NEUROBLASTOMAS AND ANAESTHESIA

BY

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SUMMARY

Neuroblastomas are malignant catecholamine-secreting tumours of children. This neoplasm is likely to be present in any young child with a mass in the retropleural or retroperitoneal regions or in the epidural space, even if symptoms attributable to increased pressor amine activity are absent. Anaesthetic management of these cases follows that laid down for phaeochromocytoma. Patients with this condition may come to operation undiagnosed and anaesthetists must be prepared to deal with the resulting complications.

Neuroblastomas are malignant tumours arising from the sympathetic nervous system in infancy and childhood. The condition can appear at any time in the first 10 or more years of life, but most cases occur before the age of 5, and it has even been described in the foetus (Birner, 1961). Bodian (1959) found that of a total of 907 neoplasms of all types seen at the Hospital for Sick Children, London, during the period 1925–58, 129 were neuroblastomas. The outcome is usually fatal, but cases of spontaneous regression have been reported, and treatment, including surgery, is successful in a quarter to a third of all cases. The most striking feature of neuroblastomas, however, which gives them their particular interest for the anaesthetist, is that they are capable of secreting catecholamines and related substances. The condition, of course, resembles phaeochromocytoma.

CLINICAL FEATURES OF NEUROBLASTOMAS

Diagnosis.

The onus of diagnosis may, as in phaeochromocytoma, rest with the anaesthetist. Where the biochemical effects are not marked and a tumour is the principal finding, a patient may come to theatre with the diagnosis of nephroblastoma or teratoma. The first sign of a catecholamine-secreting tumour may be paroxysmal hypertension during induction of anaesthesia. This may be accompanied by tachycardia, heavy bleeding, pallor and sweating. The diagnosis is often confirmed when hypertension is induced by pressing on the chest or abdomen, or when the surgeon actually squeezes a likely-looking mass.

Because the condition is still comparatively little known, it will be worth considering the diagnosis more fully. Symptoms are variable, being due either to the anatomical or to the endocrine effects of the tumour. A mass may be noticed in the abdomen, in radiographs of the chest, or occasionally at other sites such as the orbit. Neurological signs may be present, suggesting spread of the tumour into the spinal canal. The second group of symptoms includes headache, dizziness, sweating, vomiting, pallor and attacks of unconsciousness. Chronic diarrhoea is fairly common and this is also thought to be an endocrine effect. The patient may look fragile and ill or may appear quite healthy.

The diagnosis is usually suggested by persistent hypertension and tachycardia combined with the presence of a mass in the chest or abdomen. Hypertension may, however, be absent. The urinary catecholamine excretion (in the form of noradrenaline) is usually greatly raised above the normal adult level of 150 μg/24 hours, and the blood pressor amine level will also be high. Analysis of the urine by paper chromatography will reveal the presence of noradrenaline, dopamine, homovanillic acid, vanillyl-mandelic acid and normetanephrine. The hypertension can be prevented temporarily by the injection of phentolamine, which blocks the pressor action of noradrenaline; this is the basis of a diagnostic test. The condition may be confused with coarctation of the aorta, with hypertension of renal origin and with nephroblastoma. It may be difficult to distinguish clinically or biochemically between a neuroblastoma and a phaeochromocytoma, but the
Pathology.

Neuroblastomas are malignant tumours resulting from maldevelopment of embryonal neuroblasts, derived from the neural crest ectoderm, which normally differentiate into the adrenal medulla and the sympathetic nervous system. Non-malignant tumours of this type are graded as ganglioneuromas or ganglioneuroblastomas. They can arise from any part of the sympathetic chain but 40 per cent originate in the adrenal medulla itself. They tend to form large retropleural and retroperitoneal tumours and to extend through the intervertebral foramina into the epidural space, where they may compress the spinal cord. They may metastasize early to the skeleton, brain, liver and often the orbit.

Biochemistry.

It was not realized until the report of Mason and his colleagues in 1957 that neuroblastomas were capable of biochemical activity. The principal abnormality appears to be an excessive production of dopa by the tumour cells. Dopa is converted first to dopamine and may then be degraded to homovanillic acid or else hydrolyzed to noradrenaline, which in turn is broken down via normetanephrine to vanillyl-mandelic acid (fig. 1). All these substances can be recovered from the urine (Betex and Käser, 1962). In the case described by Smellie and Sandler in 1961 both dopa and dopamine were found in the urine, although histologically their tumour was a ganglioneuroma. Recently there have been further reports of similar biochemically active tumours and it seems that most neuroblastomas and some of the benign ganglioneuromas have this property.

Physiology.

The high levels of circulating noradrenaline appear to be responsible for the cerebral oedema which is a common postmortem finding in these cases (Laurence, K. M., personal communication). The exact mechanism of this is unknown.

Brunjes, Johns and Crane (1960) postulate that patients with catecholamine-secreting tumours

![Diagram](https://academic.oup.com/bja/article-abstract/37/11/866/242617/fig1)

**FIG. 1**

Principal pathways of catecholamine metabolism.
The enzymes involved are given in italics: MAO = monoamine oxidase; AH = aldehyde dehydrogenase; C.O.M.T. = catechol-o-methyl transferase.
suffer a chronic vasoconstriction which leads eventually to a lower than normal blood volume. The plasma volume is first reduced, followed later by a reduction of red cell mass. In one of their cases the pre-operative blood volume was only half the normal value. When the tumour is isolated at operation, this hitherto latent oligoæmia is revealed.

**TREATMENT**

Treatment of the early case is usually surgical, although complete extirpation is rarely possible. However, regression of the tumour, with long-term survival, has been reported after partial removal, so operation is worth attempting even in seemingly desperate cases (Chapman and Sheridan, 1960). Neuroblastomas are radiosensitive and radiotherapy is given either alone or after operation. Anti-mitotic drugs have been used with varying degrees of success. Williams and Greer (1963) report an unsuccessful attempt to treat a neuroblastoma with widespread metastases, using alpha-methyldopa. This substance interferes with the synthesis of metabolic products of dopa by competitive inhibition of dopa decarboxylase. Bodian (1959) has reported the successful use of large doses of cyanocobalamin (vitamin B₁₂), also involved in catecholamine metabolism, but other writers do not confirm its value (Koop, 1961).

**ANAESTHETIC MANAGEMENT**

Reports of cases undergoing operation for neuroblastoma go back many years, but it is interesting to note that complications have only recently been reported. Chapman and Sheridan (1960) reported thirty-three cases in a 10-year period, all of whom underwent operation or biopsy, with no operative deaths. Hope-Stone (1961) reported eight cases, Bettex and Käser (1962) three cases, and Kogut and Kaplan (1962) two cases in whom operation was completed apparently without incident. On the other hand, Mason et al. in their case, and Isaacs, Medalie and Politzer (1959) in one of their three cases, found it necessary to control the blood pressure with phentolamine and noradrenaline, and the same procedure was adopted in the cases described by Smith et al. (1961) and Smellie and Sandler (1961). In all these later reports full pre-operative investigation of pressor amine excretion had been carried out. In view of the secretory habits of the tumour it is surprising that operation should always have been uneventful in the past. Nevertheless, children have died during operations for neuroblastoma (Farman, 1965; Thornton, J. A., personal communication).

**Preparation of the patient.**

Investigation of pressor amine excretion, haemoglobin level, haematocrit and blood volume should be carried out before operation. The management of cases of phaeochromocytoma was reviewed by Mushin (1957) and more recently by Robertson and his colleagues in 1962, and it would be wise, in the light of present knowledge of neuroblastomas, to treat them in a similar way. The pre-operative use of an alpha-adrenergic blocking agent such as phenoxybenzamine is indicated (Leather et al., 1962). This has the effect of dilating the constricted arteries, allowing the blood volume to rise to a normal level before operation is attempted. Dornhorst and Laurence (1963) recommended giving a beta-adrenergic blocker before operation to prevent tachycardia and arrhythmias occurring when the tumour is handled. Montgomery and Welbourne (1963) state that adrenal cortical function may be depressed in patients with adrenal medullary tumours, either as a result of tumour growth or because the adrenals are injured or removed at operation. Additional hydrocortisone may therefore be needed.

Patients with secreting tumours may need extra sedation in the pre-operative period. Barbiturates have been shown to depress adrenal medullary output, and for this reason an oral barbiturate is a good choice for the day before operation. For the same reason it is probably best to use a short-acting barbiturate for premedication. Atropine is said to potentiate the pressor action of noradrenaline, and Kaufman (1962) therefore used hyoscine instead.

**Anaesthesia.**

There is no conclusive evidence that any particular anaesthetic agent or technique is contraindicated (Mushin, 1957). Most agents have been employed in the past for patients with catecholamine-secreting tumours. Thiopentone may be used, with the care given to any patient suspected of having a low blood volume. In most reports this has been followed with nitrous oxide, oxygen and tubocurarine. In theory this relaxant might, by releasing histamine, precipitate a paroxysm of hypertension, but in practice this does not seem to have been a problem. However,
Rollason (1964) favours halothane, which reduces both the incidence and the severity of hypertensive episodes. Neither he nor Robertson (1962) encountered cardiac irregularities when using this agent. Suxamethonium has been avoided on the grounds that muscle fasciculations might precipitate a paroxysm but Robertson used it in ten cases of phaeochromocytoma without untoward effect. To quote Robertson, “In practice the anaesthetist is likely to use the technique with which he is most familiar whatever the theoretical dangers may be”. In any case it seems wise to avoid unfamiliar methods in paediatric practice.

In patients with catecholamine-secreting tumours paroxysmal hypertension may follow induction of anaesthesia or positioning of the patient, but the commonest cause is handling of the tumour at operation. The heart rate, blood pressure and electrocardiogram should be monitored from the very start. It is best to employ an assistant who will measure the blood pressure at intervals of 1 minute or less and announce the results. The assistant must also measure the heart rate unless this can be done electronically.

The anaesthetist must be prepared to control episodes of hypertension with phentolamine; 0.5 or 1 mg is given intravenously as soon as the blood pressure starts to rise (Kaufman, 1962). In the case described by Smith et al. (1961) the systolic pressure fluctuated from about 100 mm Hg at the start to nearly 200 mm Hg during the operation. Three doses of phentolamine were given to control the pressure.

Strict attention must be paid to the replacement of lost blood and a reliable way of measuring the loss must be used. Leather and his colleagues emphasize that the volume transfused may need to be greater than that lost, to make up for the abnormally low blood volume existing before operation. It should be possible to calculate the additional amount required if the blood volume has been measured pre-operatively. Extra transfusion may not be needed if an adrenergic blocking agent has already been given to the patient.

When a catecholamine-secreting tumour is isolated the blood pressure falls profoundly, often becoming unrecordable (Robertson, 1962). An infusion of noradrenaline or metaraminol may be needed for some time afterwards to maintain a normal level of blood pressure.

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REFERENCES


Les neuroblastomes sont des tumeurs malignes secrétant des catécholamines chez l’enfant. Ce néoplasme doit être suspecté chez tout jeune enfant présentant une tuméfaction dans la région rétropleurale ou rétro-peritoneale ou dans l’espace épidural, même en l’absence des signes attribuables à une augmentation d’activité des amines hypertensives. L’anesthésie de ces cas suit les mêmes règles que pour les phéochromocytomes. Les malades porteurs de cette tumeur peuvent être opérés sans que le diagnostic ne soit fait, et les anesthésistes doivent être préparés à traiter les complications qui en résultent.

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Programme for 1966

FRIDAY, MARCH 11
Mr. R. W. Alpers, Works Manager for a well-known firm, will discuss disposable equipment from the viewpoint of the manufacturer.

FRIDAY, APRIL 22
“My Worst Moment (so far),” A discussion on emergency situations in anaesthesia, led by senior members of the Society.

FRIDAY, MAY 13
Professor A. L. Latner. “Possible Biochemical Mechanisms in Anaesthesia.”

THURSDAY, APRIL 28
Provisional date for the ANNUAL DINNER.

All meetings will be held at 8 p.m. in the New Lecture Theatre, Royal Victoria Infirmary, Newcastle upon Tyne. A buffet supper will be served in the Board Room from 6.30 p.m. onwards and coffee will be available in the ante-room to the lecture theatre from 7.30 p.m.

All business should be addressed to the Honorary Secretary, E. A. COOPER, Department of Anaesthetics, Royal Victoria Infirmary, Newcastle upon Tyne.