

## SEASONAL CHANGES IN BLOOD PRESSURE IN PATIENTS WITH END-STAGE RENAL DISEASE TREATED WITH HEMODIALYSIS

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**ABSTRACT**

**Background** Many factors contribute to the regulation of blood pressure. The role of climate has received relatively little attention.

**Methods** During a four-year period, we determined the influence of climate on blood pressure in 53 patients with end-stage renal disease treated with hemodialysis. For each patient, blood pressure was measured before each of three dialysis treatments per week for an average of 31 months. The dose of dialysis (urea clearance multiplied by the length of dialysis and divided by the distribution volume of urea) and protein catabolism rate were assessed monthly. We then analyzed the monthly mean values for blood pressure, pulse, and body weight in relation to the monthly values for temperature, relative humidity, and atmospheric pressure recorded in Montpellier, France.

**Results** The maximal monthly temperature varied from 10°C in the winter to 31°C in the summer, and the minimal monthly temperature from 1 to 20°C. The mean ( $\pm$ SE) systolic and diastolic blood pressure was highest during the winter ( $153\pm 3/82\pm 2$  mm Hg) and lowest during the summer ( $141\pm 3/75\pm 2$  mm Hg). The seasonal pattern was evident throughout the four-year period. Blood pressure was correlated inversely with monthly maximal temperature ( $r=-0.65$  and  $P<0.001$  for systolic pressure;  $r=-0.71$  and  $P<0.001$  for diastolic pressure) and directly with minimal humidity ( $r=0.45$  and  $P=0.002$  for systolic pressure;  $r=0.43$  and  $P=0.003$  for diastolic pressure). Changes in protein catabolic rate, weight gain between dialysis sessions, and dialysis dose were not related to changes in blood pressure.

**Conclusions** In patients with end-stage renal disease treated with hemodialysis, blood pressure varies seasonally, with higher values in the winter and lower values in the summer. (N Engl J Med 1998;339:1364-70.)

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**C**ARDIOVASCULAR disorders (stroke and ischemic heart disease) are an important cause of morbidity and mortality in the general population and in patients with end-stage renal disease treated with dialysis.<sup>1-5</sup> Hypertension is a major risk factor for cardiovascular events; the prevalence of sustained hypertension in patients on dialysis, indicated by the presence of left ventricular hypertrophy, has been reported to be over 50 percent,<sup>6,7</sup> and good control of hypertension prolongs survival in such patients.<sup>8</sup>

In patients with end-stage renal disease, blood pres-

sure may be maintained within the normal range by correcting extracellular volume excess with dialysis.<sup>8</sup> However, many patients on dialysis require antihypertensive-drug therapy. According to the European Dialysis and Transplantation Association Registry, only 18 percent of patients on dialysis received no antihypertensive drug in 1991.<sup>9</sup> Although failure to remove excess fluid by dialysis contributes to resistant hypertension, other factors (inappropriate response of the renin-angiotensin system, endothelium-derived vasopressor and vasodilating factors, and uremic toxins) may also contribute to its appearance.<sup>10</sup> In a study of the influence of dialysis techniques on blood pressure, patients' blood pressure did not change when they were switched from hemodialysis to hemofiltration.<sup>11</sup>

In normal subjects, genetic as well as geographic factors are determinants of blood pressure.<sup>12</sup> In pursuing our studies of the factors that influence blood pressure in patients undergoing dialysis, we analyzed blood-pressure values according to season. This analysis revealed clear seasonal changes in blood pressure that prompted us to evaluate the influence of climatic factors on blood pressure.

**METHODS****Subjects**

We studied the records of 53 patients with end-stage renal disease who were treated with hemodialysis for more than six months between November 1988 and October 1992 (Table 1). The dialysis facility had a maximal capacity of 36 patients. The room temperature was maintained between 21°C and 24°C by air cooling or heating, as required. The patients were treated three times a week, with no seasonal or temporal variation, with use of high-flux polysulfone dialyzers (FH60 and FH80, Fresenius Laboratories, Homburg, Germany) with bicarbonate-buffered dialysate and an ultrafiltration controller (model 2008-E, Fresenius). Normal hemodialysis was used from 1988 to 1990. After 1990, hemofiltration, with 18 to 20 liters of supplementary ultrafiltration of plasma (the amount of plasma water removed from the patient through the dialysis membrane) and reinfusion of substitutive fluid per dialysis session, was used. Epoetin became available during the study period, and it was given initially to 25 percent of the patients and by the end of the study to 40 percent; the mean hemoglobin concentration increased from 9.3 to 10.3 g per deciliter during the same period. Fifteen percent of the patients received antihypertensive drugs (angiotensin-converting-enzyme inhibitors, calcium antagonists, or beta-adrenergic antagonists).

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**TABLE 1.** CHARACTERISTICS OF 53 PATIENTS WITH END-STAGE RENAL DISEASE TREATED WITH HEMODIALYSIS.\*

| CHARACTERISTIC   | VALUE       |
|--|-------------|
| Sex — M/F  | 35/18       |
| Age — yr   | 54±14       |
| Length of previous treatment with dialysis — mo        | 52±65       |
| Length of treatment in the dialysis unit — mo          | 31±15       |
| Characteristics at start of treatment in dialysis unit |             |
| Blood pressure — mm Hg                                 | 144±14/79±7 |
| Systolic blood pressure ≥160 mm Hg — no. (%)           | 11 (21)     |
| Diastolic blood pressure ≥90 mm Hg — no. (%)           | 10 (19)     |
| Antihypertensive therapy — no. (%)                     | 8 (15)      |
| Cause of end-stage renal disease — no.                 |             |
| Chronic glomerulonephritis                             | 24          |
| ADPKD or other genetic disease†                        | 9           |
| Chronic interstitial nephritis                         | 9           |
| Nephrosclerosis  | 5           |
| Unknown  | 6           |

\*Plus-minus values are means ±SD. A total of 20,900 blood-pressure measurements were made from November 1, 1988, through October 31, 1992.

†ADPKD denotes autosomal dominant polycystic kidney disease.

### Study Protocol

The clinical follow-up and dialysis prescription used in this facility have been described previously.<sup>11</sup> The procedures included automatic measurements of blood pressure (Dinamap 8103, Critikon, Creteil, France) before, during, and after dialysis; continuous measurement of weight (with Gambro weight beds, Gambro, Lund, Sweden) during dialysis; monthly determinations of the

dose of dialysis (urea clearance multiplied by the length of dialysis and divided by the distribution volume of urea [Kt/V]) with modeling of urea kinetics (in vivo clearance assessment during dialysis, bubble-measured blood-pump flow, and measurement of recirculation); and routine hematologic and biochemical measurements. The protein catabolism rate was also determined monthly at a midweek dialysis session. Physical examinations, including anthropometric measurements, were performed, and chest x-ray films were obtained every three months.

Heart rate and systolic and diastolic blood pressure were measured in the supine and erect positions before every dialysis session after the patient had rested for 5 to 10 minutes. The blood-pressure devices were regularly calibrated, and their readings were always within 2 mm Hg of the calibration pressure values.

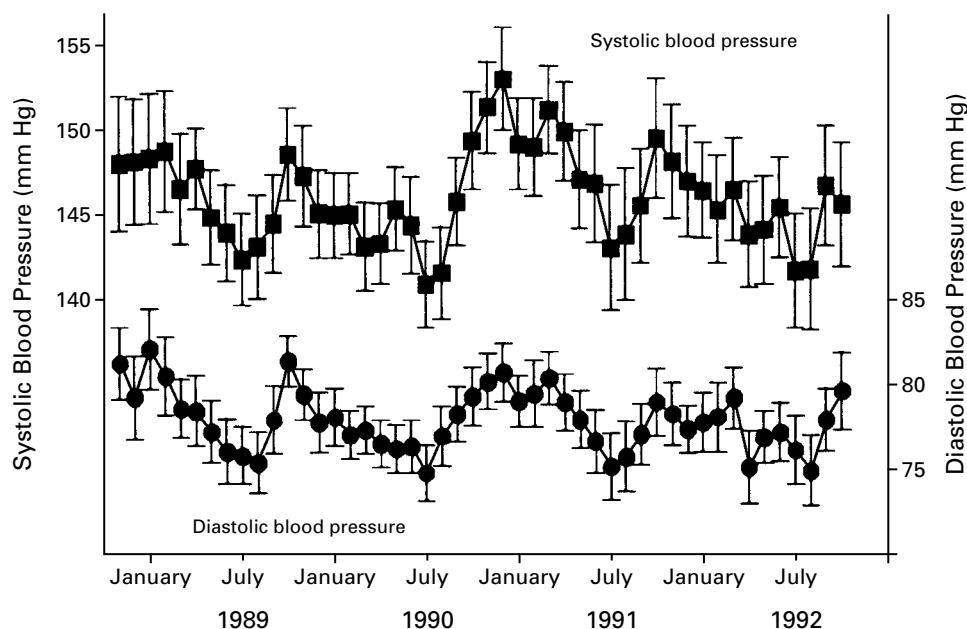
The results for each month are the means of the average values for each of the 36 patients treated at the center at any one time, each of whom was followed for at least six months.

### Climatologic Data

Montpellier is located in the south of France and has a typical Mediterranean climate. The data on the climate in this region were obtained from the local agency of the national weather service of France (Météo-France, Montpellier). The mean yearly total rainfall from 1946 to 1995 was 677 mm. The maximal monthly mean rainfall occurred in October (112 mm), and the minimal in July (19 mm). Temperature, relative humidity, and atmospheric pressure were measured eight times daily. The variables assessed included the maximal, minimal, and mean temperature, humidity, and atmospheric pressure. The monthly means of the daily averages of all these measurements were used for the study.

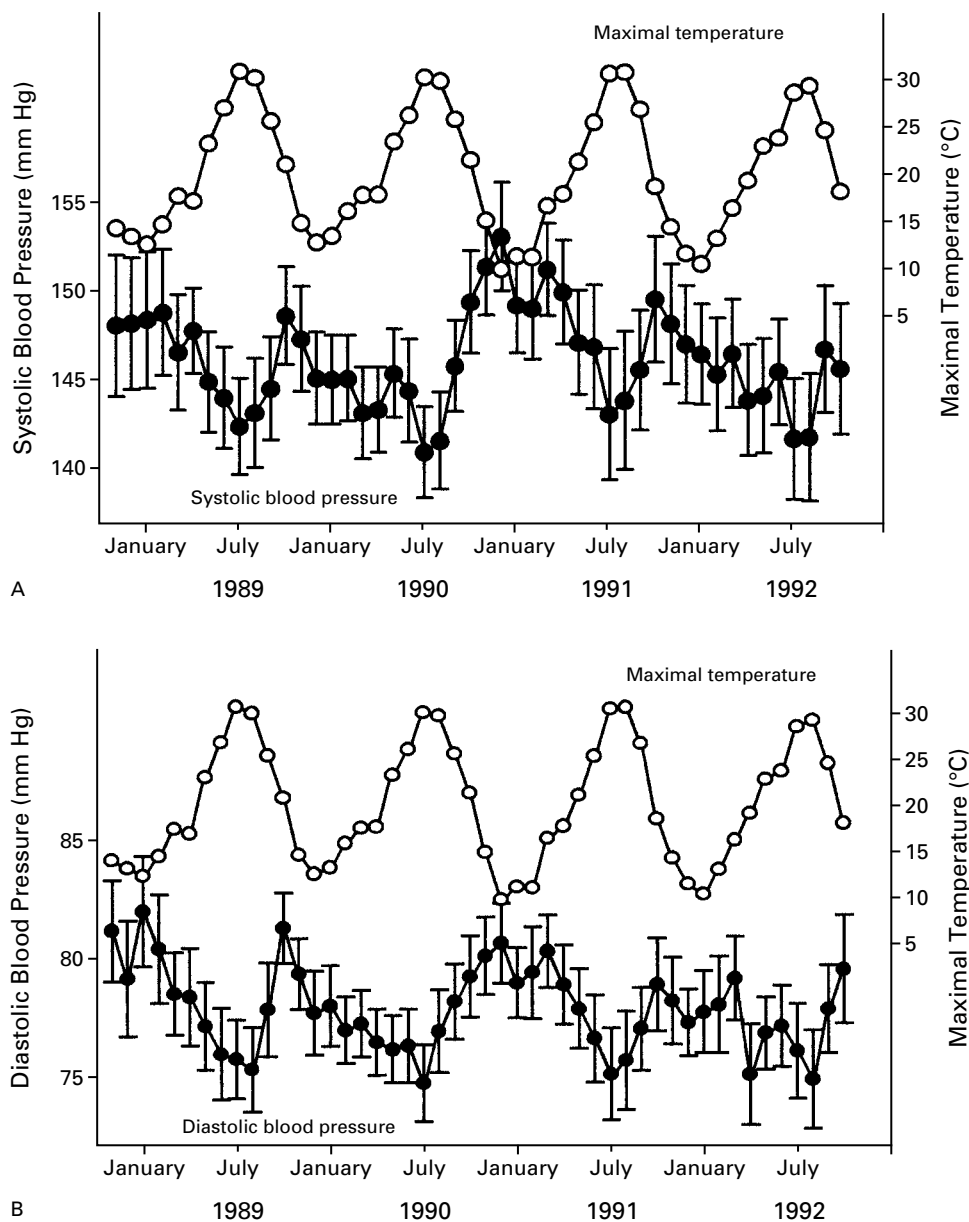
### Statistical Analysis

The data were analyzed with SAS software (version 6.12, SAS Institute, Cary, N.C.). To decrease the effect of single aberrant values on the overall analysis, the data for patients and climate are



**Figure 1.** Mean (±SE) Systolic and Diastolic Blood Pressure According to Calendar Month in Patients with End-Stage Renal Disease Treated with Hemodialysis.

The values for each month are the means of 13 measurements for each patient during that month.



**Figure 2.** Mean Monthly Maximal Temperature and Mean ( $\pm$ SE) Systolic Blood Pressure (Panel A) and Diastolic Blood Pressure (Panel B) in Patients with End-Stage Renal Disease Treated with Hemodialysis.

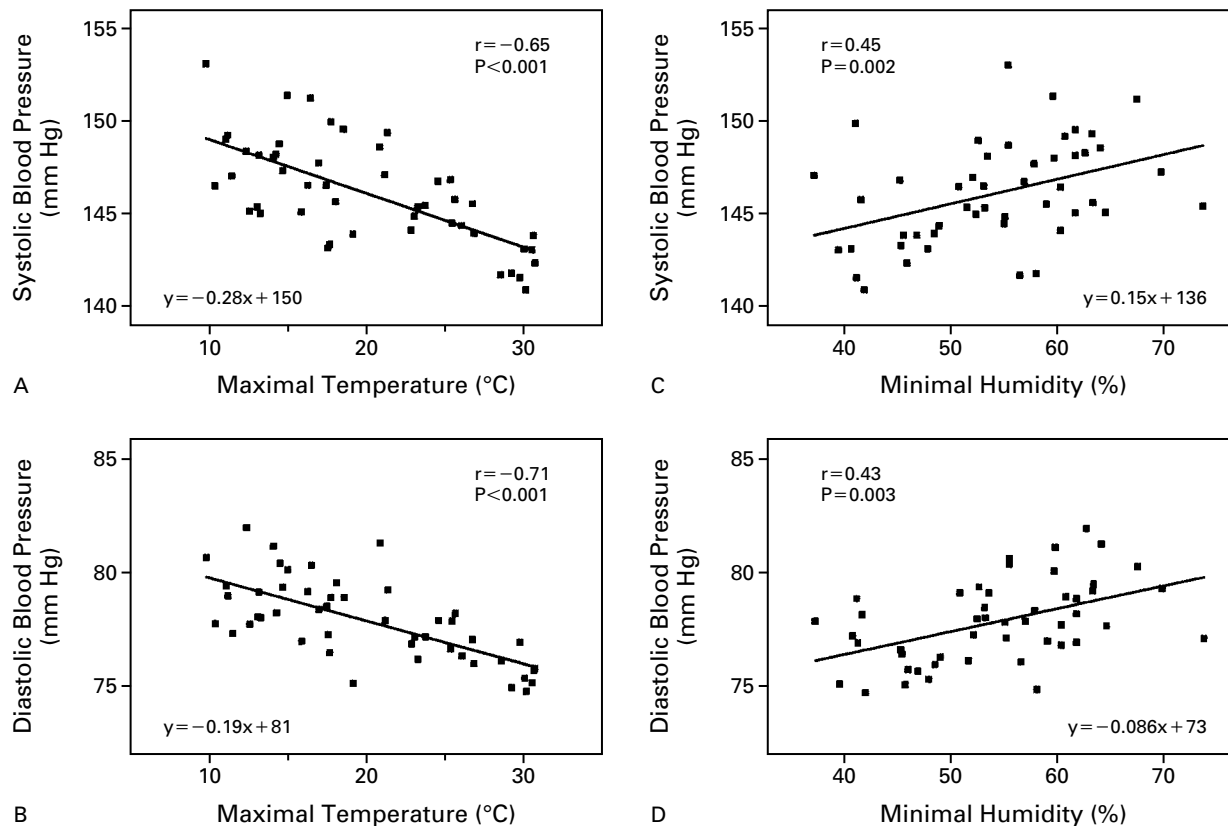
The blood-pressure values for each month are the means of 13 measurements for each patient during that month.

expressed as means  $\pm$ SE. Univariate correlations were assessed with Pearson's *r* test, and multivariate correlations with Fisher's *F* test. The effect of the longitudinal design (repeated measures) on the estimate of the correlations was taken into account after the analysis of variance by using a multivariate mixed model including a random individual effect and a fixed time effect, forcing a covariance matrix with compound symmetry. All *P* values are two-sided.

### RESULTS

There was a consistent cyclic variation in systolic and diastolic blood pressure during the four-year

study period (Fig. 1). The mean ( $\pm$ SE) peak values ( $153 \pm 3/82 \pm 2$  mm Hg) occurred in the winter, and the nadir values ( $141 \pm 3/75 \pm 2$  mm Hg) during the summer. The maximal monthly temperatures for these years ranged from 10°C in winter (December to February) to 31°C in summer (July and August). The cyclic patterns of maximal temperature and blood pressure (Fig. 2) clearly demonstrate the inverse relation between maximal temperature and blood pressure. The maximal temperature was inversely correlated with systolic and diastolic blood



**Figure 3.** Correlation between Environmental Variables and Blood Pressure in Patients with End-Stage Renal Disease Treated with Hemodialysis.

The graphs show correlations between maximal temperature and systolic blood pressure (Panel A), maximal temperature and diastolic blood pressure (Panel B), minimal humidity and systolic blood pressure (Panel C), and minimal humidity and diastolic blood pressure (Panel D).

pressure (Fig. 3), as were the minimal and mean daily temperatures (minimal,  $r = -0.59$ ,  $P < 0.001$ , and mean,  $r = -0.62$ ,  $P < 0.001$ , for systolic blood pressure; and minimal,  $r = -0.68$ ,  $P < 0.001$ , and mean,  $r = -0.70$ ,  $P < 0.001$ , for diastolic blood pressure).

In contrast, the seasonal changes in systolic blood pressure and minimal humidity paralleled one another (Fig. 4). The pattern for diastolic blood pressure was similar. Minimal humidity was directly correlated with blood pressure (Fig. 3); the same correlations were found between maximal and mean humidity and systolic and diastolic blood pressure (data not shown). There was no correlation between atmospheric pressure and blood pressure. The mean heart rate before dialysis varied from  $79 \pm 1$  to  $82 \pm 2$  beats per minute and was not correlated with temperature, humidity, or atmospheric pressure. There was a significant correlation between atmospheric pressure and temperature ( $r = -0.53$  and  $P < 0.001$  for maximal temperature;  $r = -0.45$  and  $P = 0.002$  for minimal temperature).

Multivariate regression analysis was performed to determine the association of systolic and diastolic

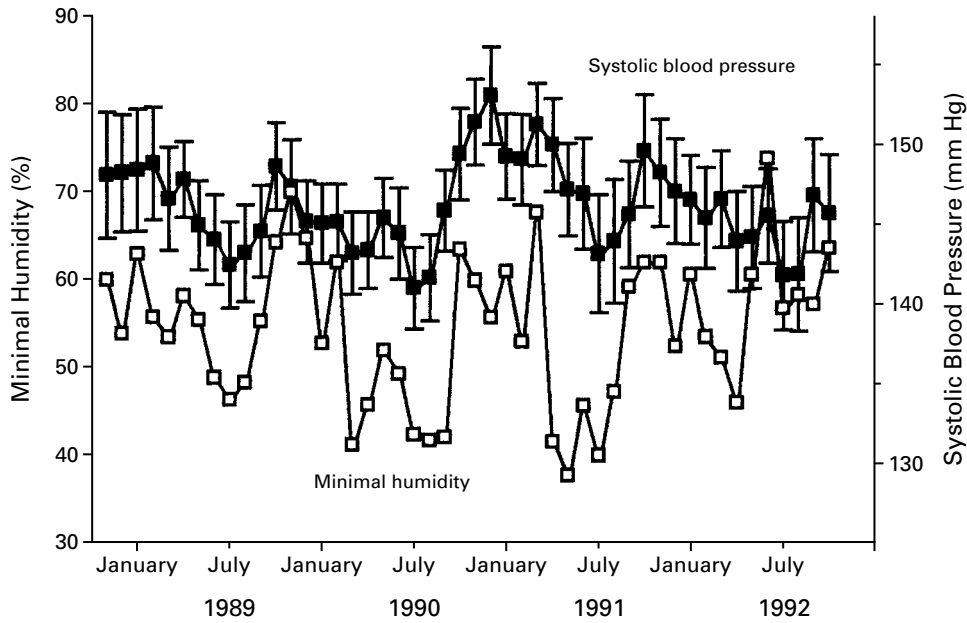
blood pressure with the climatic variables of temperature, humidity, and atmospheric pressure. Maximal temperature and maximal humidity, but not minimal humidity, were significantly associated with systolic and diastolic blood pressure in these models ( $P < 0.001$ ).

Weight gain between dialysis sessions increased from  $2.0 \pm 0.2$  kg at the start of the study period to  $2.5 \pm 0.1$  kg at the end (Fig. 5), probably because of the decrease in residual renal function. There was no seasonal pattern of change in weight gain between dialysis sessions or in protein catabolic rate.

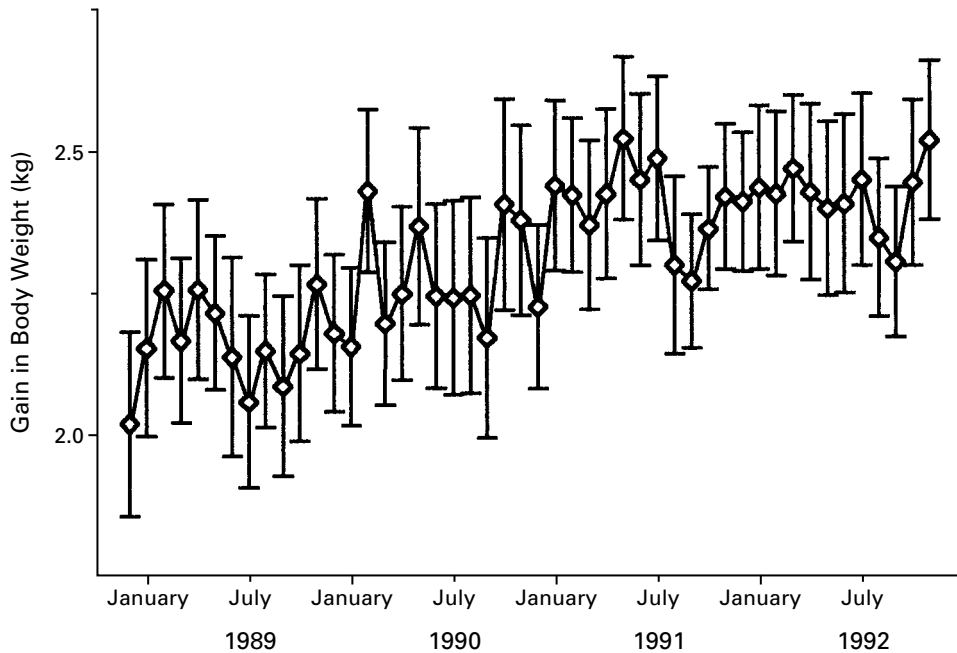
Blood pressure was not correlated with either protein catabolic rate or weight gain between dialysis sessions. This suggests that the seasonal pattern of blood-pressure change is due not to changes in intake of food or fluid, but to seasonal climatic changes. There was no seasonal variation in antihypertensive-drug therapy.

## DISCUSSION

The present study of more than 20,000 blood-pressure measurements in 53 patients over a period



**Figure 4.** Mean Monthly Minimal Humidity and Mean ( $\pm$ SE) Systolic Blood Pressure in 36 Patients with End-Stage Renal Disease Treated with Hemodialysis. The results for each month are the means of the average values for each of the 36 patients treated at the center at any one time.



**Figure 5.** Mean ( $\pm$ SE) Gain in Body Weight between Dialysis Sessions in 36 Patients with End-Stage Renal Disease Treated with Hemodialysis. The values for each month are the means of 13 measurements for each patient during that month.

of four years clearly demonstrates the influence of climate on blood pressure in patients with end-stage renal disease treated with hemodialysis. The British Regional Heart Study and the Coronary Artery Risk Development in Young Adults Study, which included large numbers of subjects, found regional differences in blood pressure that depended more strongly on where the examination took place than on the birthplace of the subject, a finding that suggested a role of geographic rather than genetic factors.<sup>13-15</sup> In a further analysis of the data from the British Regional Heart Study, a significant association between blood pressure and both environmental temperature and humidity was found, but it was considered of minor importance.<sup>16</sup> A correlation between air temperature and blood pressure has also been identified in surveys of normal schoolchildren in the United States,<sup>17</sup> Australia,<sup>18</sup> and Great Britain.<sup>19</sup> The Australian study estimated that a change of 10°C in temperature resulted in a difference in blood pressure of 5 to 7 mm Hg.<sup>18</sup>

The design of our study was different from those of the above studies, in that we studied a few subjects repeatedly (three times a week) for an average of 31 months in the same city. These characteristics enabled us to evaluate accurately the importance of the variations in blood pressure that were associated with seasonal changes. The variations, which amounted to 12 mm Hg for mean systolic pressure and 7 mm Hg for mean diastolic pressure, were greater than those noted in cross-sectional studies. When the data were analyzed with the patient's first treatment in our dialysis unit taken as time 0, as is usually done in surveys of patients with end-stage renal disease, no periodic variations in blood pressure could be identified (data not shown). Brennan et al.<sup>20</sup> reported a seasonal variation in blood pressure among hypertensive patients treated with placebo, a thiazide diuretic, or beta-blocking drugs in the Medical Research Council treatment trial. They found that the effect of ambient temperature on blood pressure increased with the age of the patients. The maximal variation, 6.1 mm Hg for systolic pressure and 2.8 mm Hg for diastolic pressure, with a 20°C difference between the hottest and the coldest months, occurred in the oldest group.<sup>20</sup> In our study, the magnitude of variation in blood pressure was greater. Blood pressure was measured more frequently in our study than in the Medical Research Council study and was always measured in the city where the meteorologic measurements were taken. These features of our study allow us to be confident about the correlations we found and may explain the differences between our results and those of the Medical Research Council study.<sup>20</sup>

Because of their limited water excretion, patients undergoing dialysis have a variable extracellular volume overload. Volume overload may result in resist-

ant hypertension and is regularly corrected three times a week by ultrafiltration during dialysis. Therefore, the magnitude of this extracellular volume overload becomes constant for a given patient. In spite of the recognized extracellular volume overload, the pattern of blood-pressure changes was clearly seasonal. This observation prompted us to analyze climatic data for the same period. The blood-pressure changes proved to be strongly correlated with climatic changes, a finding that suggests that climate may have an important role in the control of blood pressure and confirms our impression of a cyclic seasonal pattern in patients on dialysis.

Of the three variables we studied, only humidity and temperature were correlated with blood pressure. Maximal temperature was the most closely correlated with blood pressure. Since atmospheric pressure is the most variable of the three climatic measurements, analysis of the monthly mean atmospheric pressure may not be sensitive enough to detect an association with blood pressure. However, we found a significant correlation between atmospheric pressure and temperature, suggesting that if there was a strong independent correlation between atmospheric pressure and blood pressure, we should have found it.

What is the explanation of our results? High temperatures result in vasodilatation, which, in turn, may decrease peripheral vascular resistance and result in a reduction in blood pressure. This is one mechanism by which temperature could influence blood pressure. Another mechanism is the modification of total extracellular volume. When the temperature increases, loss of water by transpiration and perspiration increases. Since these may be more important mechanisms of water loss than urine output in patients with end-stage renal disease, variations in transpiration and perspiration may influence extracellular-volume homeostasis in these patients more than in normal subjects. However, total body-weight gain between dialysis sessions did not have a seasonal pattern, suggesting that if water loss increased during the summer it was compensated for by increased fluid intake. Although protein intake is known to vary throughout the year, we found no correlation between protein catabolic rate and climatic changes. Neither protein catabolic rate nor weight gain between dialysis sessions was correlated with blood pressure, suggesting that the changes in blood pressure were not due to changes in food intake or in weight gain during dialysis, but were very likely to be due directly to the variations in climate.

Hypertension causes accelerated atherosclerosis in patients undergoing dialysis.<sup>2,21,22</sup> Indeed, although normalizing blood pressure reduces mortality among patients on dialysis,<sup>23</sup> control of hypertension is not often enough assigned the highest priority in dialysis centers.<sup>24</sup> Climatic factors have been shown to influ-

ence not only hypertension but also its complications.<sup>25</sup> Rainfall and temperature were among the five principal factors that explained a doubling of mortality due to stroke and heart disease in some areas of the United Kingdom.<sup>25</sup>

The present study shows that high temperature and low humidity facilitate the control of hypertension in patients with end-stage renal disease who are being treated with dialysis and provides strong evidence of an influence of climate on blood pressure in these patients. The risk of hypertension and its consequences in these patients may therefore vary according to the pattern of seasonal climate change in the part of the world in which they live.

*We are indebted to the Météo-France service of Montpellier for providing climatologic data; to Ms. Marie Thomas and the nursing staff of the Unité de Dialyse à Structure Allégée at the Association pour l'Installation à Domicile des Epurations Rénales; to Drs. Roman Lorho, Jean Ribstein, Carlos Vela, Marie-Françoise Servel, Jean-Louis Flavier, Bernard Canaud, and Jean-Luc Fabre for their encouragement; and especially to Drs. Danielle Granger, Jacques Haiech, Patrick Redont, and Robert Sabatier for their invaluable help in the statistical analysis of the data and Dr. Peter G. Kerr for his help in preparing the manuscript.*

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