# Catechol Amine Metabolism: *

## Peripheral Plasma Levels of Epinephrine (E) and Norepinephrine (NE) During Laparotomy Under Different Types of Anesthesia in Dogs, During Operation in Man (Including Adrenal Vein Sampling), and Before and Following Resection of a Pheochromocytoma Associated with von Recklinghausen's Neurofibromatosis

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### General Remarks

### Historical Background

**The Humoral Transmission of Nerve Impulses.** The nature and functions of epinephrine and norepinephrine are of far-reaching physiologic significance. This is due in large measure to their relation to the sympathetic nervous system and its manifold activities. In delivering the Ferrier Lecture before the Royal Society in 1935, Otto Loewi [48] outlined the evidence for the humoral transmission of nerve impulses. He had shown in 1921 [47] that by stimulation of the nerves to the frog's heart substances were released into the fluid filling the heart which could produce on a test heart the same effects as had nerve stimulation itself. The identification of acetylcholine release on stimulation of vagal fibers was soon established.

In contrast, the chemical transmitter released at the ends of postganglionic sympathetic fibers was not to be identified positively for many years. As early as 1905 T. R. Elliot [14] had suggested such a role for epinephrine but proof had been lacking. In 1909, Sir Henry Dale and his associates [1] studied a series of amines which approached by successive stages the structure of adrenaline itself, and the term "sympathomimetic" was coined; it was found that the more closely the chemical structure approached that of adrenaline, the more specific the sympathomimetic properties of the substance became. In the following years Walter B. Cannon and his group [7] exerted a great influence through their research and publications on sympathin E and sympathin I. The adrenal medulla was identified as an organ which prepared the animal for flight or defense, and epinephrine was spotlighted as the hormone principally responsible for the associated physiologic changes.[5, 6] In retrospect, Dale has stated that Cannon's sympathin E may have represented norepinephrine.[18] Stoltz [65] had synthesized norepinephrine in 1904, and had noted that it was as active as adrenaline in raising the blood pressure in animals but less toxic. However, it was not until 1946 that the experiments of von Euler [17, 18, 20] at the Karolinska Institute in Stockholm led to the demonstration of norepinephrine in adrenergic nerves and in the organs supplied by them. This provided the evidence needed to identify norepinephrine (the levo form) as the chemical transmitter of the neural impulses in adrenergic nerves. Subsequently Holtz [35] demonstrated the

* Presented before the American Surgical Association, San Francisco, Calif., April 15–17, 1959.

This work was supported by Army Contract No. DA-49-007-MD-627.

presence of norepinephrine in the normal adrenal and Holton [34] demonstrated this amine in a pheochromocytoma of the adrenal medulla.

Thus acetylcholine is formed at the end of somatic nerves, parasympathetic nerves, and in the synapse at the end of the preganglionic sympathetic nerve fibers. *But norepinephrine is formed at the end of the postganglionic sympathetic fibers.*

## Sources of E and NE and Their Control

**Sources.** Much investigation has been devoted to the sources of E and NE. In essence, E is secreted only by the adrenal medulla whereas NE is elaborated by sympathetic postganglionic nerve endings everywhere, including those in the adrenal medulla. Goodall and Kirshner,[25] using labeled precursors, demonstrated the biosynthesis of NE by sympathetic ganglia and nerves. None was formed by the vagus nerve. This afforded additional proof that NE is the neurohormone of the postganglionic sympathetic nerves.

In considering the comparative pharmacology of the adrenal medulla, West [71] concluded that there is probably a differential release of E and NE from the adrenal medulla, depending upon the functional requirements of the organism. Thus NE might be released during conditions which involve circulatory needs—whereas E would be primarily concerned with certain metabolic functions and with the regional blood supply to organs. West noted further that NE may be selectively stored by certain specific cells in the adrenal medulla, a belief concurred in by Hillarp and Hokfelt.[33] It would appear that NE is not only a precursor of E but is also an independent hormone. Bulbring and Burn [2] demonstrated the formation of E from NE in the perfused adrenal gland.

**Control of Adrenal Medullary Secretion.** The release of E and NE is intimately related to factors which control autonomic nervous system activity and, in particular, that of the sympathetic nerves. Through the hypothalamus the autonomic nervous system has widespread representation at the higher centers of the cerebral cortex.

The response to hypoglycemia induced by insulin has been used to evaluate the spinal pathways which regulate the secretion of adrenaline in the dog. By studying samples of adrenal vein blood, Suzuki and his associates [67] in Nagasaki found that in dogs the E secretion caused by hypoglycemia was wholly abolished by the total section of the spinal cord at the level of C7-C8. However, after only hemisection of the cord at this level the E secretion was increased by insulin hypoglycemia in the contralateral as well as in the ipsilateral adrenal gland. It was concluded that the descending spinal pathways of the adrenal medullary secretory fibers decussate partially below the lower cervical segments.

## Significance of Epinephrine and Norepinephrine in Clinical Practice

The practical importance of catechol amine metabolism is implicit in much of the foregoing discussion. In its role as neurotransmitter of the postganglionic sympathetic nerve impulses, norepinephrine exerts a profound effect upon normal and abnormal cardiovascular function. As for epinephrine, it serves as an emergency hormone and is capable of modifying the circulation and various other physiologic activities.[15] To cite a single specific role of these hormones, von Euler [19] found that the tilting of normal subjects 75° resulted in a sharp increase in the urinary excretion of norepinephrine but only a slight increase in epinephrine excretion. Hickler and his associates [32] demonstrated a rise in the venous concentration of both E and NE in six normal subjects following tilting, but in four subjects with postural hypotension there was no significant change. There was also no collateral evidence of increased autonomic activity in the postural hypotensive

group, in contrast to that exhibited by the normal subjects. These findings further support the concept that NE release by the sympathetic nerves is an important factor in vascular homeostasis, the implications of which are far-reaching.

Finally, the widespread clinical use of norepinephrine to support vascular tone and blood pressure comprises, in itself, sufficient indication for further study and understanding of the metabolism of the catechol amines.

## The Present Studies

The investigations to be reported fall readily into the following three groups of observations:

A. *Anesthesia in Dogs: Comparison of Effects of Different Agents Upon Peripheral Plasma E and NE Levels During and Following Laparotomy.*
B. *Operations in Man: Peripheral and Adrenal Venous Plasma E and NE Levels with Estimates of Rates of Secretion.*
C. *Pheochromocytoma: General Considerations and Case Study with Catechol Amine Values.*

**Method for Catechol Amine Analyses.** All plasma E and NE levels were determined by the method of Weil-Malherbe and Bone [69, 70] as described by Mangan and Mason,[53] but using Richardson's filters.[60]

### A. *Anesthesia in Dogs: Comparison of Effects of Different Agents Upon Peipheral Plasma E and NE Levels During and Following Laparotomy.**

**Objectives.** The primary purpose of this study was to compare the physiologic effects of electrical narcosis with those of agents commonly used clinically. It was felt that the catechol amine response to a standard operation using one anesthetic agent, as compared with another, would afford useful data regarding the metabolic impact of the various drugs. Conversely, failure of an anesthetic agent to permit a response at least equal to that occurring during operation under procaine would presumably reflect a depression of this physiologic activity by the drug.

**Procedure.** Four groups of seven dogs each were used to compare the effects of electrical narcosis, ether, procaine (local), and nembutal anesthesia. In each animal a standard celiotomy incision was performed lasting 30 minutes from "skin to skin." The current used for the electrical narcosis had characteristics similar to those used previously by Knutson and associates.[42] The apparatus (Fig. 1) was set at 700 cycles per second, operating at about 15 volts and 50 milliamperes.[56] The electrodes were applied to a shaved area on either side of the animal's head after intubation for artificial ventilation had been accomplished using a topical anesthetic and from 5 to 10 units of d-tubocurarine. Blood samples for E and NE levels were drawn immediately before the anesthetic was begun, after 15 minutes of surgery, at the end of surgery, and at 1, 2, and 2.5 hours thereafter.

**Results.** The data are shown graphically in Figures 2 and 3. The group that received procaine locally to permit the operative incision was considered as a control group, from which the effect of the surgical procedure alone might reasonably be deduced. Any deviation from the response exhibited by this group was interpreted as being due largely to the effects of the anesthetic agent under investigation.

It may be seen that the levels of both E and NE rose following local, ether and electrical narcosis but were depressed by nembutal. The response to surgery under local anesthesia exceeded that observed when ether anesthesia was used, and the response with electrical anesthesia was the highest of all. The increases in the plasma level of norepinephrine were much less than those exhibited by epinephrine.

* Certain of these data were presented in a preliminary report.[56]

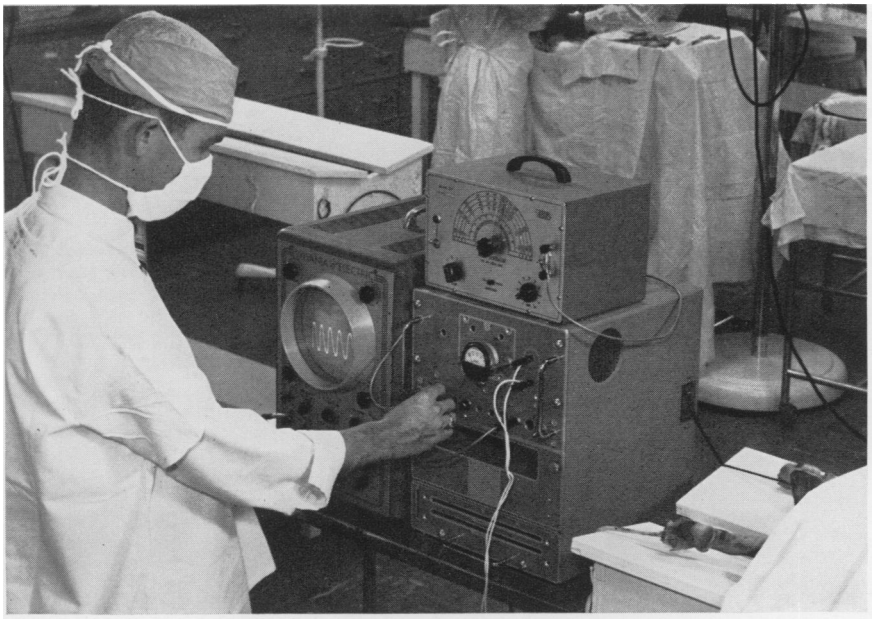

FIG. 1. Equipment for production of electrical narcosis.
(Assembled by C. Don McNeil.)

## Results Reported by Others

In 1943 Elmes and Jefferson [16] at Oxford reported the effect of anesthesia on the E content of the adrenal glands. Under ether anesthesia 6.7 per cent of the original adrenaline content was lost per hour, under cyclopropane 4.5 per cent, and under pentobarbitone-morphine 2.7 per cent. In 1955

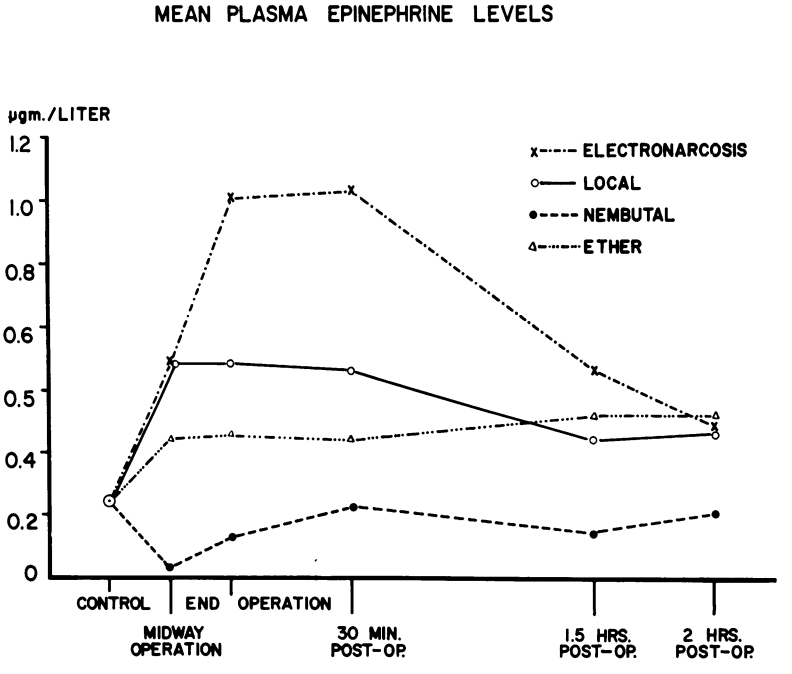


FIG. 2. Epinephrine secretion in response to a standard laparotomy: A comparison of different agents for anesthesia. The points on each curve represent the average values from 7 dogs. Electronarcosis and laparotomy produced the greatest rise in E secretion, with response to procaine and to ether next in order, respectively. Nembutal depressed the epinephrine level of plasma despite the associated surgery.

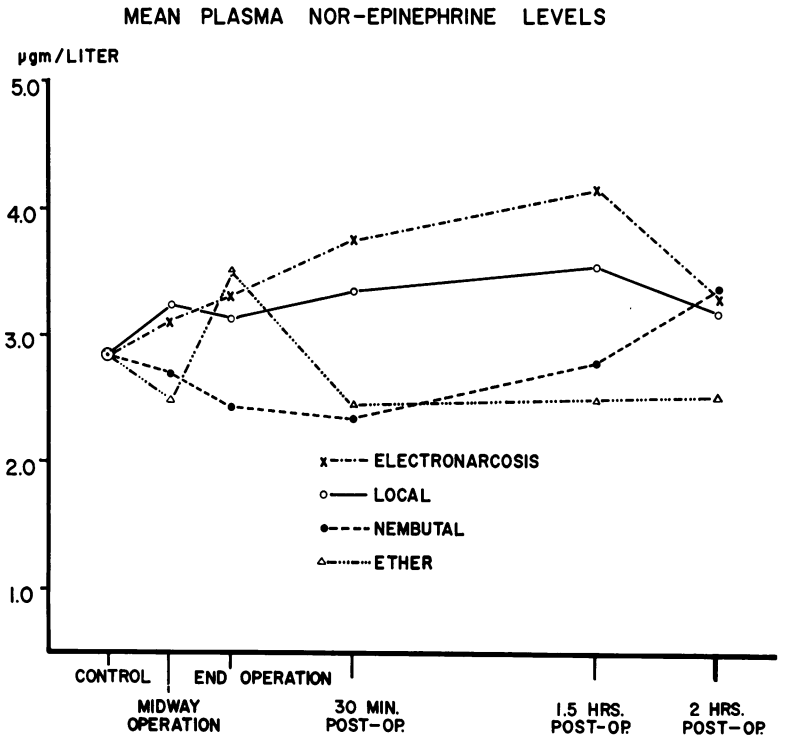


FIG. 3. Norepinephrine secretion in response to a standard laparotomy: A comparison of different agents for anesthesia. Electronarcosis with laparotomy produced the most marked increase in NE levels with the response to procaine and to ether next in order, respectively. Nembutal depressed the plasma NE level.

Watts [68] reported plasma epinephrine levels in rabbits and dogs during various stages of ether anesthesia. There were significant increases in plasma epinephrine in the rabbit at the end of induction of surgical anesthesia and after 30 minutes of surgical anesthesia. In dogs the plasma epinephrine levels during quiet ether anesthesia were variable, ranging from undetectable levels in most experiments to very high levels during hypertensive episodes in a few animals. During ether overdosage significant quantities of epinephrine were observed in the plasma of most dogs at the time of respiratory arrest and increased to very high levels at the time of cardiovascular failure with hypotension.

More recently Price and his associates [57, 58] have investigated the effect of cyclopropane upon the circulating plasma levels of E and NE, and have evaluated the role of these agents in the etiology of cardiac arrhythmia during anesthesia produced with this agent. Cyclopropane in man increased the concentration of NE but not of E. Hypercarbia elevated both. High spinal anesthesia prevented the arrhythmias during hypercarbia and virtually abolished the increase in plasma catechol concentration. Intravenous infusions of E and NE that duplicated the plasma catechol concentrations found during hypercarbia did not produce arrhythmias. Blockade of the stellate ganglion bilaterally prevented the occurrence of arrhythmias during hypercarbia but did not prevent increases in the plasma catechol amine concentration. It was concluded that arrhythmias produced by hypercarbia during cyclopropane anesthesia in man are therefore more likely caused by an increase in the activity of the cardiac sympathetic nerves than by an increase in circulating catechol amines.

TABLE 1. *Epinephrine and Norepinephrine Levels in Peripheral and Adrenal Vein Plasma in Twelve Patients*** †

| Patient and Operation | Control E | Control NE | During Op. E | During Op. NE | Adrenal Vein E | Adrenal Vein NE | 4 Hrs. Postop. E | 4 Hrs. Postop. NE | 24 Hrs. Postop. E | 24 Hrs. Postop. NE | Anesthesia | Length of Anesthesia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| J. C. S. #30017<br>Exploratory laparotomy<br>Cholecystojejunostomy | 0.96 | 4.37 | 1.00 | 4.04 | 5.39 | 5.49 | 1.84 | 3.90 | 2.17 | 3.92 | $C_3H_6$ | 3 hrs. 50 min. |
| E. N. #8790<br>Cholecystectomy | 1.01 | 3.88 | 2.00 | 2.81 | 14.62 | 8.92 | — | — | 1.10 | 4.00 | Ether, $C_3H_6$ | 3 hrs. 20 min. |
| E. B. #30047<br>Exploratory laparotomy | 0.90 | 2.21 | 1.57 | 3.30 | 8.72 | 2.46 | 1.39 | 3.55 | 1.52 | 3.12 | Ether | 4 hrs. 15 min. |
| G. M. #28488<br>Subtotal gastrectomy | 1.93 | 4.21 | 1.76 | 3.80 | 10.37 | 4.01 | 1.72 | 3.81 | 1.86 | 4.00 | Ether, $C_3H_6$ | 3 hrs. 30 min. |
| W. G.<br>Exploratory laparotomy<br>Subtotal gastrectomy | 1.00 | 4.00 | 2.10 | 3.00 | 12.50 | 5.76 | — | — | — | — | Ether | — — |
| E. M. | 0.92 | 7.04 | 1.42 | 5.94 | 32.50 | 6.80 | 1.60 | 6.18 | 1.00 | 7.00 | — | — — |
| E. A. #28584<br>Cholecystectomy | 0.98 | 5.00 | 1.20 | 4.80 | 15.10 | 4.60 | 1.20 | 4.90 | 0.90 | 4.90 | Ether | 3 hrs. |
| J. P. B. #12558<br>Exploratory laparotomy,<br>Subtotal gastric resection | 2.60 | 6.50 | 2.06 | 4.80 | * | * | 2.24 | 5.12 | — | — | Ether | 4 hrs. 35 min. |
| E. H. #29056<br>Exploration common duct | 0.00 | 0.56 | 0.84 | 1.30 | * | * | 2.46 | 3.40 | 2.34 | 3.73 | Ether | 3 hrs. 35 min. |
| M. C. #30366<br>Exploratory laparotomy | 0.98 | 4.02 | 2.70 | 1.55 | * | * | — | — | 0.99 | 3.87 | Ether | 3 hrs. 25 min. |
| M. S. #30352<br>Cholecystectomy | 0.069 | 2.99 | 1.02 | 3.01 | * | * | — | — | 0.81 | 3.00 | Ether | 2 hrs. |
| L. E. #28043<br>Exploratory laparotomy<br>Cholecystojejunostomy | 1.00 | 5.40 | 2.60 | 5.60 | * | * | 2.20 | 4.80 | 1.00 | 5.50 | Balanced anesthesia $N_2O_2$, $C_3H_6$ | 3 hrs. 35 min. |
| Average | 1.029 | 4.18 | 1.69 | 3.66 | 14.17 | 5.43 | 1.83 | 4.46 | 1.37 | 4.30 | | |

* Adrenal blood not obtainable.
** All catechol amine values expressed as mcg./L. of plasma.
† The increment afforded by the adrenal gland itself may be obtained by subtracting the values of the peripheral plasma from the values of the adrenal vein plasma.

### B. *Operations in Man: Peripheral and Adrenal Venous Plasma E and NE Levels with Estimates of Rates of Secretion.*

**Objective.** In view of the increasing evidence of the major role which E and especially NE play in the regulation of vascular tone and blood pressure stability, it was elected to determine peripheral plasma levels of E and NE during surgery in man. In addition, the left central adrenal vein was exposed at surgery and timed samples of adrenal venous blood were obtained to achieve further delineation of the respective sources of E and NE; these samples also permitted an estimation of rates of secretion for E and NE.

**Procedure.** Twelve patients were studied and their anesthesia and operations are given in Table 1. Plasma samples were drawn from a peripheral vein at intervals noted in Table I and Figure 4. During operation, after the primary surgical objective had been safely achieved and the patient remained in good condition, the left central adrenal vein was exposed using the approach of Hardy and Turner [30] and timed collections of flow were taken. Thus the adrenal vein samples were usually taken from one to three hours after anesthesia had been started.

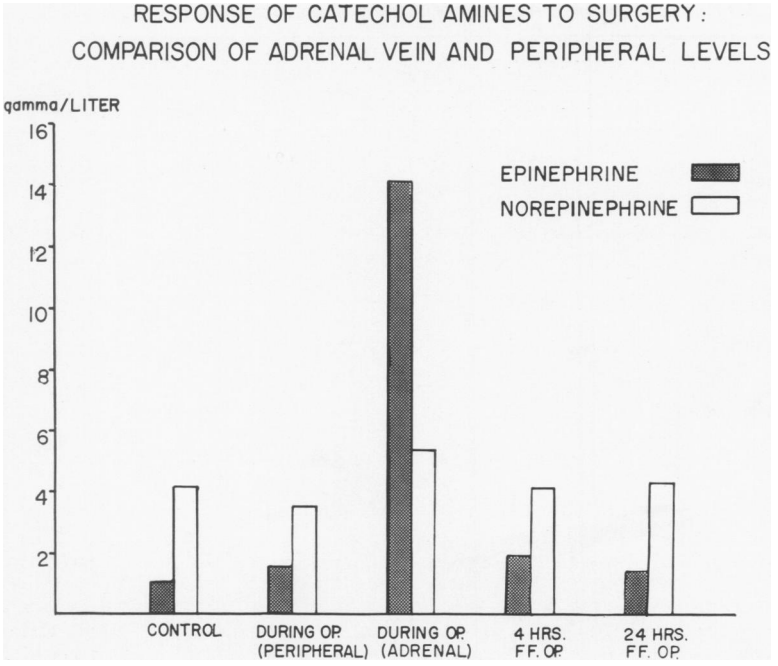


FIG. 4. The peripheral plasma values represent the averages of 12 patients and the adrenal vein values those of 7 patients. The E level in peripheral plasma rose consistently with surgery, while that of NE rose but slightly if at all in the given patient. In adrenal vein blood the levels of both E and NE were elevated over those in peripheral plasma, but the degree of elevation of E far exceeded that of NE. Epinephrine is thought to be formed entirely in the adrenal medulla, while NE is formed in the adrenal medulla and at sympathetic nerve endings elsewhere in the body.

**Results.** The levels of E and NE in peripheral plasma and in adrenal venous blood are listed in Table 1 and are presented graphically in Figure 4. The level of E in peripheral plasma averaged 1.03 mcg./L. preoperatively, 1.69 during surgery at the same time the adrenal venous sample was taken, 1.83 four hours after surgery, and 1.37 the day after surgery. The average level of E in adrenal venous blood was 14.17. The level of NE in peripheral plasma did not rise significantly. The average level of NE in adrenal venous blood was 5.43 mcg./L. In two patients the adrenal output was zero.

Estimations of rates of secretion of E and NE in five patients are given separately in Table 2. Whereas the adrenal plasma levels of E and NE for seven patients were obtained, in only five patients was the evaluation of timed flow considered to be sufficiently accurate to permit reasonably valid calculations of hormone output. It so happened too that in these five patients the average adrenal venous blood flow per minute was relatively low. In general the average rate of adrenal blood flow per minute is higher than these values, and thus our approximations of average rates of E and NE output are probably on the low side.

### Results Reported by Others

The effect of anesthesia-operation upon plasma concentrations of the catechol amines have previously been reported from several laboratories. Hammond, Aronow and Moore [29] found in studies of human subjects that the usual postoperative elevation of the plasma 17-hydroxycorticosteroids need not be accompanied by a rise in plasma E or NE levels. Moreover, of the E-NE values found to be elevated, a significant fraction occurred from one to 24 hours prior to operation. In two extensively burned patients there were elevations of both epinephrine and norepinephrine, and in the case of the former the elevation was particularly striking. In one patient following adrenalectomy the plasma epinephrine level was reduced substantially to zero while the plasma norepinephrine level was unchanged. In one patient suffering from

TABLE 2. *24-Hour Adrenal Secretion of Epinephrine and Norepinephrine in Five Patients*

| Patient | | Adrenal Plasma Epinephrine | | Adrenal Plasma Norepinephrine | |
|---|---|---|---|---|---|
| | | mcg./min. | mcg./24 hr. | mcg./min. | mcg./24 hr. |
| J. C. S. | Control* | 0.020 | 28.8 | 0.007 | 10.1 |
| | During** | 0.021 | 30.2 | 0.007 | 10.1 |
| E. N. | Control | 0.047 | 67.7 | 0.055 | 79.2 |
| | During | 0.093 | 133.9 | 0.045 | 64.8 |
| W. G. | Control | 0.099 | 142.6 | 0.064 | 92.2 |
| | During | 0.206 | 296.6 | 0.055 | 79.2 |
| E. A. | Control | 0.135 | 194.4 | No Output | No Output |
| | During | 0.153 | 220.3 | | |
| E. M. | Control | 0.103 | 148.3 | 0.006 | 7.9 |
| | During | 0.156 | 224.6 | 0.005 | 6.5 |
| Mean | Control | 0.081 | 116.4 | 0.033 | 47.4 |
| | During | 0.126 | 181.1 | 0.028 | 40.1 |

* Control values were calculated from concentrations obtained during surgery, from actual control peripheral levels and on the basis of the following assumptions: (1) a constant relationship was maintained between adrenal venous plasma concentrations and peripheral concentrations during the control period and during surgery; (2) adrenal epinephrine output does not depend upon blood flow; and (3) the hematocrit in each case was 45 per cent.

** Calculated from an assumed hematocrit of 45 per cent.

ulcerative colitis but not acutely ill and with an inflamed colon in place, the plasma epinephrine level was elevated but returned to normal following colectomy. Preoperative medication, the threat of operation and anesthetic agents alone (including ether, pentothal-nitrous oxide-curare, and spinal) did not seem to produce any significant increase in peripheral venous plasma E-NE.

Hume [36] reported the effects of operation and anesthesia upon E-NE plasma levels in dogs. Ether anesthesia alone produced an increased adrenal secretion of both epinephrine and norepinephrine over that seen in the resting conscious dog. Operative trauma under ether anesthesia produced an additional increase in epinephrine and norepinephrine secretion, even in the presence of profound shock. Nembutal anesthesia alone depressed the secretion of epinephrine and norepinephrine. Operative trauma under nembutal anesthesia was accompanied by no significant increase in epinephrine, and only slight increase in norepinephrine, secretion. When present, the increased adrenal medullary secretion began within 2 minutes after injury. A second operation in the convalescent period produced an adrenal response which was equal to or greater than that seen with the first operation.

In studies of adrenal venous blood in man, Hume and Bell [37] found the blood flow to vary widely, from 2.8 cc./minute to 54.6 cc./minute. Somewhat more epinephrine than norepinephrine was secreted by the human adrenal under the circumstances of the investigation. The average values were 0.337 micrograms (gamma)/minute for epinephrine and 0.115 gamma/minute for norepinephrine. These rates of secretion were greater than ours (Table 2), but the average adrenal blood flow per minute was greater in the patients studied by Hume and Bell. The discrepancy may lie in the fact that our values were calculated on the basis of plasma instead of blood flow. If Hume and associates calculated on the basis of blood flow, their values would be approx-

imately twice those found by the present authors. These authors noted a greater *urinary* excretion of norepinephrine than epinephrine following surgery in the human, most of the former coming from the extra-adrenal sources.

C. *Pheochromocytoma: General Considerations and Case Study with Catechol Amine Measurements.*

### General Considerations

The clinical management of pheochromocytomas involves many fascinating problems, not to mention the valuable information derived concerning catechol amine metabolism. While space limitations preclude an elaborate discussion of the extensive pertinent material, certain particularly useful facts regarding these lesions will be presented in essentially outline form.

**Historical Aspects.** The tumor was first described by Manasse [52] in 1893, but not until 1922 did Labbe, Tinel and Doumer [45] record the first careful clinical study of a classic case. The patient died in acute pulmonary edema and autopsy revealed a pheochromocytoma in the region of the left adrenal gland. The first case successfully treated with surgery was operated upon by Charles H. Mayo in 1927.[55]

**Embryology and Possible Locations.** The adrenal medulla and the extra-adrenal chromaffin tissues of the human fetus develop from sympathetic elements derived from the neural crest.[72] In the embryo the primitive sympathetic cells have been observed extending into the adrenal glands.[10] Thus *pheochromocytomas may arise wherever chromaffin tissue exists in the ganglia of the cervical,*[8] *thoracic* [51] *or abdominal sympathetic chains.* These tumors have been found in locations extending from the neck to the urinary bladder. Surprisingly, Isaacs and his associates [39] have reported the formation of norepinephrine in three neuroblastomas, which were not chromaffin tumors.

**Age and Familial Factors.** Pheochromocytomas have been reported at all ages, and numerous cases have involved children.[9, 11, 63] There are also multiple reports of a familial factor [4, 26, 40, 62, 73] with one or more tumors occurring in individual patients with a blood relationship.

**Pheochromocytoma and Neurocutaneous Syndromes.** There is a definite association between these chromaffin tumors and neurocutaneous syndromes, first pointed out by Suzuki [66] in 1910. This relationship was recently reviewed by Glushien and his associates.[22] Though the incidence of association is believed to be at least 10 per cent, only approximately 5 per cent of reported cases of pheochromocytoma are definitely known to have been associated with one or more of the following syndromes: (a) multiple neurofibromatosis (of von Recklinghausen), (b) von Hippel-Landau's disease (multiple hemangioblastomas), (c) tuberous sclerosis, and (d) Eturge-Weber syndrome. Stigmata of neurocutaneous disease in a patient with hypertension should always suggest the possibility of pheochromocytoma.[31, 41, 61]

**Cause of Death in Patients with Pheochromocytoma.** It will be recalled that the first reported patient with pheochromocytoma died in pulmonary edema during a severe hypertensive episode, and acute heart failure is a not uncommon cause of demise. In fact, the mode of death in the acute paroxysm is not unlike that exhibited by patients with acute epinephrine poisoning,[12, 50] where intracranial hemorrhage and cardiac arrhythmias with failure are prominent complications. Furthermore, the reported plasma catechol amine levels in fatal cases of epinephrine poisoning are similar in magnitude to those found during the severe hypertensive attacks exhibited by the patient with pheochromocytoma. A drip of Regitine or of Dibenamine should be set up to control hypertension during excision of a pheochromocytoma.

Untreated, the hypersecreting tumor may produce chronic renal disease.

**Diagnosis of Pheochromocytoma.**[13, 23, 38, 44] The typical attacks of the patient with paroxysmal hypertension are now commonly recognized. However, the hypertension may be sustained and, unless all patients with hypertension possibly due to pheochromocytoma are properly screened, cases will be missed. Patients wth hypermetabolism and/or "diabetes" in association with hypertension should also be screened for pheochromocytoma.[13, 23, 38] The lesion should also be suspected if marked hypertension develops during surgery for other conditions.[64] *Roentgenography* is perhaps most safely limited to plain films of the abdomen for soft tissue detail and intravenous pyelogram.[44] Aortography caused death in two reported cases.[43, 49] *Regitine* [21, 27] is useful diagnostically in lowering the blood pressure when it is elevated due to pheochromocytoma, but a small percentage of both false positives and false negatives must be anticipated.

*Catechol amine* determinations in plasma and urine have in recent years provided an increasingly satisfactory basis for the diagnosis of pheochromocytoma.[24, 54] In the patient whose tumor secretes at a substantial rate continuously, the urinary catechol amines will be elevated. However, if the hypersecretion occurs in paroxysms the 24 hour urinary excretion may not be elevated,[46] and plasma E and NE levels must be measured during an attack, whether spontaneous or provoked with histamine; in this instance multiple plasma samples (3 to 5) should be taken at 2-minute intervals after the onset of the paroxysm, to avoid missing the elevation of E or NE or both.[59] If the levels of blood E and NE are elevated, the tumor is probably situated in or adjacent to the adrenal medulla; for whereas NE is produced by sympathetic tissue everywhere in the body (including that in the adrenal) E is produced largely or entirely in the adrenal medulla.

**Cause of Hypotension Following Excision of the Pheochromocytoma.** This controversial problem appears to be nearing a solution. For years it was believed by many that the shock was due to heart failure, secondary to excessive levels of circulating E. More recently, however, the accumulating evidence indicates that the peripherovascular collapse is due to the abrupt withdrawal of the high levels of circulating catechol amines. In studying the fall in blood pressure which may follow the cessation of a norepinephrine drip, Burn and Rand [3] concluded that one should inject a pressor amine but not resume the NE infusion. It was suggested that the vascular sensitivity to NE diminishes because the vessels take up NE and hold it in "some kind of store" which is slowly discharged. This discharge leaves few receptors free on which the NE present in the blood stream can act. Furthermore, some such phenomenon may be advanced to explain the decreasing effectiveness so often observed with a norepinephrine drip, where the drug must be infused in greater and greater concentrations to achieve a blood pressure above shock levels. Rather than reflecting deterioration in the patient's general condition per se, this phenomenon may but reflect a diminished local reactivity of the blood vessels to NE.

Thus the peripherovascular collapse which may follow resection of a pheochromocytoma and persist for days [44] would appear to be due to an altered vascular sensitivity [28] to normal levels of the usual hormonal mediators of vascular tone, epinephrine and norepinephrine.

## Case Study

### Pheochromocytoma Associated with von Recklinghausen's Neurofibromatosis

**Clinical Data:** E. T., a 39-year-old Negress with extensive neurofibromatosis (Fig. 5) of many years' duration, was admitted to the obstetrical service of the University Hospital on October 11,

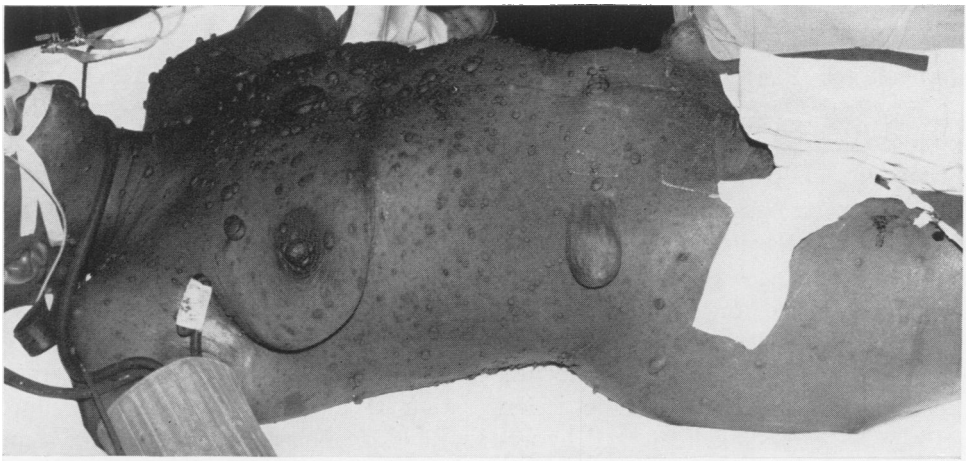

FIG. 5. Patient with co-existing pheochromocytoma and von Recklinghausen's neurofibromatosis. Pheochromocytoma is associated with neurocutanous syndromes in approximately 10 per cent of cases.[22] In view of the familial incidence of both pheochromocytoma and neurocutaneous syndromes, plus the fact that in the embryo both peripheral and sympathetic nerve elements derive from the primitive neurol crest, either a disease or genetic defect affecting nervous system development might be postulated.

1958 in active labor with her seventh pregnancy. The blood pressure was recorded at 140/70. Unfortunately, the labor did not proceed smoothly as it always had in the past, and it was soon apparent that cephalo-pelvic disproportion existed. A cesarean section was decided upon and pontocaine was injected for spinal anesthesia. However, no sooner had the patient been turned back to the supine position than she had a severe attack of headache and nausea, associated first with marked hypertension and then a brief period of peripherovascular collapse. The resident who had given the spinal injection was apprehensive that he might have injected an inappropriate material, but a quick check disclosed no apparent error. At this point he telephoned his chief, Dr. Leonard W. Fabian, who suggested the possibility of pheochromocytoma and requested the the obstetrician examine the adrenal areas before closing the abdomen. Since the patient had recovered from the attack, the cesarean section was performed and, just prior to closing the abdomen, the obstetrician did palpate a mass in the right adrenal region and precipitated a startling hypertensive attack (240/120) quite as severe as the previous one. Again the hypertension was followed by a brief period of hypotension which was managed with ephedrine. The baby was normal.

The mother convalesced satisfactorily and was discharged on October 19, 1958 to return two weeks later for excision of the pheochromocytoma.

**Plasma Catechol Amine Values Prior to Resection of Tumor:** She was re-admitted on November 4, 1958 for general preoperative evaluation. At this time a histamine provocative test (0.025 mg. I. V.) was performed, with Regitine (2.5 mg.) available through an infusion in the opposite arm. The pertinent data are shown in Figure 6. When she began to experience headache, nausea, and chest pain the Regitine was run in rapidly and the symptoms had all disappeared within minutes. It may be seen that during the hypertensive period the levels of both epinephrine and norepinephrine, previously within normal limits, were very markedly elevated. However, the levels declined abruptly upon the infusion of the sympatholytic drug Regitine. Thus in this patient (whose 24 hour urinary excretion of catechol amines was not then available) the plasma E and NE levels were normal between attacks. Only by taking plasma samples during an attack was an elevated plasma catechol amine level demonstrable.

**Resection of Pheochromocytoma:** On November 7, 1958, under nitrous oxide-oxygen-ether anesthesia, the abdomen was explored through a right subcostal incision extended well into the flank. First the left adrenal area was palpated to exclude the presence of a second pheochromocytoma on that side. Then the previously demonstrated tumor involving the right adrenal was excised. Regitine was kept ready for instant infusion, if required, but it was withheld to permit sampling of adrenal vein blood, if possible. However, such sampling did not prove to be technically feasible. The tumor (Fig. 7) was removed without precipitation of an attack,

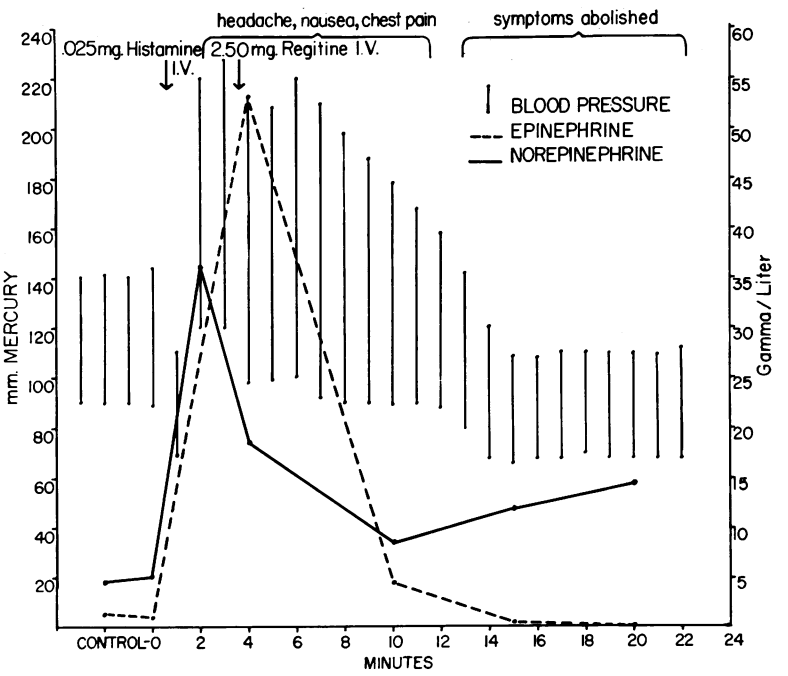


FIG. 6. The injection of histamine produced a sharp rise in the plasma levels of both E and NE. The rise in blood pressure was associated with an onset of headache, nausea and chest pain. The infusion of 2.5 mg. of Regitine caused rapid disappearance of the symptomatology. The fact that both E and NE rose sharply reflected the fact that the adrenal medulla was involved by the functioning chromaffin tumor.

and only briefly did the blood pressure rise above a level of 210/110.

The neurofibroma in the true pelvis which had prevented delivery of the fetus after six previous normal deliveries was also excised.

**Postoperative Data:** The patient recovered from the operation uneventfully. Late in the postoperative period the histamine provocative test was repeated (Fig. 8). This time there was again a sharp increase in the plasma NE level from the normal control value but no increase in the plasma E level. Presumably certain of the extensive deposits of nervous tissue elements were still capable of secreting NE, while the adrenal medullary source of E had been removed. The histamine test has produced no significant rise in either E or NE in normal subjects.

**Urinary Catechol Amine Levels:** The 24-hour urine collections for the day of operation and for selected days thereafter were analyzed for total catechol amine excretion. Through a misunderstanding the concentration of only 17-hydroxycorticosteroids was analyzed in the urine collected during the 24-hour period preceding that in which the operation was performed. It may be seen in Table 3 that there was a markedly elevated level (547.2 micrograms as against a normal range of 40–100 micrograms [59]) during the 24-hour period which included anesthesia and operation. Therefore one must assume that the tumor was either secreting at a high level preoperatively or that the trauma of anesthesia-operation produced the high rate of excretion recorded. During the first 24-hour period following that which included the operation the level of catechol amine excretion in the urine was within normal limits. Thereafter it again rose, though not to the very high level recorded for the day of operation. It will be recalled that the injection of histamine late in the postoperative period again produced a rise in the plasma NE level but no longer produced a rise in the plasma E level. This suggests the possibility of another tumor, one which is secreting only NE and thus presumably not involving the adrenal medulla. Since this patient has a vast number of neurogenic tumors, the identification of the specific tumor responsible for the increased NE secretion could prove exceedingly difficult.

## Summary and Conclusions

1. The humoral transmission of nerve impulses is a subject of much practical importance. Acetylcholine is elaborated at the

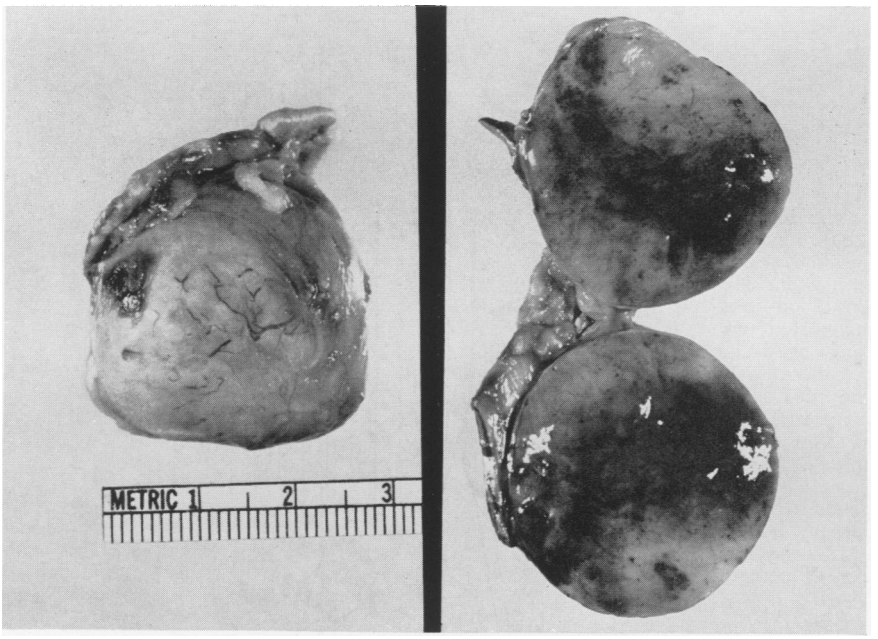


FIG. 7. Pheochromocytoma removed by means of right adrenalectomy using abdominal approach.

ends of somatic, parasympathetic, and preganglionic sympathetic nerve fibers; norepinephrine (NE) is elaborated at the ends of the postganglionic sympathetic fibers.

2. Epinephrine is formed only in the adrenal medulla, but NE is formed both here and at sympathetic nerve endings elsewhere in the body. Both hormones have multiple supportive functions but NE has a particular role in maintaining normal vascular tone. For example, it has been shown that the elaboration of both E and NE is increased by tilting normal subjects on a tilt-table, but that such a response is absent in patients with postural hypotension.[32]

3. A comparison of the effects of electrical, ether, nembutal, and local (procaine) anesthesia in 28 dogs is reported, a standard laparotomy being performed in all animals. With electrical narcosis the animal recovered immediately when the current was turned off. This form of narcosis produced the greatest rise in the plasma levels of both E and NE. Nembutal depressed the plasma levels of both despite the superimposed laparotomy.

4. The effect of operations upon the E and NE levels in peripheral plasma was investigated in 12 patients. In addition, during laparotomy timed collections of blood flow through the left central adrenal vein were taken and concentrations (7 patients) and rates of secretion of E and NE (5 patients) were determined. The level of E in peripheral venous plasma was 1.03 mcg./L. preoperatively, 1.69 during surgery at the same time the adrenal venous sample was taken, 1.83 four hours after surgery, and 1.37 the day after surgery. The average level of E in adrenal venous blood was 14.17 mcg./L. (7 patients). The level of NE in adrenal venous blood was 5.43 mcg./L. (5 patients), as compared with the level of 3.66 in peripheral plasma (12 patients). This difference in E and NE levels in adrenal venous plasma reflected the fact that presumably all E is formed in the adrenal medulla whereas only a relatively small part of the total NE elaborated is formed in the adrenal medulla.

5. The rate of formation of E during operation is estimated to be on the order of

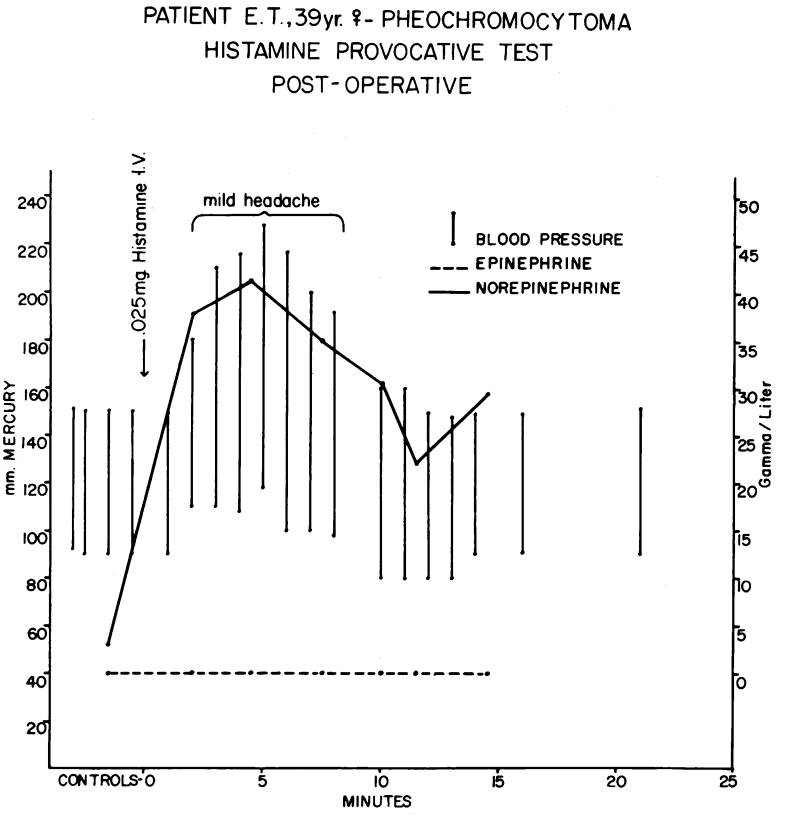


FIG. 8. Whereas preoperatively the histamine provocative test had produced a sharp rise in the plasma levels of both E and NE, postoperatively the test produced a rise in only NE. The E level was unaffected because the adrenal medullary tumor had been resected by means of right adrenalectomy and no tumor had been found in the left adrenal area. Why, then, did the histamine produce a rise in the plasma NE level postoperatively when it does not do so in normal subjects? One must suppose that in this patient (Fig. 5) with many, many tumors other deposits of nonadrenal chromaffin tissue exist which, like sympathetic nerves elsewhere, can elaborate norepinephrine.

0.126 mcg./min. and 181.1 mcg./24 hr.; for NE, the estimated rates were 0.028 and 40.1, respectively. These values are somewhat lower than some reported in the literature.

TABLE 3. *ELT: Total Urinary Catechol Amines* and 17-Hydroxycorticosteroids*

| Date | Urine Vol./ 24 Hr. | Catechol Amines mcg./24 Hr. | 17-Hydroxy-corticosteroids mg./24 Hr. |
|---|---|---|---|
| 11/6/58 | 750 cc. | ** | 6.0 |
| 11/7/58† | 1710 cc. | 547.2 | 15.6 |
| 11/8/58 | 650 cc. | 91.0 | 19.3 |
| 11/9/58 | 1220 cc. | 341.6 | 24.6 |
| 11/10/58 | 450 cc. | 238.5 | 10.5 |

(Analyses by Bio-Science Laboratories under contract.)

* Normal range, 40–100 mcg./24 hr. (approx.) (59).

** Preoperative control level not determined through misunderstanding.

† Day of operation.

6. Pheochromocytomas may arise in sympathetic chromaffin tissue anywhere, and have been found in locations extending from the neck to the urinary bladder. They frequently occur in children and have a familial tendency. About 10 per cent are associated with neurocutaneous syndromes such as von Recklinghausen's neurofibromatosis.

7. A case study of a patient with coexisting pheochromocytoma of the right adrenal and von Recklinghausen's neurofibromatosis is presented. The first known paroxysmal attack followed the injection of spinal anesthesia for cesarean section when she was placed again on her back. Later a histamine provocative test produced a rise in the plasma E level from a control value of 1.5 mcg./L. to 54.2 mcg./L.; with NE, from 5.0 to 35.1. After resection of the adrenal pheochromocytoma the histamine test

produced no rise in E but a rise in NE from a control value of 3.0 to 40.4. In each instance there was an associated rise in blood pressure. The implications of these findings are discussed.

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## Discussion

Professor Jack Adams Ray: Mr. President, I am very happy to have the opportunity to speak here.

The former author said that norephedrine was produced at the endings of sympathetic nerve fibers. I think so, too, but there is also, we have found now, a system of cells distributed in the vessel walls of the human body containing chromaffin granules. This piece of work has been corroborated by, among others, Burch, in New Orleans.

These granules give chromaffin reactions. They have the same ultra structure as the granules of adrenal medulla, and as Burns has shown now in Oxford, they are emptied out by reserpin, and we have seen that in the red inflammatory skin these chromaffin granules are emptied out. So we have indications that we have a widespread system of cells containing chromaffin reacting granules that we believe produce and store not only norephedrine but also ephedrine.

Just before I left Stockholm we had a report about 15 patients that had been adrenalectomized. Immediately after the operation there was practically no output of ephedrine, but half a year up to three years after the operation these patients produced a normal amount of ephedrine through the urine.

If you are interested, I have some slides in my room if you want to see what these cells look like. I thank you.

Dr. David M. Hume: We have been doing some studies similar to those of Dr. Hardy which I thought might be worth mentioning, since our results differ in some respects from those reported by him.

Our experiences with norepinephrine and epinephrine measurements consist of several thousand determinations of these substances in dog adrenal venous blood, 24 hour urinary measurements in 159 hypertensive patients, 25 normals, and four patients with pheochromocytomas; peripheral blood levels in 69 patients and four patients with pheos, adrenal venous blood output in 18 human patients, and 4 hourly urinary outputs and blood levels in 26 patients undergoing surgery, taken in the first 24 hours prior to operation, the day of operation and three days thereafter.

These results may be summarized as follows: The urinary output of norepinephrine was always markedly elevated in patients with pheochromocytoma, sometimes as much as 100 times that seen in the normal patient. Urinary epinephrine and norepinephrine levels in hypertensive patients were in no way different from those seen in the normal patient, unless the hypertensive patient had a pheochromocytoma. Blood epinephrine and nore-