Current Experience in the Diagnosis of Pheochromocytoma

By Sheldon G. Sheps, M.D., Gertrude M. Tyce, Ph.D., Eunice V. Flock, Ph.D., and Frank T. Maher, M.D., Ph.D.

ALTHOUGH hypertension is only rarely caused by pheochromocytoma, when it is, it usually is completely reversible by excision of the tumor. Since 1927, when Mayo¹ demonstrated that removal of an adrenal tumor resulted in cessation of hypertensive episodes, physicians have been looking for ways to detect the presence of this tumor when assessing patients who have hypertension. Even though Oliver and Schäfer² in 1895 demonstrated that adrenal medullary extract produced hypertension in animals, and Stolz³ synthesized epinephrine in 1904, it was not until 1957 that the first catecholamine metabolite, vanilmandelic acid (VMA), was described by Armstrong and associates.⁴ During the ensuing decade much progress has been made in outlining the metabolic pathways of catecholamines (CA). Whereas the diagnostic tests of the previous decade were pharmacological in nature, in the past few years more specific chemical techniques for assaying catecholamine and metabolite levels have been developed and have greatly simplified the screening of large numbers of hypertensive patients for pheochromocytoma.

This study reviews the experience of the authors and their colleagues in the diagnosis of pheochromocytoma in 28 patients, and in the screening of 148 patients suspected of having it, during the 5 years ending December 1964.

Methods

Case records were reviewed of all patients for whom a determination of urinary VMA or total metanephrines (MN) or both was done at the Mayo Clinic from 1960 through 1964. (This 5-year period began just after completion of a study by Bollman and co-workers⁵ of the CA data on 48 patients with pheochromocytoma studied at the Mayo Clinic. Very little information was available then on metabolites of CA. The clinical data on the tumor patients seen through 1960 were reviewed by Gifford and co-workers.⁶) There were 28 patients with histologically proved pheochromocytoma and 148 other patients in whom this diagnosis was suspected but not confirmed either by surgical exploration (in 18) or by repeated study. In two cases, operation was performed specifically to search for tumor, while in the remaining cases the examination of the adrenals was incidental to abdominal surgery for other lesions.

The standard cold pressor-histamine test and the phentolamine (Regitine) test in combination with the determination of plasma CA were used as previously described.⁷ The tyramine provocative test⁸ also was used toward the end of the study period. A positive result in the histamine test was defined as a pressor response of 20/10 mm Hg greater than the response to the cold pressor test; a positive result in the phentolamine test was a pressure decrease of 35/25 mm Hg compared to base-line values; a positive result in the tyramine test was a systolic pressor response of 20 mm Hg above base-line values.

Fluorometric procedures were used to determine the concentrations of plasma and urinary CA.⁹-¹¹ Paper chromatographic methods were used to measure urinary concentrations of VMA,⁴ and homovanillic acid (HVA).¹² Concentration of total MN in urine was measured by the method of Pisano.¹³ During the first part of the study period the urines with abnormally high MN values had not been checked routinely for transmission at a wavelength of 333 mμ as well as at 347 and 360 mμ (this has been recommended by Crout and co-workers¹⁴ for detection of the contribution to the apparent MN values of p-hydroxybenzaldehyde formed from synephrine in the oxidation procedure). However, the normal values for urinary CA and VMA and plasma CA and the negative results on pharmacological tests lend confidence to the exclusion of pheochromocytoma in the few nontumor patients in whom the sole abnormality was a small increase in urinary output of MN. More recently, observations have been made at all three wavelengths when the

From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
value for MN at 360 mg/24 hr. Dopamine (3-hydroxytyramine) in tissue was determined by the method outlined by Sourkes and Murphy. The normal means and upper limits of normal (expressed as three standard deviations of the mean) are: plasma CA, 2.4 and 5.7 μg/liter; urinary CA, 119 and 338 μg/24 hr; VMA, 2.6 and 6.5 mg/24 hr; and MN, 0.5 and 1.3 mg/24 hr. Shaw and co-workers reported the normal range for urinary HVA in adults to be 3 to 8 mg/24 hr.

Results

Pheochromocytoma (28 Patients)

The 24-hour urinary excretion of CA and VMA in 28 patients and of MN in 14 patients with pheochromocytoma is shown in figure 1. The relationship of the urinary outputs of MN and VMA in 42 specimens is shown in figure 2. In multiple specimens from the same patient there was often considerable variation in output of CA, but less so in VMA and MN. Thus abnormal urinary values were found for CA in 21 of 28 patients, for VMA in 22 of 28 patients, and for MN in 13 of 14. In two patients, the outputs of VMA and CA were normal while the output of MN was increased. In one patient, all urinary values in repeated collections were normal, including one collection during which a histamine test was performed which produced a high plasma CA value and a positive pressor response. Normal values were noted 2 to 3 days after total removal of functioning pheochromocy-

![Figure 1](http://circ.ahajournals.org/)

Each major division along the axes represents one multiple of the upper limit of normal, thus showing degree of abnormality for each determination. The upper limit of normal for each determination is also indicated. (Left panel) Comparison of urinary CA to urinary VMA in 65 specimens from 28 patients with pheochromocytoma. In 11 specimens both VMA and CA outputs were normal; in nine, CA was normal but VMA was abnormal; in 11 CA was abnormal but VMA was normal; and in 34 both VMA and MN were abnormal. In 23 of these 34 specimens, CA was more abnormal than was MN. (Right panel) Comparison of urinary CA to urinary MN in 36 specimens from 14 patients with pheochromocytoma. In three specimens, the MN output was normal and in only one of these was the CA output abnormal; in 11 others CA was normal but MN was abnormal; and in 22 both MN and CA were abnormal. In 14 of these 22 specimens, MN was more abnormal than was CA.
toma tissue in the few cases in which analyses were done.

Pharmacological tests with both histamine and phentolamine were done in 22 patients. Only a histamine or a phentolamine test was done in two and three additional patients, respectively. A positive response to histamine was noted in 18 of 24 patients (75%) and a positive response to phentolamine was noted in 10 of 25 patients (40%).

In 16 phentolamine tests, the drug was administered about 3 minutes after the histamine—that is, after the peak response to histamine; two of these tests were positive. Eight of the remaining nine tests were positive; in these, only phentolamine was given because the resting blood pressure exceeded 170/115 mm Hg, precluding a provocative test with histamine. Figure 3 shows the results of the histamine tests in these patients, divided into positive responses and negative ones. The former were associated with a marked increase in plasma CA to abnormal levels in all but one instance. Those patients not responding to histamine by showing an increase in blood pressure had very little, if any, change in plasma CA in eight tests, thus confirming that the pressor response to histamine is due to release of CA. Moreover, the level of plasma CA (or urinary metabolites) was not related to the development of a pressor response to histamine. Indeed, in one patient with metastatic pheochromocytoma studied many times over a period of 15 years, dozens of histamine tests have been negative with greatly varying levels of tumor activity.

Figure 2

Axes marked as in figure 1. Comparison of urinary MN to urinary VMA in 42 specimens from 14 patients with pheochromocytoma. In three specimens, the output of MN was normal, but in only one of these was VMA abnormal; in 13 specimens, the MN output was abnormal but VMA was normal; and in 26, both MN and VMA were abnormal. In 23 of these 26 specimens, MN was more abnormal than was VMA.

Figure 3

Plasma CA concentrations before and after injection of histamine in 34 tests in 24 patients with pheochromocytoma. The left column illustrates 26 positive responses in 18 patients. In 15 of these tests, the plasma CA increased from a normal value to an abnormal one; in one instance, it remained normal; in 10, the resting value was abnormal and it increased further in the test. The right column illustrates eight tests in six patients in whom no pressor response was observed. Very little change in plasma CA was seen.
On the other hand, a positive phentolamine test was always associated with abnormal resting or basal values for plasma CA among the tumor patients: The 10 patients in this series had plasma CA values of 6.4 to 31.3 μg/liter (mean, 13.8). Of the 15 patients with a negative phentolamine response, 10 had normal basal plasma CA values and the remainder had values ranging from 5.8 to 22.9 μg/liter (mean, 11.0). However, there was no direct relationship between the level of plasma CA and the degree of blood pressure reduction.

Tyramine tests were performed on two patients in this series and additional tyramine studies have been done more recently on five other patients with pheochromocytoma, as well as on patients with essential hypertension and patients with vascular hyperreactivity. These studies indicated that the pressor response to tyramine was greater in some patients with pheochromocytoma as compared to nontumor patients, but the separation of values was not great and multiple injections were needed, making the test tedious. Plasma CA was not increased by administration of tyramine.

We have been studying the excretion of HVA, a derivative of dopamine, in patients with neuroblastoma and in recent pheochromocytoma patients (table 1). Normal values of 3 to 8 mg/24 hr have been reported with this method, but the nontumor patients in our series had somewhat lower values. The values for HVA in our tumor patients were normal with the exception of one patient whose tumor had neuroid elements on histological examination. In this patient the urinary output of HVA was 91.2 mg/24 hr preoperatively and was 9.8 mg/24 hr in the immediate postoperative period and 2.7 mg 6 months later, at which time there was no clinical, pharmacological, or biochemical indication of functioning neural crest tumor. In this case, noninvasive, circumscribed, adrenal medullary tumor had expanded the adrenal cortex. In sections, the tumor exhibited vascular zones of typical pleomorphic pheochromocytes in irregular clusters. Many of these cells were chromaffin positive. However, the tumor was unusual since, in many zones, fascicles of spindling neurilemmal cells were seen interlacing with and separating cells indistinguishable from ganglion cells. No sharp distinction could be made between chromaffin-positive pheochromocytes and these ganglion-like cells. In addition, there were less abundant, smaller, polygonal cells in clusters or sheets, and some of these were chromaffin positive and probably represented less mature pheochromocytes or neuroblastic elements. The pathological diagnosis by Dr. E. G. Harrison, Jr., was "pheochromocytoma which had associated elements of ganglioneuroblastoma, components which are in keeping with the neural crest origin of these tumors."

The tumors of another patient contained relatively small concentrations—100 μg/g and 39.3 μg/g—of dopamine. This patient had multiple intra-abdominal tumors during a period of a few years, and finally hepatic invasion was noted, but there was never involvement of the adrenals. Bollman and co-workers reported three tumors with dopamine concentrations of 100 to 300 μg/g (including one of the tumors just noted) but did not report any clinical correlations. Sub-

<table>
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<td>1</td>
<td>91.2</td>
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</table>

Table 1

Excretion of Homovanillie Acid (HVA)
sequent review of their other two patients, of a patient with a positive test (not quantitated) for dopamine in tumor tissue, and of a patient in whom the dopamine concentration was 250 μg/g of tumor tissue did not reveal any correlation with recurrence or metastases with the exception of the patient mentioned.

Nontumor Patients (148 Patients)

All of the available excretion data on the 148 patients in whom pheochromocytoma had been excluded are plotted in figures 4 and 5. CA output was determined in 201 specimens and VMA and MN in 189 each. There was an increased content of CA in 40 (only six were more than twice the upper limits of normal), increased MN in 20, and increased VMA in two. All MN and VMA values were less than twice the upper limit of normal and in no instance were both VMA and MN values increased. Those urines with abnormal contents of both MN and CA (fig. 4) were obtained from patients who had received either epinephrine or pargyline parenterally. Similar medication also had been given to those patients who had normal CA values but MN values of 1.8 or greater. Pargyline is a monoamine oxidase (MAO) inhibitor; it inhibits the formation of VMA, thus increasing the excretion of MN and CA. Since it is long act-

**Figure 4**

(Left panel) Comparison of urinary CA to urinary VMA in 162 specimens from nontumor patients. In two specimens the output of VMA was abnormal, and in one of these the CA output was normal; in 35 other specimens CA was abnormal but VMA was normal; and in 125 both VMA and CA outputs were normal. (Right panel) Comparison of urinary CA to urinary MN in 134 specimens from nontumor patients. Values for MN less than 1.0 mg/24 hr are grouped together. In 18 specimens, MN output was abnormal and in four of these, CA also was abnormal. In 23 additional specimens only CA was abnormal, and in 93 both CA and MN were normal.
ing, it must be discontinued 7 to 10 days before a 24-hour sample of urine is collected for MN determination, and this had not been done in these cases. The effect of exogenous CA, increasing urinary CA and MN but not VMA, probably is related to the fact that the primary role of MAO is in metabolism of bound CA whereas O-methyltransferase is primarily involved with circulating CA.20

The two minimally increased values for VMA were seen in two patients in whom no medication could be incriminated; in one, the CA was slightly increased as well but, as shown in figure 5, the MN was normal in both. The one patient with markedly increased output of CA (3,621 µg/24 hr) had received both sodium nitroprusside and methyldopa. It was not clear whether or not the latter had been given before the urine had been collected. It is well known that methyldopa produces a false-positive increase in CA,16,21 but the effect of sodium nitroprusside on CA is unknown although it can control the blood pressure adequately in cases of pheochromocytoma.22 It also is well known that stress can increase CA excretion transiently.20, 23–25 This patient had undergone pneumoencephalography 48 hours before the urine collection and this, too, may have contributed to the high CA value. Another patient had urinary CA values of 1,083 and 677 µg/24 hr 6 and 7 days, respectively, after a second-stage thoracolumbar sympathectomy. No pheochromocytoma was found at autopsy a few weeks later. The possibility that the increased CA excretion was a reflection of release of CA from degenerating sympathetic tissue was explored in dogs. It was found that, within 10 days, the urinary CA increased as much after a sham procedure as after either the first or second stage of a total sympathectomy, thus confirming the clinical impression that this patient's high CA values were a response to nonspecific stress.

Histamine tests were positive in eight (11%) of 71 nontumor patients, and phentolamine tests were positive in five (11%) of 44; both tests were done in 14 of these cases. In none of these cases was plasma CA concentration increased although, on occasion, an increase in urinary output of either CA, MN, or VMA (once) was associated with a positive pharmacological test; in all instances, repeat pharmacological and biochemical studies gave normal results. Plasma CA concentrations were abnormal in two of 101 nontumor cases. In one patient a value of 6.1 µg/liter was obtained once, but five additional basal values were normal; slightly increased urinary values for CA were found in two of four urine specimens but VMA was normal and two phentolamine tests were negative (exploration was not done but follow-up has not revealed clinical evidence of pheochromocytoma). The other patient had abnormal plasma CA concentrations (7.5 to 10.0 µg/liter) five times, slightly abnormal urinary CA values twice, slightly abnormal MN value once (of two determinations), and normal VMA values twice; a histamine test was negative. A mass was noted in the para-aortic area on nephrotomography, but the patient refused to undergo operation and, 1 year later, was unchanged.

Figure 5

Comparison of urinary MN to urinary VMA in 189 specimens from nontumor patients. The values of MN less than 1.0 mg/24 hr are grouped together. In two specimens, the output of VMA was increased but MN was normal in both; in 20, MN was abnormal but VMA was normal; and in 167 both VMA and MN were normal.

Circulation, Volume XXXIV, September 1966
clinically. This patient has been included in the nontumor group because of the inconsistency of the data as compared to that of the patients with known pheochromocytoma.

Discussion

The recent elucidation of the pathways of metabolism of CA has greatly enhanced the accuracy of diagnosis of functioning tumors of neural crest origin, including pheochromocytomas and ganglioneuroblastomas. The time-consuming bioassay techniques, which were limited to the biologically active forms of CA, have been replaced largely by biochemical methods suitable also for measurement of various metabolites and precursors. There has been a tendency to regard the pharmacological tests as being difficult to perform and interpret, and thus they were considered to be superfluous with the availability of the urinary and plasma measurements. However, current interest, particularly in the development of additional provocative pharmacological tests, illustrates the continuing need for these tests especially for patients with intermittently secreting tumors in whom urinary and plasma values may be normal between paroxysms.

In screening large numbers of patients for pheochromocytoma, the measurement of CA or its metabolites in urine has many advantages compared to pharmacological studies. In contrast to our earlier experience, at a time when only plasma and urinary CA measurements were available, the additional determinations of VMA and MN have demonstrated the relative inaccuracy that results from sole reliance on determination of urinary CA as a screening test. In table 2 is a summary of the pharmacological and biochemical tests reviewed here. Seven (25%) tumor patients had normal urinary CA values, and 40 (20%) of 201 specimens of urine from 148 nontumor patients were abnormal, although only six had values greater than twice the upper limit of normal. The determinations of VMA and MN gave far fewer false-positive results. However, VMA was falsely normal in six (21%) of 28 tumor patients. All of the urinary data were normal in one tumor patient, but MN values were abnormal in the other 13 tested, including two in whom both VMA and CA were normal. In addition, the increase above normal in MN excretion usually was far greater in most tumor patients than that seen for either VMA or CA. Thus, the determination of MN has become our screening test for pheochromocytoma. No additional false-negative results have come to our attention since we initiated this screening program in April 1965; in the period since then, five new tumor patients have been discovered. These observations and those of Kelleher and co-workers confirm the value of determining MN, as proposed by Crout and co-workers in the diagnosis of pheochromocytoma.

Table 2

<table>
<thead>
<tr>
<th>Results of Pharmacological and Biochemical Tests for Pheochromocytoma</th>
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<tr>
<td><strong>Test</strong></td>
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<td>Phentolamine</td>
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<td>Urine: CA</td>
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<td>VMA</td>
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<td>MN</td>
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*These data represent all the urine specimens from the 148 nontumor patients. All other numbers refer to patients.

Circulation, Volume XXXIV, September 1966
Since normal values for CA and metabolites usually are noted within a week after total removal of the tumor, these studies are important in detecting residual functioning tumor tissue or recurrences. We have been able to detect and follow the activity of recurrences or metastases in the absence of symptoms. Thus, along with Sunderman,\(^26\) we routinely repeat these tests not only postoperatively but at intervals thereafter for a few years.

Recently, Robinson and co-workers\(^27\) suggested that patients with malignant pheochromocytoma selectively excrete excessive amounts of dopamine, as occurs with neuroblastomas. Sankoff and Sourkes\(^28\) reported variable amounts of urinary dopamine and 3,4-dihydroxyphenylacetic acid (dopac) but persistently increased HVA in their patient with metastatic pheochromocytoma; in five other of their patients with pheochromocytoma there were variable amounts of urinary dopamine. We have reported previously on the presence of methoxymephalin in a patient with metastatic pheochromocytoma.\(^16\) No biochemical evidence for malignancy was noted in our present group of patients. Although excessive excretion of HVA did not distinguish malignancy, it did indicate a tumor whose histological features suggested a closer relationship than usual to other neural crest tumors.

The determination of plasma CA concentration has been a most useful adjunct to urinary measurements. The resting or basal level was high in the five tumor patients with sustained hypertension and in all those with a positive phentolamine test. Although half of the patients with paroxysmally functioning tumors also had abnormal basal plasma CA concentrations (12 of 23), all but one of the 18 tumor patients with positive pressor responses to histamine had plasma CA concentrations increased to abnormal levels after histamine injection. Thus, all but one tumor patient had at least one high value for plasma CA, but only two of 101 nontumor patients had a falsely positive value. The determination of CA in plasma has continued to be a most valuable adjunct in the diagnosis of pheochromocytoma in three particular instances: when high basal blood pressures preclude provocative pharmacological tests, for interpretation of a positive pressor response to histamine, and during spontaneous paroxysms of hypertension. An additional interesting use of the plasma CA value is a "search" through the systemic veins for the location of the highest concentration of CA to localize a primary tumor\(^29\) or subsequent metastatic lesions.\(^21\)

Pharmacological tests for pheochromocytoma have been utilized at this institution since the description of the histamine test by Roth and Kvale\(^30\) in 1945. Our results with the phentolamine test were first described by Gifford and co-workers\(^31\) in 1952. Our experience with both of these tests up to 1961 was reviewed by Gifford and co-workers\(^6\) and illustrated the value of both tests in 72 patients with pheochromocytoma. Repeated pharmacological tests in five of these 72 patients gave negative results, and in four of these five the chemical tests gave positive results. In the present study, the established value of the histamine test is reconfirmed: 75% of tumor patients had positive results and only 11% of nontumor patients had false-positive results. The addition of plasma CA determinations further increased the diagnostic accuracy of this test.

Because of the frequent minor side effects (headaches, flushing) noted with histamine, other provocative agents have been proposed. Engelman and Sjoerdsma\(^8\) reasoned that, since tyramine is able to release CA from tissue depots and since these depots are greater in patients with pheochromocytoma, it would be a useful provocative agent. They were able to demonstrate a greater pressor response in six patients with pheochromocytoma than in normal subjects. We were able to confirm this in five of seven tumor patients, but the nature of the response made the test less suitable than the histamine test.\(^17\) More recently, glucagon\(^32\) and the \(\beta\)-blocking agents, propranolol and pronethanol,\(^33\) have been proposed as provocative agents; these interesting concepts will need confirmation.

The use of phentolamine in a pharmacological test for pheochromocytoma was based on
its ability to block briefly the effects of circulating CA. Thus, its greatest usefulness seems to be in testing patients with basal blood pressure so high that histamine was contraindicated and also in abbreviating a marked pressor response to histamine to provide an additional pharmacological test. In the latter situation it often was difficult to interpret the response of the blood pressure because there was no appropriate basal value for comparison, particularly when basal readings (before histamine) were normal. In the former situation, the degree of the response seemed to depend also on the basal pressure values, the greatest decreases being seen with the highest basal pressures. Patients with essential hypertension not infrequently had rather striking decreases in pressure; these decreases could be of quite long duration on rare occasions, and they occurred in the absence of any other predisposing diseases or drugs. Myocardial infarction has been reported to occur as a consequence of such hypotension. Taylor and co-workers studied the effect of intravenous administration of phentolamine in normal and in hypertensive men and demonstrated in both a predominant and prompt vasodilating effect more potent than the sympathetic blockade effect. This is the likely explanation for the positive results in phentolamine tests in nontumor patients (with normal plasma CA concentrations). In the present series, the phentolamine test was used alone in only nine tumor patients. In eight of these (and in two others in whom the test was done after the histamine test), the phentolamine test was positive; in 11% of nontumor patients tested, this test was falsely positive. Because all of the tumor patients who had positive phentolamine tests also had increased resting concentrations of plasma CA and urinary outputs of CA or metabolites and because of the problems in performing and interpreting the phentolamine test, we now tend to limit use of this drug to controlling pheochromocytoma crises—for example, during operation or during spontaneous or induced paroxysms of hypertension.

In screening patients for pheochromocytoma, the biochemical or the pharmacological tests occasionally may give false results. Results of subsequent studies are nearly always normal in nontumor patients. For reasons that are not clear, some tumor patients never respond to histamine; others may have normal excretion of CA or of one or another of its metabolites on repeated determinations. In these cases, additional biochemical or pharmacological tests are necessary to confirm the diagnosis of pheochromocytoma. Other functioning tumors of the neural crest (ganglioneuroblastoma) and chemodectomas can excrete CA and its metabolites and must be considered in the differential diagnosis. Reliable diagnosis of pheochromocytoma still must be based on multiple studies in an appropriate clinical setting.

Summary

The pharmacological and biochemical tests available for the diagnosis of pheochromocytoma were evaluated among 28 patients with proved tumors and 148 other patients in whom the diagnosis was suspected. Of the biochemical tests on urine, determinations of total metanephrines (MN) and of vanilmandelic acid (VMA) were much less subject to false-positive results than was determination of catecholamines (CA). Since urinary MN values changed the most in tumor patients, MN determination is preferred as the current screening test. Of the pharmacological tests, the histamine test continues to be the most valuable, especially when combined with determination of plasma CA concentration. The phentolamine (Regitine) test has not proved to be of any distinct value as a primary diagnostic aid. Any of the chemical or pharmacological tests occasionally may give a false-positive result. The urinary output of excessive amounts of homovanillic acid (HVA) was an indication of the presence of pheochromocytoma with some features histologically similar to other neural crest tumors but was not an indication of malignancy. Reliable diagnosis of pheochromocytoma still must be based on multiple studies in an appropriate clinical setting.
References


200 Years Ago—Reflection of an Aged (Curmudgeonish?) Genius

When Linnaeus, at an advanced period of life, published for the last time in the year 1766, his System of Nature, that monument of his immortality, he concluded it with the following declaration of his past conduct. "I have ranged through the thick and shady forests of "nature, I have to and fro found sharp and perplexing thorns, I have "as much as possible avoided them; but I learned at the same time, that "foresight and attention do not always conciliate perfect and entire safety. "I have therefore "quietly borne the derision of grinning satyrs, and the "jumps of monkies upon my shoulders. I have entered the career and "completed the course assigned by fate."—D. H. Stoever: The Life of Sir Charles Linnaeus. (Translated by Joseph Trapp.) London, B. & J. White, 1794, p. 139.
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