The Yalca Journal of Biology and Medicine 57 (1984), 259-272

A Clinical Scoring System for Detection of Patients with Pheochromocytomas

HENRY R. BLACK, M.D., AND STUART L. BURSTEN, M.D.

Department of Internal Medicine, Section of General Medicine, Primary Care Center, Hypertension Clinic, Yale University School of Medicine, New Haven, Connecticut

Received September 7, 1983

We analyzed the medical records of patients admitted to 11 hospitals over a 15-year period, looking for those with metabolically active sporadic pheochromocytomas (Group A) and those in whom the diagnosis was highly suspect but excluded (Group B). Fifty-three patients in Group A and 25 patients in Group B were found. We then devised a scoring system based on the presence or absence of typical symptoms and signs (SSS) and another which also included the results of routine 24-hour urine studies for catecholamines or metabolites (SSLS). The point values given for each symptom and sign were based on those felt to be most characteristic of the disease and points were subtracted if the typical manifestation was absent. Additional points were given if the symptom or sign were paroxysmal. In a high-risk population, the sensitivity of the SSS and the SSLS was 96 percent and the specificity was 64 percent and 88 percent, respectively. The predictive value of a positive SSS was 85 percent and of a positive SSLS was 94 percent. In a large group of patients with essential hypertension (Group C) only 17 of 395 (4.4 percent) had a positive SSS and only one of 385 had a positive SSLS. We feel this scoring system can help detect those hypertensive patients in whom further extensive and potentially invasive evaluation is warranted.

Pheochromocytoma is perhaps the most reliably curable and dangerous cause of secondary hypertension [1]. Although the prevalence of pheochromocytomas in hypertensive patients is less than 0.1 percent [1,2,3], it is critically important to find patients with this tumor. Not only can most patients be cured of their hypertension by surgery, but also they run serious additional risks due to the metabolic and cardiovascular consequences of catecholamine excess and the small but definite possibility of malignancy [4,5].

The detection of patients with pheochromocytomas is not difficult. All cases could presumably be found if every patient with hypertension or symptoms suggestive of pheochromocytoma were screened using urine catecholamines, vanillylmandelic acid (VMA), and/or metanephrines [6]. The cost and inconvenience of this approach, however, would be prohibitive. Manger and Gifford calculated that $34,000 (1977 dollars) would be spend for each patient with pheochromocytoma found using urinary screening [1]. Since most patients with pheochromocytomas are symptomatic, often dramatically so, we felt that we could devise a scoring system based on the symptoms and signs commonly seen in these patients and identify the segment of the hypertensive population most likely to have the tumor. We hoped to

Address reprint requests to: Henry R. Black, M.D., Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510
Copyright © 1984 by The Yale Journal of Biology and Medicine, Inc.
All rights of reproduction in any form reserved.
BLACK AND BURSTEN
device a system sensitive enough to include all or almost all patients with pheochromocytomas but specific enough to reduce substantially the population at risk for further unnecessary evaluation, and thus reduce the cost per tumor found. The system was tested in patients with known pheochromocytomas (Group A—the cases) and two control groups. One (control Group B) were patients admitted to the hospital for evaluation presumably because their attending physician had a strong clinical suspicion that they may have a pheochromocytoma. In all these patients the tumor was excluded. A second control group were 385 consecutive unselected patients of the Yale–New Haven Hospital Hypertension Clinic with essential hypertension (control Group C).

METHODS

We devised a scoring system prior to chart analysis. This system assigned weighted values to the symptoms and signs felt to occur with highest prevalence and to be most typical of patients with pheochromocytomas (Table 1) [1]. Points were subtracted from a patient’s score if a characteristic manifestation of the disease was absent. The number of points subtracted when a symptom or sign was missing was also based on our estimation of the importance of that feature. Specific urinary

| TABLE 1  |
|----------|
| Scoring System for Case-Finding of Pheochromocytoma |

| Symptoms | If Present | With Paroxysm | Absent |
|----------|------------|---------------|--------|
| Headache | +6 | +8 | -3 |
| Palpitations | +6 | +8 | -4 |
| Sweating | +5 | +6 | -3 |
| Fatigue | +3 | - | -2 |
| Weight loss | +2 | - | -1 |
| Flushing | +1 | - | -1 |
| Other symptoms (including dyspnea, anxiety, weight gain, dizziness and syncope) | +1 | - | - |

**Signs:**

If BP is less than 140/90, −5.
If systolic BP is less than 140, diastolic BP 90–110, +5.
If systolic BP, 140–170, diastolic BP 90–110, +6.
If systolic BP is greater than 170, diastolic BP 90–110, +7.
If systolic BP is greater than 170, diastolic BP greater than 110, +8.
For documented paroxysm, add +2.
If resting pulse rate is greater than or equal to 100, +2.
If resting pulse rate is less than 100, −1.

Blood pressure in mmHg and pulse rate in beats per minute.

**Urine Chemistries:**

If test is not done, 0.
If test is “positive” for catecholamines, +4. If “negative,” −5.
If urine was fractionated into epinephrine and norepinephrine, and is positive for either, +2 for each positive value. If negative, −3.
If test is “positive” for VMA, +1. If “negative,” −2.
measurements of catecholamines or their metabolites were the only laboratory data used in calculation of a score for each patient.

Cases (Group A) and control Group B were found by retrieving all of the charts of patients discharged from eleven New England hospitals from 1962-1980 for whom the diagnosis of pheochromocytoma or "suspected pheochromocytoma" was made. Three of these hospitals, two private and one Veterans Administration Hospital, were major teaching hospitals, while the other eight were community hospitals affiliated with the Yale University School of Medicine. The charts were reviewed and points assigned without knowledge of whether or not the patient had a pheochromocytoma. The admission history and physical examination of the attending physician and house officers was the major source of data, but we used any pertinent information reported in the chart, either obtained prior to admission or discovered during the hospitalization. We paid special attention to whether or not the symptoms reported were paroxysmal. The presence or absence of each sign, symptom, and urinary catecholamines or other metabolites was determined and summed, and each patient was assigned a score.

The patients of the Yale–New Haven Hypertension Clinic served as an additional control population (Group C). This was a consecutive and unselected group of patients self-referred or referred for care from several sources in the community and is representative of the general hypertensive population. All of these patients had been followed for at least a year when this analysis was done and have been followed for another 36 months. None had or have developed a pheochromocytoma. Complete data about the presence or absence of the symptoms included in the scoring system, blood pressure and heart rate levels at referral and first visit, and urinary catecholamine values when obtained had been previously abstracted from the patients' medical records and stored in the Yale IBM 370. Data was analyzed using SAS, release 79.4B [7]. Each patient in this group was assigned a score, as were the patients in Groups A and B.

**Criteria for Symptoms**

*Headache* A characteristic headache is the most common symptom in patients with pheochromocytoma [1]. Since headaches are so prevalent in the general population, in Groups A and B we chose to consider only those described in the record as throbbing and bilateral as positive. We gave six points if this symptom was present, eight additional points if this symptom was paroxysmal, and subtracted three if this characteristic symptom was absent. In Group C, any complaint of headache was considered positive. Since we did not review each of these charts to obtain a description of the headaches, we chose to consider any notation of a headache as positive. This may artificially increase the scores in Group C but, since a screening test should be 100 percent sensitive and not leave out any patients who might have the disease in question, we felt this was justified.

*Palpitations* Palpitations are, perhaps, the next most common symptom in patients with the tumor. Those patients who reported palpitations were given six points, eight additional if paroxysmal, and one more if the palpitations were associated with chest pain. Four points were subtracted if no palpitations were reported.

*Sweating* Sweating is also a characteristic complaint in patients with pheochromocytoma. Patients in whom this symptom was recorded were given five points, six additional if paroxysmal, and three points were subtracted if the symptom was not mentioned in the medical record.
Other Symptoms Several other symptoms are commonly reported in patients with pheochromocytoma but are not seen as often as headache, palpitations, or sweating. These include fatigue, weight loss of greater than ten pounds since the onset of hypertension, and flushing. These and other less common and more non-specific symptoms were also looked for and assigned what we felt were more appropriate point values. (Refer to Table 1.)

Criteria for Signs

Hypertension An elevated blood pressure is, of course, the most common sign in patients with this tumor. We chose to use the highest blood pressure noted or recorded in the medical record, whether or not that reading represented a value actually obtained on that admission. Patients were defined as having paroxysmal hypertension if we could document a sudden change or at least 30 mmHg systolic and 15 mmHg diastolic on at least two or more occasions not associated with anti-hypertensive therapy. (Refer to Table 1 for point values.)

Orthostatic hypotension is often described as being a characteristic feature in patients with pheochromocytoma. In our study, however, we could not use this finding since postural changes in blood pressure were rarely recorded.

Tachycardia We considered resting pulse rates only and those which were not affected by therapy (Table 1). Standing pulse rates may exceed 100 beats per minute for many reasons and so are not specific enough to be useful. As with blood pressure, data on the change in pulse rating with sitting or standing was not complete enough to be used for the scoring system.

Other Signs We neither added nor subtracted for other physical signs commonly reported such as hyperhidrosis, severe retinopathy, fever, or abdominal masses.

Criteria for Laboratory Values

Urinary Catecholamines and Their Metabolites Total urinary catecholamines were used as a screening test in most of those patients in Groups A and B although several only had VMA studies. We recorded the actual level of the highest reported sample when available. In a few patients, urinary samples were fractionated into norepinephrine and epinephrine. We considered the value as "normal" or "abnormal" according to the norms for each hospital. Point values were assigned if the levels were abnormal and subtracted if not, whatever the absolute level (Table 1).

Other Laboratory Tests Although some routine laboratory values such as serum glucose and hematocrit are often abnormal in patients with pheochromocytoma, we felt these tests were too nonspecific to warrent being included in our point score. No patients in this group had plasma catecholamines measured as a screening test. In all instances, radiological procedures were undertaken after the diagnosis of pheochromocytoma was already suspected.

Criteria for Diagnosis

Pheochromocytoma Present (Group A) All patients classified as having a pheochromocytoma had a surgical or postmortem specimen considered consistent with this diagnosis by the attending pathologist at the respective institution. In no patients in this group was there any doubt expressed about the proper histologic diagnosis.

Pheochromocytoma Absent (Group B) All of these patients had negative arteriograms and no evidence of pheochromocytoma after at least eighteen months
follow-up. This was either documented later in the medical record or, in four instances, by direct contact with the attending physician. No patients were directly contacted. In one patient (number 61), the clinical suspicion of pheochromocytoma was so high that she underwent bilateral adrenal vein catheterization and eventual unilateral adrenalectomy but no tumor was found. Any patients whose adequate diagnostic or follow-up information was incomplete was excluded from the study.

We arbitrarily defined 9 as a positive symptom and sign score (SSS), and 13 as positive when laboratory work, urinary catecholamine, or metabolite studies were included (symptom, sign, and laboratory score—SSLS).

RESULTS

Sixty patients with proven pheochromocytomas were found (Table 2). Fifty-four were patients with sporadic pheochromocytomas and six were patients with multiple endocrine adenomatosis (MEA), Type 2. Since the pheochromocytomas in several patients with MEA, Type 2, were discovered because of their family history rather than their symptoms, we have chosen not to include them in any further analysis. Similarly, we have excluded the one asymptomatic, normotensive patient whose tumor was found at autopsy and probably was metabolically inactive. The remaining 53 patients constitute Group A. Two of these tumors (3.3 percent) were malignant and four patients had died (one post-operatively of shock, the case discovered incidentally at autopsy, and the two with malignancies). Twenty-five patients in Group B were found.

Of the patients with metabolically active sporadic pheochromocytomas (Group A), 51 had a symptom and sign score (SSS) of nine or more and 50 of the 53 had a symptom, sign, and laboratory score (SSLS) of 13 or more. In Group B (Table 3) 9 patients had an SSS of 9 or more, but only 3 had an SSLS of 13 or more. These results are graphically represented in Fig. 1. The symptoms and signs found in the patients of Groups A and B are shown in Table 4.

Of the 385 patients in Group C, only 17 (4.4 percent) had an SSS of 9 or more, thereby suggesting that screening urine studies were indicated. In these 17 patients, urinary studies had been obtained in 14 and all were normal. Adequate follow-up data eventually confirmed that none of these patients had a pheochromocytoma. Only one of these patients had an SSLS of 13 or more. No further diagnostic procedures have been done, and the patient is well with no evidence of a pheochromocytoma after more than three years of follow-up.

Treating the SSS and SSLS as if they were laboratory tests, we calculated the sensitivity, specificity, accuracy of a positive prediction (predictive value) and the accuracy of a negative prediction (exclusion value) as recommended by Ransohoff and Feinstein [8].

We first performed these calculations for the high-risk patients (Groups A and B) (Table 5). Then, in order to get a better idea of the value of this scoring system in a more general population, we recalculated the data for Groups A, B, and C combined (Table 6). Since three of the patients in Group C did not have urinary catecholamines obtained, we assumed, for the sake of the analysis, that these had been done and were positive.

The sensitivity, specificity, predictive value, and exclusion value are listed in Table 5 for high-risk patients (Groups A and B) and in Table 6 for our estimate of the more general population (Groups A, B, and C).
| Case Number | Sex, Age | Referred for | BP, in mmHg | Urinary Catecholamines (C) or Vanillylmandelic Acid (VMA) | SSS | SSLS | Arteriogram |
|-------------|---------|--------------|-------------|-----------------------------------------------------------|-----|------|-------------|
| 1           | M, 24   | HBP, retinopathy | 170/120-220/140 | C+, 1,800                                                  | 32  | 36   | +           |
| 2           | M, 53   | HBP, palpitations | 200/130-280/150 | C+, 1,690                                                  | 32  | 36   | +           |
| 3           | F, 44   | HBP, sweating   | 150/100-175/110 | C+, nepi = 1,710                                           | 32  | 38   | +           |
| 4           | F, 13   | HBP, headache   | 150/80-250/110  | C+, 1,150                                                  | 32  | 36   | +           |
| 5           | M, 22   | HBP             | 140/80-160/100  | C+                                                        | 31  | 35   | +           |
| 6           | F, 16   | HBP             | 140/80-190/120  | C+, nepi = 980                                            | 29  | 35   | +           |
| 7           | M, 59   | HBP             | 200/100-230/110 | C+, VMA+                                                   | 28  | 33   | +           |
| 8           | F, 35   | Flushing, palpitations | 100/70-170/120 | C+                                                        | 28  | 32   | +           |
| 9           | M, 39   | HBP             | 160/110-180/120 | C+                                                        | 27  | 31   | +           |
| 10          | M, 36   | HBP             | 180/90-210/150  | C+, 930                                                    | 27  | 31   | +           |
| 11          | F, 22   | Headache        | 200/120        | C+, 1,120                                                  | 27  | 31   | +           |
| 12          | M, 31   | HBP             | 140/100-240/120 | C+, 1,000                                                  | 27  | 31   | +           |
| 13          | M, 49   | Palpitations    | 150/100-250/130 | VMA+                                                      | 27  | 38   | +           |
| 14          | F, 30   | HBP             | 140/90-160/120  | C+, 1,274                                                  | 26  | 30   | +           |
| 15          | M, 19   | Headache, flushing | 160/100-180/120 | C+, 980                                                    | 25  | 29   | -           |
| 16          | F, 61   | HBP             | 160/70-210/140  | C+                                                        | 25  | 29   | +           |
| 17          | M, 23   | HBP, headache   | 150/120-220/180 | C+, 875                                                    | 25  | 31   | -           |
| 18          | F, 14   | HBP, headache   | 150/110        | C+, 1,500                                                  | 24  | 28   | -           |
| 19          | F, 39   | HBP             | 140/70-260/110  | C+, 415                                                    | 24  | 28   | +           |
| 20          | M, 63   | HBP             | 150/90-260/140  | C+, 750                                                    | 24  | 28   | +           |
| 21          | M, 53   | HBP             | 140/90-200/100  | C+                                                        | 23  | 27   | +           |
| 22          | F, 65   | HBP             | 180/90         | C+, 1,240                                                  | 22  | 26   | +           |
| 23          | F, 35   | HBP             | 170/100-190/110 | C+, 960                                                    | 22  | 26   | +           |
| 24          | F, 51   | HBP             | 170/100        | C+, 1,262                                                  | 21  | 16   | -           |
| 25          | F, 23   | HBP             | 130/90-170/120  | C+, 1,262                                                  | 19  | 23   | +           |
| 26          | M, 82   | HBP             | 160/100-180/110 | C+                                                        | 19  | 13   | -           |
| 27          | F, 28   | HBP, palpitations | 128/90-175/110 | C+                                                        | 19  | 23   | +           |
| 28          | F, 51   | HBP             | 150/110-230/150 | C+, 969                                                    | 18  | 22   | +           |
| 29          | M, 58   | Paroxysmal HBP  | 120/80-250/140  | C+, 990                                                    | 18  | 22   | +           |
| 30          | M, 48   | HBP             | 120/80-140/90   | C+                                                        | 18  | 22   | +           |
| 31          | F, 59   | Headache, weight loss | 140/100-250/110 | C+                                                        | 18  | 22   | +           |
| PHEOCHROMOCYTOMA SCORING SYSTEM | 265 |
|----------------------------------|-----|
|                                |     |
|                                |     |
| Case Number | Sex, Age | Referred for      | BP, in mmHg | Urinary Catecholamines (C) or Vanillylmandelic Acid (VMA) | SSS | SSLS | Arteriogram |
|-------------|----------|------------------|-------------|--------------------------------------------------------|-----|------|-------------|
| 61          | F, 45    | HBP, sweating    | 170/90-310/140 | —            | 33  | +31  | —           |
| 62          | F, 56    | Weight loss      | 160/100     | VMA+         | 18  | 22   | —           |
| 63          | F, 39    | Tremulousness    | 140/100     | C+           | 16  | 20   | —           |
| 64          | M, 54    | Palpitations     | 130/110-170/120 | —       | 14  | 12   | —           |
| 65          | F, 56    | HBP, anxiety     | 190/100     | —            | 14  | 12   | —           |
| 66          | F, 21    | Headache, weight loss | 160/90     | —            | 13  | 11   | —           |
| 67          | F, 46    | HBP, back pain   | 160/100     | —            | 12  | 10   | —           |
| 68          | M, 25    | Flushing         | 180/100     | VMA+         | 10  | 11   | —           |
| 69          | M, 31    | HBP, palpitations | 136/80-170/100 | —       | 9   | 7    | —           |
| 70          | M, 48    | HBP              | 160/100     | C+           | 5   | 9    | —           |
| 71          | M, 24    | HBP, tachypnea   | 136/80      | C+           | 1   | 5    | —           |
| 72          | F, 26    | HBP, palpitations | 110/70     | C+           | 0   | 4    | —           |
| 73          | M, 49    | HBP              | 170/90      | —            | -3  | -5   | —           |
| 74          | M, 45    | Weight loss      | 140/90      | C+           | -3  | +1   | —           |
| 75          | M, 19    | HBP              | 170/80      | C+           | -5  | -1   | —           |
| 76          | F, 34    | HBP              | 160/70      | —            | -6  | -8   | —           |
| 77          | F, 47    | HBP              | 150/90      | —            | -6  | -8   | —           |
| 78          | F, 85    | Syncope          | 140/90-170/100 | VMA+ | -6  | -2   | —           |
| 79          | M, 27    | HBP              | 140/90      | C+           | -8  | -4   | —           |
| 80          | M, 58    | HBP, syncope     | 150/100-200/110 | —       | -8  | -10  | —           |
| 81          | M, 19    | HBP              | 140/90      | —            | -10 | -12  | —           |
| 82          | M, 24    | HBP              | 150/100     | VMA+         | -13 | -9   | —           |
| 83          | F, 34    | HBP              | 160/80      | —            | -15 | -17  | —           |
| 84          | M, 24    | HBP, tachypnea   | 136/80      | C+           | -17 | -13  | —           |
| 85          | M, 47    | Epigastric pain  | 110/70      | —            | -19 | -21  | —           |
TABLE 4
Symptoms in Patients with Metabolically Active Sporadic Pheochromocytoma (Group A)

| Symptom                             | Percentage of total patients (N = 53) | Paroxysmal |
|-------------------------------------|--------------------------------------|------------|
| Headache                            | 96                                   | 70         |
| Excess sweating                     | 74                                   | 64         |
| Palpitations                        | 70                                   | 64         |
| Chest and epigastric pain           | 50                                   | 48         |
| Anxiety, dread                      | 46                                   | -          |
| Fatigue, weakness                   | 40                                   | -          |
| Weight loss (>10 pounds)            | 25                                   | -          |
| Dyspnea                             | 10                                   | -          |
| Flushing                            | 8                                    | -          |
| Nausea with and without vomiting    | 10                                   | -          |

Symptoms in Patients without Pheochromocytoma (Group B)

| Symptom                             | Percentage of total patients (N = 25) | Paroxysmal |
|-------------------------------------|--------------------------------------|------------|
| Headache                            | 67                                   | 12         |
| Excess sweating                     | 37.5                                 | 8          |
| Palpitations                        | 29                                   | 5          |
| Fatigue, weakness                   | 33                                   | -          |
| Anxiety, dread                      | 29                                   | -          |
| Weight loss                         | 8                                    | -          |
### TABLE 5
High-Risk Patients—Groups A + B

| Pheochromocytoma | SSS | SSLS |
|-------------------|-----|------|
| Yes (+)           |     |      |
| No (−)            |     |      |
| (> 8)             | 51  | 9    |
| (≤ 8)             | 2   | 16   |

| Pheochromocytoma | SSS | SSLS |
|-------------------|-----|------|
| Yes (+)           |     |      |
| No (−)            |     |      |
| (> 12)            | 51  | 3    |
| (≤ 12)            | 2   | 22   |

#### Sensitivity
- SSS: 51/51 = 96%
- SSLS: 51/51 = 96%

#### Specificity
- SSS: 53/53 = 100%
- SSLS: 16/16 = 100%

#### Accuracy of positive prediction (predictive value)
- SSS: 51/51 = 100%
- SSLS: 51/51 = 100%

#### Accuracy of negative prediction (exclusion value)
- SSS: 16/16 = 100%
- SSLS: 18/18 = 100%

### TABLE 6
More General Hypertension Population (Groups A, B, and C)

| Pheochromocytoma | SSS | SSLS |
|-------------------|-----|------|
| Yes (+)           |     |      |
| No (−)            |     |      |
| (> 8)             | 51  | 26   |
| (≤ 8)             | 2   | 384  |

| Pheochromocytoma | SSS | SSLS |
|-------------------|-----|------|
| Yes (+)           |     |      |
| No (−)            |     |      |
| (> 12)            | 51  | 4    |
| (≤ 12)            | 2   | 406  |

#### Sensitivity
- SSS: 51/51 = 96%
- SSLS: 51/51 = 96%

#### Specificity
- SSS: 384/410 = 94%
- SSLS: 406/410 = 99%

#### Accuracy of positive prediction (predictive value)
- SSS: 51/51 = 100%
- SSLS: 51/51 = 100%

#### Accuracy of negative prediction (exclusion value)
- SSS: 384/386 = 99.4%
- SSLS: 406/408 = 99.5%
DISCUSSION

The conscientious and thorough physician who is also cost-conscious has a serious dilemma when evaluating patients with hypertension. Curable secondary causes of hypertension are very rare, but usually there are clinical or laboratory clues which help raise the physician’s index of suspicion and guide him or her to the right diagnosis. For primary aldosteronism, serum $K^+$ is almost always abnormal, and this inexpensive non-invasive test is an excellent case-finding tool to discover patients with this disease. Patients with renovascular hypertension will often have abdominal bruits, and Grim and colleagues have recently shown that the presence of this physical finding is as good as any laboratory or radiological test in finding patients with this condition [9]. The patient with a pheochromocytoma, on the other hand, can be very difficult to diagnose, and there is a strong possibility of a rapidly lethal outcome, if the tumor is missed or the patient mismanaged. Fortunately, a reliable case-finding test exists for this tumor, namely, timed urine collections for catecholamines or metabolites. Unfortunately, as Manger and others have pointed out [1,10,11], the cost of screening all hypertensive patients to find the one in a thousand with the tumor would be financially prohibitive [1].

Most patients with pheochromocytomas are symptomatic, often in a characteristic way. We felt that a clinical scoring system, based on a properly weighted score, could first help us select those patients in whom urine studies should be done and then, second, when those results were available, predict which patients were most likely to have the tumor, and thus warrant more invasive and dangerous studies.

The choice of which symptoms and signs to include in the system was based on those reported most commonly to occur in patients with pheochromocytomas. We gave special weight to the paroxysmal nature of the symptoms and blood pressure, not only because these are often seen in patients with pheochromocytomas, but because such “attacks” are relatively unusual in patients with other causes for hypertension, even if they have many of the characteristic complaints. We hoped to improve the sensitivity and specificity of the system by subtracting points when typical symptoms or signs were not present and when urine studies were not elevated. Since we felt that our results could be seriously biased if the chart reviewer (SB) knew whether the patient did or did not have a pheochromocytoma when he abstracted the medical record, all records were requested at the same time and the scores assigned before he knew if the patient had a tumor. The way the system was designed, most of the data which required subjective assessment was obtained from the initial history and physical examination and most, if not all, these patients would not have had a definite diagnosis made until considerably later in their hospitalization.

Our series of cases is reasonably large, but the fact that we could only find 60 patients in an eighteen-year period in eleven hospitals emphasizes the rarity of this condition. We feel that we have included all patients with the disease who were admitted during this time period and that there were no other evident sources of bias in the assignment of the scores.

Patients with tumors associated with familial conditions are different. They are often discovered before symptoms occur. Once a member or members of their family are found to have a medullary carcinoma of the thyroid or other features of the MEA type 2 syndrome, medical surveillance increases and asymptomatic disease is found. Thus, we did not include this group in our analysis.
Our scoring system appears a very valuable tool. It uses only data obtained from a careful history and physical examination and non-invasive and inexpensive laboratory tests and adds neither risk nor cost to the evaluation of patients likely to have a pheochromocytoma. We have chosen to both add and subtract points in an attempt to make this system a more powerful discriminator. When studying a disease with such a characteristic clinical presentation, the absence of a typical symptom is just as important as its presence and so we chose to take points away if the finding was not in evidence. Others have also subtracted points when using clinical information to generate a score to assist in clinical decision making [12]. The symptom and sign score is sensitive enough (96 percent) to select those patients who should undergo the expense and inconvenience of collecting a 24-hour urine with the assurance that few patients with the disease will be missed. In fact, this sensitivity is comparable to that reported in the literature for arteriography (83 percent) [13] and the 87 percent sensitivity (46 of 53) arteriography had in Group A in our series. The specificity in an unselected group of hypertensive patients, none of whom had the disease, was 95.6 percent. So in only 4.4 percent of the hypertensive population would it be necessary to collect urinary studies, and only one of 385 patients had a high enough SSLS to warrant further work-up to exclude a pheochromocytoma. Even in the patients whose history and physical examination suggested they had a pheochromocytoma (Group B), only 9 of 25 (36 percent) would have had urine studies done and only 3 of 25 (12 percent) would have been evaluated with invasive and expensive procedures, which had been done in all of those patients.

The ability of any diagnostic test or scoring system to find cases of a rare disease in a large population is limited. If there are any false-positive tests, the predictive value of a positive test becomes small, and the test loses its utility. The value of any test can be increased, if the prevalence of the disease can be increased by more carefully defining the population in whom the test should be done. Since we did not screen an unselected group of patients to find our cases, we do not really know how valuable our scoring systems would be in the general hypertensive population. We attempted to overcome this shortcoming in two ways. First, since we feel that we have included all cases admitted to these eleven hospitals during the years of the study, we feel we can accurately calculate the accuracy of a positive or negative prediction of the SSS or SSLS and in high-risk populations (Groups A and B). For both scores, the accuracy in these groups is quite good (Table 5). By adding in the patients from a large unselected population from the Yale Hypertensive Clinic (Group C), we tried to estimate more correctly the predictive and exclusion values of the scoring systems in a general hypertensive population. The values of 66.1 percent and 99.4 percent for SSS and 93 percent and 99.5 percent for SSLS appear to make the tests valuable, but the prevalence of pheochromocytoma in these undetermined populations is inordinately high (11 percent, 53/463) and may not offer an estimate of the value of the test. By using it, however, we are able to pick out the 4.4 percent of the patients most likely to need urine studies and the one in 385 in whom invasive work-up might have been indicated.

Recently, a group of French workers have published a study similar to ours. They questioned 2,585 unselected hypertensive patients, looking for those with attacks of headaches, palpitations, and sweating [14]. In their series, only 6.5 percent had all three symptoms and 10 of the 11 patients with pheochromocytomas were included in that group. The sensitivity (93.8 percent), specificity (90.8 percent), and exclusion value (99.9 percent) appear quite good. But the predictive accuracy was only 5.9 percent (10/170) in their high-risk population (those with all three symptoms), com-
pared to 85 percent using the SSS in Groups A and B in our study. Thus we feel the additional data obtained to generate our SSS and SSLS contribute significantly to the value of this approach.

Many new laboratory techniques to diagnose pheochromocytomas have been proposed. None of our patients, for example, had plasma catecholamines measured. Several authors have recently suggested that measuring these levels may be very helpful in screening hypertensive patients for pheochromocytomas [15,16]. It is our feeling that the conditions under which these studies should be performed are still unclear, that the methodology is difficult to perform properly in routine laboratories, and that the cost would be prohibitive if these measurements were done in the general hypertensive population. Abdominal computerized axial tomography has recently become a valuable adjunct to the radiologic methods used to locate pheochromocytomas [17]. The sensitivity of this test is excellent (91 percent), but the expense and the risk of contrast-induced catecholamine crisis is too high to expect that this test will be useful as a case-finding tool in unselected hypertensive patients.

The utility of other new methods such as $^{131}$I meta-iodobenzylguanidine scanning [18] or measurements of platelet catecholamine concentrations [19] are still uncertain. All of these techniques may make positive diagnosis more rapid and certain, but clinical tools will still be needed to select properly those patients in whom the tests should be performed.

We feel that our scoring system properly quantifies the signs and symptoms in patients with pheochromocytoma so that the clinicians can apply case-finding techniques in a population where the prevalence of this rare disease has been significantly augmented. Should this prediction prove valid, then historical data and careful blood pressure and pulse measurements will cheaply and accurately find the patients at risk of this lethal tumor without spending our limited resources needlessly. We would hope that when the clinician suspects that his or her patients might have a pheochromocytoma, he or she will use Table 1 to determine SSS and to decide whether it's worth spending money on urinary catecholamines or metabolites. If so, once these studies have been done, then he or she can then determine the SSLS and decide whether to proceed on to more expensive, invasive, and dangerous procedures. Whether or not this scoring system will be discriminating enough to quantify clinical judgment cannot be determined from this retrospective analysis. Only its use in a prospective fashion in large groups of hypertensive patients can answer that question.

ACKNOWLEDGEMENTS

The authors are very grateful to Ms. Joanne Tuscano for her expert secretarial help; to Robert Silton and Susan Eberle Levy for assistance in analyzing the data; and to Dr. Lewis Landsberg of the Beth Israel Hospital in Boston, and to the Chiefs of Medicine at the Hospital of St. Raphael (Norman Marieb), Norwalk Hospital (Martin Floch), St. Vincent's Hospital (Everett Cooper), Greenwich Hospital (James Bernene), Danbury Hospital (Joseph Belsky), St. Mary's Hospital, Waterbury (Robert Piscatelli), Waterbury Hospital (George Thornton), and Lawrence and Memorial Hospital (David Lauler) for allowing us to study and include patients seen at their institutions.

REFERENCES

1. Manger WM, Gifford RM: Pheochromocytoma. New York, Springer-Verlag, 1977
2. Graham JB: Pheochromocytoma and hypertension: An analysis of 207 cases. Int Abstr Surg 92:105-121, 1951
3. Minno AN, Bennett WA, Kvale WF: Pheochromocytoma: A study of 15 cases diagnosed at autopsy. New Eng J Med 251:959-965, 1954
4. Baumgarten EC, Cantor MO: Pheochromocytoma: Case report. Ann Surg 111:112-116, 1940
5. Ross EJ: The management of cases of pheochromocytoma: Clinical Staff Conference, University College Hospital, London. Proc R Soc Med 55:427-436, 1962
6. Sjoerdsma A, Egneiman K, Waldman TA, et al: Pheochromocytoma: Current concepts of diagnosis and treatment. Ann Int Med 65:1302-1325, 1966
7. Helwig JT, Council KA (ed): SAS User's Guide. Raleigh, NC, SAS Institute, 1979
8. Ransohoff DF, Feinstein AR: Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. New Eng J Med 299:926-930, 1978
9. Grim CE, Luft FC, Weinberger MH, et al: Sensitivity and specificity of screening tests for renal vascular hypertension. Ann Int Med 91:617-622, 1979
10. Oliver DO: The diagnosis and management of pheochromocytoma. Hosp Med 2:1279-1284, 1968
11. Philops PJ, Colas ME, Wise PH: Cost of diagnosis of pheochromocytoma. Med J Aust 2:406-407, 1975
12. Kramer MS, Leventhal JM, Hutchinson TA, et al: An algorithm for the operational assessment of adverse drug reactions. JAMA 242:623-632, 1979
13. Zelch JV, Meaney TF, Belhobell GH: Radiologic approach to the patient with suspected pheochromocytoma. Radiology 111:279-284, 1974
14. Plouin PF, Degoulet P, Tugaye A, et al: Le depistage du pheochromocytome: chez quels hypertendus? La Nouvelle Presse Medicale 10:869-872, 1981
15. Bravo EL, Tarazi RC, Gifford RW, et al: Circulating and urinary catecholamines in pheochromocytoma. New Eng J Med 301:682-686, 1979
16. Aronoff SL, Passamani E, Borowsky BA, et al: Norepinephrine and epinephrine secretion from a clinically epinephrine-secreting pheochromocytoma. Am J Med 69:321-324, 1980
17. Stewart BH, Brown EL, Haaga J, et al: Localization of pheochromocytoma by computed tomography. New Eng J Med 299:460-461, 1978
18. Sisson JC, Frager MS, Valk TW, et al: Scintigraphic localization of pheochromocytoma. New Eng J Med 305:12-17, 1981
19. Zweifler AJ, Julius S: Increased platelet catecholamine content in pheochromocytoma. New Eng J Med 306:890-894, 1982