in having some intrinsic sympathomimetic activity, in being less potent, and having a longer duration of action. \(^{15} \)

### Anesthetic considerations

Although many anesthetic agents and methods have been recommended for the procedure of removal of pheochromocytoma, it is felt that a smooth induction of anesthesia and avoidance of hypoxia and hypercarbia are the most important principles underlying the use of any anesthetic in the operative management of the patient with this disease.

There are, in general, two serious hazards related to the operative phase. The first hazard is related to the excessive discharge of pressor hormones which may occur during the induction of anesthesia and during the surgical manipulation of the tumor. The second hazard occurs approximately 10 to 15 minutes following the resection of the tumor and is characterized by a precipitous fall in blood pressure resulting from the rapid uptake of catecholamines from the synapse. These two hazards must be kept in mind when considering the choice of major anesthetics and their adjuncts.

The effects of general anesthesia can best be evaluated by their stress-ablating activity; that is, their ability to suppress catecholamine response to induction and surgical manipulation. *Morpheine sulfate and diazepam*. The use of morphine as a sole agent has shown substantial increase in both epinephrine and norepinephrine plasma concentrations. Hoar et al. \(^{18} \) have shown
that when morphine was administered at doses of 3 mg/kg, the mean plasma concentration of epinephrine increased fourfold over preanesthetic control levels, and the concentration of plasma norepinephrine doubled. With the administration of diazepam, catecholamine levels returned to preinduction levels, but again increased markedly following surgical incision.

The mechanism by which morphine raises the preincisional level is presumably through its histamine medicated effect on the adrenal medulla.\textsuperscript{19} Diazepam seems to exert its effect by enhancing the effects of gamma-aminobutyric acid (GABA) in the central nervous system, which in turn decreases the release of norepinephrine by adjacent neural cells.\textsuperscript{20} The addition of 60\% nitrous oxide to morphine decreased the required dosage of morphine, but the median effective dose (ED\textsubscript{50}) for blocking an adrenergic response still remained quite high at 1.13 \pm 0.09 mg/kg.\textsuperscript{21} Roizen demonstrated that increasing the dosage of morphine to 1.45 mg/kg while administering 60\% nitrous oxide only decreased adrenergic responses, and indicated that such responses may be altered in debilitated patients.\textsuperscript{21}

\textit{Neuroleptanesthesia.} Fentanyl, droperidol, and nitrous oxide may be an excellent choice of agents, at least from a theoretical perspective, for the anesthetic management of pheochromocytoma.\textsuperscript{22} The use of high dose fentanyl and oxygen for coronary artery operations has demonstrated that fentanyl is an effective agent in decreasing catecholamine response during induction and surgical intervention.\textsuperscript{23,24} Perhaps the reason for this response is that fentanyl does not release histamine. Droperidol would seem to be an appropriate agent, for it prevents catecholamine-induced dysrhythmias in man and, because of its milk alpha-blocking properties, it has a blunting effect on blood pressure.\textsuperscript{15,22} However, because of surprising reports from Japan and Massachusetts\textsuperscript{22,25} implicating droperidol as a triggering agent for severe hypertensive episodes following its administration to patients with pheochromocytoma, coupled with the studies by Oyama\textsuperscript{24} that glucagon levels are increased during fentanyl, droperidol, and nitrous oxide anesthesia (glucagon stimulates the chromaffin cells of the adrenal medulla to produce catecholamine), it would appear that the value of these agents is in question and perhaps their use in anesthetizing the patient with pheochromocytoma should be curtailed.

\textit{Halothane.} Several authors have chosen this agent because of its ability to suppress the sympatho-adrenal axis, but all of them have reported
dysrhythmias with its use.\textsuperscript{26,27} Because halothane sensitizes the myocardium to catecholamines and produces a rise in plasma glucagon, its use in the anesthetic management of the patient with pheochromocytoma is also questionable.

\textit{Methoxyflurane.} In the past, this agent was advocated for the anesthetic management of the patient with pheochromocytoma because of its excellent cardiovascular stability.\textsuperscript{28,29} However, Cousins and Mazze have shown conclusively that there is a relationship between the total amount of methoxyflurane administered and the incidence of renal damage.\textsuperscript{30} Thus, the use of this drug is now restricted to short-term administration, and it would not be appropriate for an operative procedure that might require several hours to perform.

\textit{Enflurane.} Unlike methoxyflurane, enflurane does not produce nephrotoxicity, and because of its excellent cardiovascular stability has been advocated for use in the patient with pheochromocytoma.\textsuperscript{31,32} Kreul and his colleagues reported a case of a 38-year-old woman who received enflurane for the removal of an extra-adrenal tumor. Although their data indicates no significant myocardial depression caused from the administration of 1.0-1.5\% enflurane in 50\% nitrous oxide, their study did reveal a progressive rise in plasma norepinephrine levels during induction and surgical exploration.\textsuperscript{33}

Furthermore, Roizen and his associates\textsuperscript{21} have demonstrated that while halothane or morphine may block the cardiovascular response to incision in a dose-dependent fashion, enflurane does not. It was only when enflurane was delivered at a concentration of 2.57 MAC concomitantly with 60\% nitrous oxide that the adrenergic response to incision was ablated in 95\% of the cases. As the authors pointed out, ". . . this data results from study of unpremedicated healthy patients in acid-base balance; premedicated or sick patients or those not in acid-base balance may respond differently," and, "when the use of such a high dose is being considered, the risks and benefits should be compared with those associated with an alternative dose."\textsuperscript{21}

Thus, the assurance of ablatting the neuroendocrine response to incision using this high concentration of enflurane may be overshadowed by its cardiovascular toxicity, especially in patients who are debilitated. It may be concluded, therefore, that although enflurane may not sensitize the myocardium to catecholamines like halothane, variability of neuroendocrine depression seen with enflurane may make it unsuitable as an agent for the management of pheochromocytoma.
**Isoflurane.** While tachycardia may occur at various levels of isoflurane anesthesia, the mechanism of this increased heart rate is apparently due to a greater depression of vagal activity than sympathetic activity. Studies by Byles et al. and Perry et al. have shown that norepinephrine and epinephrine levels actually decrease with isoflurane anesthesia. This makes isoflurane an ideal agent for the anesthetic management of patients with pheochromocytoma, especially since it is capable of reducing total peripheral resistance at clinically used concentrations (between 1 and 2 MAC) which are not myocardially depressing.

**Muscle relaxants.** The use of muscle relaxants is a necessary adjunct to most general anesthetics which are currently employed for the removal of intra-abdominal pheochromocytoma tumors. All of these muscle relaxants have the potential for increasing plasma catecholamine levels and should be used with caution in the patient with this pathology.

**d-Tubocurarine.** The extensive investigations of Landmesser in the 1940s showed that bronchoconstriction resulted from the liberation of histamine from body tissues by d-Tubocurarine. It must be remembered that histamine can directly stimulate the chromaffin cells of a pheochromocytoma, resulting in a preponderance of serum catecholamine.

**Gallamine (Flaxedil).** The liberation of histamine by this agent is minimal and its ability to protect the heart against epinephrine-induced arrhythmias ostensibly makes it an excellent adjunct for the anesthetic management of pheochromocytoma. But its vagolytic activity and its propensity for releasing norepinephrine from sympathetic nerve endings would probably negates its use in this type of anesthetic situation.

**Pancuronium bromide.** The use of this drug as an anesthetic adjunct in the management of the patient with pheochromocytoma has been advocated by several authors. However, there have been reported cases of hypertension following the administration of pancuronium bromide. Nana et al. have demonstrated a statistically significant increase in plasma levels of epinephrine and norepinephrine within five minutes following the administration of pancuronium bromide. Although the mechanism of this increase in catecholamine level is not definitely known, it has been postulated that the drug facilitates ganglionic transmission by blocking vagal muscarinic receptors. These receptors play an integral part of an inhibitory pathway through sympathetic ganglia.

In addition, it is thought that pancuronium bromide inhibits muscarinic receptors in adrenergic postganglionic nerve terminals, thereby facilitating transmitter release. Thomlinson has also demonstrated that, at least in rats, the increase in norepinephrine is due to pancuronium's ability to block neuronal uptake of this catecholamine.

**Sucinylcholine (Anectine).** Because of its rapid onset of action, this muscle relaxant is usually used to facilitate intubation. Again, caution must be employed in using this drug because of its ability to produce tachycardia resulting from its predominant stimulation of sympathetic ganglia. Brown also cautions against its use in the patient with pheochromocytoma because of its tendency to cause fasciculations which result in the "milking of the quadratis lumborum and psoas muscles." Wig and Bali have demonstrated that even the administration of small doses of non-depolarizing muscle relaxants does not guarantee against the incidence of fasciculation, which seems to occur more readily in patients defasciculated with pancuronium than in groups pretreated with gallamine or d-Tubocurarine.

The proponents of general anesthesia advocate the use of deep levels of anesthesia for intubation and anesthetic management. The study by Roizen indicated that inspired MAC values of 2.10 for halothane and 2.57 for enflurane may be necessary to obtain adrenergic responses to surgical stimuli in the majority of patients. However, at these concentrations not only is there decreased myocardial contractility, but also the circulatory signs of hypoxia may be masked. Manninen and Knill have reported that at a steady endtidal concentration equivalent to 1.1 MAC of either halothane or enflurane, the circulatory signs of acute moderate hypoxia and mild hypercarbia are markedly depressed.

**Epidural Anesthesia.** Regional anesthesia is certainly a feasible alternative to general anesthesia. In fact, some authors contend that the problems inherent to general anesthesia can be circumvented by the use of high continuous epidural anesthesia supplemented by light general anesthesia in the form of 50/50 nitrous oxide oxygen. Phillip Bromage writes, "the anesthetic should not obscure diagnostic peaks of blood pressure during the search for the primary tumor or for multiple tumors... nor should it permit irrelevant fluctuations of blood pressure arising from other causes that might mislead the surgeon during his difficult search." Bromage further outlines three principal aims of what he deems a logical approach to anesthesia for the patient with pheochromocytoma.
He feels that the anesthetic “should allow for the retention of the vascular receptor function so that the response of these vascular receptors can be modified by the use of adrenergic blocking drugs...” He has demonstrated the importance of the preoperative use of alpha blockers in restoring blood volume. They have shown that even after the removal of the tumor there was no appreciable drop in blood pressure even with a sensory block to a T1 level.

Bromage and Cousins have shown the ability of the vascular receptors to respond to both adrenergic receptor blocking agents as well as alpha receptor stimulating drugs, thus underlining the fact that epidual blockade is able to retain the ability of vascular receptors to respond to alpha blockers and agonists. High epidural anesthesia with a T1 sensory blockade has been recommended for the intraabdominal exploration and removal of pheochromocytoma. It has been demonstrated that at this level the impulse traveling through the sensory afferent components of the respiratory reflex is greatly diminished. The administration of light general anesthesia accompanied by mild hyperventilation not only completely obliterates this reflex but also depresses the phrenic reflex. This latter reflex is also partially mitigated by blocking the thoracic afferent components of it. Thus, a sensory block at a T1 level not only allows for sufficient blockade of splanchnic innervation of the adrenal medulla which occurs at a T11-12 level, but also assures a quiet surgical field without the use of muscle relaxants.

Furthermore, endotracheal intubation performed when a spinal blockade has reached a T1 level and after a sleep dose of thiopental (250-350 mg) has been administered does not produce any appreciable rise in catecholamine levels. Intubation carried out under high epidural anesthesia can decrease the need for large doses of depolarizing muscle relaxants, which seem to be necessary if a defasciculating dose of a nondepolarizing agent is used. If succinylcholine is used to facilitate endotracheal intubation, it can be administered without pretreatment of a nondepolarizing agent. The clinical findings of Fahmy and others have established that diazepam 0.05 mg/kg administered five minutes before succinylcholine obfunds the fasciculations and attending postoperative muscle pain associated with this depolarizing muscle relaxant.

Postoperatively, the patients who are administered high epidural anesthetics for the removal of pheochromocytoma should do very well. They should be able to withstand a vigorous recovery routine of coughing and deep breathing without the attending pain that is frequently encountered in the patient who has received a general anesthetic. Furthermore, patients who have received continuous epidurals can continue to receive analgesia via the epidural catheter if it is left in place following surgery, thereby lessening the need for postoperative narcotics and the problems associated with them.

Pheochromocytoma is encountered infrequently. However, an understanding of the pathophysiology of pheochromocytoma and the effects of anesthetics can remove the enigma surrounding the management of this endocrinopathy.

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