CLINICOPATHOLOGIC CORRELATIONS

De Subitaneis Mortibus

XIX. On the Cause of Sudden Death in Pheochromocytoma, with Special Reference to the Pulmonary Arteries, the Cardiac Conduction System, and the Aggregation of Platelets

THOMAS N. JAMES, M.D.

SUMMARY Pheochromocytoma may cause sudden and unexpected death. In this study of three fatal cases of pheochromocytoma the small pulmonary arteries were narrowed by a variety of chronic and acute processes which included medial hypertrophy and fibrosis, endothelial proliferation and fibrosis, and endothelial cellular edema; within the sinus node, atrioventricular (A-V) node and His bundle of all three cases there was focal degeneration and fibrosis similar to that also observed throughout the ventricular myocardium; and in addition to the focal narrowing of many small coronary arteries produced by medial hypertrophy, intimal fibrosis, and fibromuscular dysplasia, there were also focal aggregations of platelets clogging the lumen and occasionally mixed with a varying amount of fibrin. In patients known to have pheochromocytoma it may be necessary to direct new attention to the possibility of abnormal pulmonary vascular resistance, instability of normal cardiac rhythm, and perhaps difficulty in restoring it when disordered and to the effects of platelet aggregations, both causing acute obstruction and possibly contributing to the pathogenesis of chronic vascular disease.

NOT MANY PEOPLE DIE OF PHEOCHROMOCYTOMA and even fewer should once they come to medical attention. Unfortunately, some will always die of this disease and the terminal event is often sudden and unexpected death.1-11 There are numerous possible explanations for such deaths, including cerebral vascular accidents, abrupt hemorrhage into the tumor, acute left ventricular failure and other consequences of severe paroxysmal hypertension.

While one may say that sudden death in pheochromocytoma is a problem not in need of still additional explanations, a number of other pathophysiological events may be illuminated by a close understanding of the many important physiological and biochemical processes that are involved in pheochromocytoma. Three aspects of fatal pheochromocytoma will be considered in this report, particularly in respect to sudden death, and they are: 1) changes observed in the pulmonary arteries, 2) abnormalities found in the sinus node, A-V (atrioventricular) node and His bundle, 3) the possible importance of platelet aggregations.

Case Reports

Case 1

A 58-year-old white female had developed progressively worsening spells over a period of several years. These were initially characterized by nervousness and slight nausea, both relieved by eating candy, but gradually came to include severe headaches, pallor, sweating and a rapid pulse. During that time her blood pressure which was initially about 180/90 mm Hg was found paroxysmally elevated to as high as 260/160. Fasting blood sugar levels were about 160 mg% on several occasions. A diagnosis of probable pheochromocytoma was made and she was admitted to the hospital for the removal of a left suprarenal mass. Blood pressure on admission was over 300 mm Hg systolic and 170 diastolic and soon became unstable. Before surgery could be performed she became hypotensive and unresponsive to treatment, which included the intravenous administration of norepinephrine. She died on the fourth hospital day of progressive cardiac failure. At necropsy there was pulmonary and cerebral edema, congestion of the liver and other abdominal viscera, generalized cardiac enlargement, and extensive hemorrhage into a pheochromocytoma of the left adrenal gland.

Special postmortem examinations included dissection of the blood supply to the sinus node and A-V junctional region of the heart, and careful study of the pulmonary arteries. A moderate degree of atherosclerosis involved the left circumflex coronary artery, which crossed the crux of the heart to supply the A-V node and His bundle. The sinus node artery originated from the right coronary artery which was entirely patent. There was no gross evidence of myocardial infarction. A block of tissue containing the entire sinus node and another for the A-V junctional region were excised and cut into serial slices about 2 mm thick in a fashion described in previous reports of this series. About ten sections per block were prepared for study of the sinus node and the A-V junctional tissues.

There were scattered but widely prevalent small necrotic foci throughout the myocardium similar to those described by others in patients with pheochromocytoma.12-14 This focal necrosis was observed not only in the ventricular myocardium (fig. 1) but also in the A-V node (fig. 2). Small arteries in the A-V node and in the sinus node were focally narrowed (fig. 3). Platelet aggregates filling the lumen of small coronary arteries were found both in degenerating and preserved myocardium (figs. 4, 5). Phosphotungstic acid hematoxylin stains demonstrated that fibrin was not present.
FIGURE 1. Focal degeneration and inflammation was present within the left ventricular myocardium of case 1. The two arrows indicate small arteries containing platelet aggregates, shown in more detail in other vessels in subsequent figures. Goldner trichrome stain was used here and in all other photomicrographs unless otherwise indicated.

FIGURE 2. The focal degeneration and fibrosis found in the ventricular myocardium of case 1 also was present in the A-V node (AVN). CFB marks the central fibrous body underlying the AVN. B is a portion of A shown at higher magnification.
in many of these aggregates but was seen in a disorganized pattern in others (fig. 6). Scirrhous fibrosis replaced most of the substance of the sinus node (fig. 7). Small pulmonary arteries were narrowed by endothelial proliferation and fibrosis, and there was extensive fibrosis of the tunica media of most small pulmonary arteries (fig. 8).

Case 2

A 70-year-old white male complained of spells beginning one year before he died. These initially included severe headaches, tremor and profuse perspiration but later there was also dizziness and near syncope. His blood pressure was known earlier to have been normal but at the start of the period of spells was found to be 220/120 mm Hg and thereafter fluctuated from normal levels to 195/160. During one such spell he was admitted to the hospital with a diagnosis of probable pheochromocytoma. Blood sugar determinations were normal. One bout of hypertension responded well to intravenous administration of phentolamine, but similar fluctuations of blood pressure had previously also occurred spontaneously. A few hours after admission he suddenly became hypotensive and cyanotic with shallow respirations. Efforts to restore the blood pressure by the intravenous administration of epinephrine and methoxamine were unsuccessful and he died despite extensive resuscitative efforts. At necropsy examination there was generalized cardiac enlargement and a large pheochromocytoma of the right adrenal gland.

The major coronary arteries contained some atheromata but none narrowed the main lumen more than half. The right coronary supplied the A-V node and His bundle, and the sinus node artery originated from the main left coronary artery (a rare site of origin). There was no gross evidence of myocardial infarction. Widely scattered small foci of degeneration and fibrosis were present throughout the myocardium, but much less extensively than in the first case. Focal hemorrhages and degeneration were present in the A-V node and His bundle, the A-V node artery was moderately narrowed, and there was chronic focal degeneration of the sinus node (fig. 9). The small pulmonary arteries exhibited medial hypertrophy and fibrosis, and in many areas an extensive endothelial edema (figs. 10, 11).

Case 3

A 47-year-old white male began having bouts of dyspnea with profuse perspiration two years before his death, and over the next year noticed an unexplained 26 pound weight loss. Blood pressure was 160/120 mm Hg and pheochromocytoma was suspected; however, diagnostic studies at several different medical institutions were inconclusive. His spells not only persisted and worsened but came to be accompanied by intense nervousness and ap-
prehension. He also began to wheeze during the dyspneic attacks. His electrocardiogram which had previously demonstrated evidence for left ventricular hypertrophy now also showed first degree heart block with a P-R interval of 260 msec. Blood sugars were normal in the first 18 months of illness but in the last few months a delayed glucose tolerance curve was found. The terminal hospitalization was because of worsening of his dyspnea which had now become sustained and associated with orthopnea. Four days after admission there was an embolus to the left popliteal artery.
FIGURE 8. Medial fibrosis and endothelial proliferation and fibrosis were observed throughout the small pulmonary arteries of case 1.

and several hours later one to the right popliteal region, for which he was treated with epidural anesthesia and anticoagulation with heparin. His blood pressure in that period fluctuated from 140/90 to 180/130 mm Hg with no consistent trend upward or downward. Several hours before death (on the sixth hospital day) his heart rate increased to 150 beats/min due to a sustained sinus tachycardia. He then became acutely cyanotic and suffered cardiorespiratory arrest which failed to respond to resuscitative efforts. At necropsy examination there was generalized cardiac enlargement and a pheochromocytoma of the left adrenal gland which contained a large amount of chocolate colored blood.

FIGURE 9. Focal degeneration and fibrosis were present in both the sinus node and the A-V node of case 2, and the A-V node artery was moderately narrowed.

FIGURE 10. There was mural fibrosis and luminal narrowing of small pulmonary arteries in case 2.
There was no gross evidence of myocardial infarction and no occlusions were present in the major coronary arteries. Focal degeneration and fibrosis were present throughout the ventricular myocardium (fig. 12). There were no mural thrombi within the heart. Blood supply to the A-V node was from the right coronary artery and that to the sinus node from the left circumflex. Histologically there was focal degeneration and excessive fibrosis of the sinus node (fig. 13). The lumen of the sinus node artery appeared normal. Similar focal degeneration was less extensive in the A-V node and His bundle; however, the lumen of the A-V node artery was markedly narrowed (fig. 14). Small pulmonary arteries exhibited widespread focal fibrosis of the tunica media, marked intimal proliferation and fibrosis, and extensive endothelial edema (figs. 15-17). In this case and in case 2 there were occasional small coronary and pulmonary arteries which contained a few platelet aggregates, but these were not as extensive or numerous as those found in case 1. However, case 3 had clinical evidence of thromboembolic disease for which he was being treated with heparin at the time of his death.

Discussion

Experienced forensic pathologists routinely consider pheochromocytoma as one of the possible causes in any case of sudden unexpected death.1-3 In addition to certain obvious mechanisms by which such tumors may lead to sudden death, the findings in the three cases presented here suggest some other and perhaps more insidious mechanisms. All three patients had narrowing disease of multiple small pulmonary arteries, each had focal disease involving the cardiac centers of impulse formation and conduction, and the first case had extensive platelet aggregations especially within the small coronary arteries. These findings as well as many others associated with pheochromocytoma are not simple to interpret either as to their pathogenesis or their functional significance.

Every pheochromocytoma is thought to release variable amounts of epinephrine and norepinephrine, which must normally pass first through the pulmonary circulation before reaching the rest of the body, but there has been little attention to the possible effect of these powerful vasoconstrictor agents on the pulmonary arteries. Two reasons for this may be the overwhelming and more familiar action on the systemic circulation, and also some question as to whether these catecholamines actually do have much vasoconstricting action on the human pulmonary circulation,1,2 although such action is demonstrable in experimental animals.17 Furthermore, there are numerous other plausible explanations for abnormalities to be present in the pulmonary arteries, such as the effect of recurring or sustained left ventricular failure, the influence of intermittent hypoxia, and

---

**Figure 11.** In many areas the small pulmonary arteries in case 2 were further narrowed by intimal edema with the swollen endothelial cells crowding into the lumen. A is Goldner trichrome stain, and B Verhoeff-Van Gieson elastic.

**Figure 12.** Throughout the left ventricular myocardium of case 3 there was both focal degeneration (A) and fibrosis (B).
the possible direct pulmonary vascular effect of many forms
of treatment administered to patients with pheo-
chromocytoma, including agents with powerful vasodilat-
ing or vasoconstricting actions (depending on the status
of the patient being treated). There is another possible indirect
action of catecholamines since they are known to cause
aggregation of platelets, which might in turn adhere to
pulmonary arterial endothelium for varying periods of time.

Still other naturally occurring and iatrogenic factors may
also affect the small pulmonary arteries of patients
with pheochromocytoma, but the important point is that
those vessels were abnormally narrowed in all three of these
patients and the narrowing was due both to chronic
processes such as medial hypertrophy and fibrosis and in-
timal proliferation as well as to more recent endothelial
edema. The possibility of direct or indirect action of cate-
cholamines on small pulmonary arteries thus deserves
further consideration as a factor contributing to the
pathogenesis of various events causing morbidity or death in
patients with pheochromocytoma.

One would expect to find a variety of lesions within the
small coronary arteries in patients with paroxysmal severe
hypertension, particularly when carbohydrate metabolic ab-
normalities coexist as they do in some patients with
pheochromocytoma. Such lesions combined with the power-
ful positive inotropic influence of the catecholamines lead to
simultaneous occurrence of increased oxygen demand by the
myocardium and impaired coronary blood flow, so that
focal myocardial degeneration and micro-infarction are the
result. While these focal lesions within the working myo-
cardium may themselves contribute to the pathogenesis of
electrical instability of the heart, in the three present cases
there were also significant focal lesions within the sinus
node, A-V node, and His bundle. The abnormalities in the
conduction system would be of even more direct importance
in the pathogenesis of potentially lethal electrical distur-
bances of the heart.

Platelet aggregations are known to occur as the conse-
quence of the administration of norepinephrine or epineph-
rine. Such aggregates not only have been shown to
develop in the small coronary arteries, but have been
specifically suspected as a possible cause of sudden
death. It has been demonstrated that an increased
tendency for platelets to aggregate in patients with pheo-
cromocytoma is decreased following removal of the
tumor. In case 1 reported here there were numerous
platelet aggregates in the small coronary arteries, but fewer
in the pulmonary circulation. This discrepancy is puzzling if
the sole cause was catecholamines liberated by the
pheochromocytoma, unless one considers a different suscep-
tibility of platelets in venous compared to arterial blood.
The prevalence of platelet aggregability within different
organs is known to vary in a number of systemic diseases in-

FIGURE 13. The sinus node (SN) of case 3 also exhibited focal
degeneration and fibrosis, as shown here at two different
magnifications.

FIGURE 14. In case 3 focal degeneration and fibrosis was also
present in the A-V node (two arrows in A). The A-V node artery
was narrowed by fibromuscular dysplasia, as shown with Goldner
tricrome stain (A) and a higher magnification with elastic stain (B).
fluencing platelet function, but may nevertheless contribute to the development of cardiac lesions and sudden death in homocystinuria,77 thrombotic thrombocytopenic purpura78 and disseminated intravascular coagulation.79 If one attributed the platelet aggregation observed in case 1 to the influence of catecholamines, however, it is uncertain whether this was due to spontaneously released or therapeutically administered norepinephrine or to both.

As with the consideration of the pulmonary arterial lesions, it is the demonstrated presence of extensive platelet aggregations which cannot be ignored, whatever the pathogenesis. These platelets appeared to adhere to each other without formation of the usual fibrin-platelet lattices which are so orderly in normal thrombosis,90 and as are characteristic of the lesions seen in congenital homocystinuria.77 It is now known that disseminated intravascular coagulation may develop as a complicating event in a large number of different diseases, and it is possible that pheochromocytoma is one of these in some nonspecific way.

However, in case 1 there was conspicuously little fibrin incorporated in or about the platelet aggregates, whereas fibrin strands and fragments are a major component of the process in disseminated intravascular coagulation.78 It seems more likely that the platelet aggregates in case 1 were the consequence of an effect of norepinephrine, and that the histologic appearance is a natural counterpart of those previously reported lesions seen in association with sudden death in man.23-25 If that interpretation is correct, then the contribution of periodically developing platelet aggregates within either the pulmonary or coronary circulation may be an important component of the pathogenesis of chronic lesions observed in those vessels. Since it is known that platelet aggregates may occlude a vessel for a long enough time to be functionally significant, and yet later disaggregate,91 any demonstrated presence of such aggregates may be only a small sample of their more frequent transient occurrence and larger functional significance.

This is only a small group of patients with fatal pheochromocytoma and the findings at postmortem examination may not be representative of what is present in most such cases. But the narrowed small pulmonary arteries, focal lesions within the impulse forming and conduction system of the heart, and widespread aggregation of platelets are all potentially so important in the pathogenesis of some of the complications encountered that they deserve special consideration in the clinical management of such patients. Some evidence to support or refute these possibilities can be obtained during successful clinical treatment of patients with pheochromocytoma. If future study of other fatal cases confirms the prevalence of abnormalities as reported here, then some fundamental revisions of the clinical therapy of patients with pheochromocytoma may be required.
References

20. Hafer GI: Cardiovascular injury induced by sympathetic catecholamines. Prog Cardiovasc Dis 17: 73, 1974
De subitaneis mortibus. XIX. On the cause of sudden death in pheochromocytoma, with special reference to the pulmonary arteries, the cardiac conduction system, and the aggregation of platelets.

T N James

Circulation. 1976;54:348-356
doi: 10.1161/01.CIR.54.2.348

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1976 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/54/2/348

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/