Redefinition of the Normal Range for Serum Sodium

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The serum sodium concentrations of three groups of patients selected from laboratory records and of one group of outpatients selected for a prospective study were examined. The mean serum sodium concentration of inpatients with normal serum urea concentrations was 8.5 mEq./L. lower than that of a group of healthy normal subjects. Part of this difference (2.6 mEq./L.) could be attributed to a nonspecific effect of illness. It was not possible to demonstrate any effect due to the hospital environment, but the results do not exclude the possibility of such an effect. It was concluded that all or most of the remaining difference was due to weighting of the inpatient data by low values of pathologic significance; the proportion of these low values was too great to allow a normal range to be extracted from the data by statistical methods.

The concept of the normal range is discussed. It is suggested that two ranges are required for serum sodium. a normal range (137–147 mEq./L. in this laboratory) to make assertions about alterations in specific diseases, and a range derived from patients likely to have no manifest disturbances of salt and water metabolism (135–144 mEq./L.) to detect such disturbances.

THE NORMAL RANGES published for the concentration of sodium in serum (*1*) seem high when compared with results from hospital laboratories. In most illnesses which are known to affect the serum sodium, its concentration is reduced. The low values seen in the majority of patients might therefore be interpreted as indicating that most of the patients for whom sodium analyses are requested suffer from such illnesses. An alternative interpretation would be that they do not suffer from such illnesses and that their sodium levels should be judged against a lower norm—that a range derived from healthy, active individuals is irrelevant to the situation of the patients (*2, 6*).

Attempts have been made to allow for nonspecific general effects in a population by using data derived from the population itself to establish the "normal range." This technic, developed by Pryce and

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Wootton (*2*) and applied by them to a number of analytic methods (but not to serum sodium) assumes that only a minority of patients have results of clinical significance. We have tried to assess whether this assumption is valid for serum sodium by examining the serum sodium concentrations of patients selected from laboratory records: Group 1, inpatients; Group 2, inpatients on whom no further sodium requests were made; and Group 3, outpatients. A further group of patients were selected for a prospective study: Group 4, outpatients on whom sodium analysis was not requested; Group 5, a group of healthy normal individuals, was also studied.

Methods

Analytic Methods

Serum sodium was measured by flame photometry and urea by a diacetyl monoxime method, both using the AutoAnalyzer (*3*). A single analysis was done on each specimen. In this laboratory at the time of this study, the 95% confidence limit for the sodium method was $\pm$ 2.9 mEq./L. at 140 mEq./L. Single standard quality control charts (*4*) and analysis of control serums (*5*) showed that the drift in the sodium method during the period of this investigation was less than 1 mEq./L.

Selection of Data

Three groups of sodium results were taken from the laboratory records of a large teaching hospital which performed about 50 serum sodium analyses each day during the period of study. All samples were taken at the same time of year (January to March). Because a large proportion of requests originated from the renal-dialysis unit, results on uremic patients were excluded from the groups. In Groups 1 and 3, patients were excluded who had had a serum urea concentration greater than 42 mg./100 ml. at the time the sodium analysis was requested. Excluded from Group 2 were all patients who had had uremia at any time during the admission. The 3 groups were defined as follows:

Group 1 A consecutive series of 324 sodium analyses requested for inpatients. (We took the daily results at 15-day intervals to minimize the chance of including more than 1 result on the same patient.)

Group 2 The final sodium analysis requested for each of a consecutive series of 301 inpatients.

Group 3 A consecutive series of 79 sodium analyses requested for outpatients.

Two further groups, 4 and 5, were obtained prospectively:

Group 4 A consecutive series of 92 sodium analyses for outpatients who had had blood specimens taken for biochemical analyses other than sodium, potassium, chloride, bicarbonate, or urea.

Group 5 Sodium analyses of a normal group comprised of 50 blood donors (unpaid; thus, selected for social conscience) and 27 members of the university staff.

Statistical Treatment

The distribution of the results in the first three hospital groups was asymmetrical, with a tail of low values. Normally distributed populations were derived from these skew populations by applying the convention of Pryce (*6*). This convention consists of calculating the mode, and then taking this as the mean of the derived population. The values on the normally distributed side of this (in our case the upper side) are used to calculate the standard deviation. Chauvenet's criterion was applied to this half-distribution to eliminate the occasionally very high values, and the standard deviation was recalculated. The 95% ranges for the skewed distributions were obtained by eliminating 2.5% of the observations equally from each of the upper and lower ends. The 95% ranges for the normal distributions were calculated from the mean ± 2 S.D.

Results

The number of subjects, the mean serum sodium, and the 95% range for each of the groups studied are shown in Table 1. The figures in italics were derived by applying the convention of Pryce (*6*) and Chauvenet's criterion.

The sodium results from healthy volunteers (Group 5) and from outpatients who did not have sodium analyses requested (Group 4) appeared to be normally distributed.

The values in each group were examined for possible differences due

Table 1. Serum Sodium in Groups of Patients with Normal Serum Urea, and in Normal Individuals

Group	*No.*	*Mean (mEq./L.)*	*S.E.M.*	*95% range (mEq./L.)*	*Distribution*
1 Inpatients, Na requested	324	133.3	0.36	123–142	Negatively skewed
	260	*135.1*	*0.25*	*127–143*	*Normal*
2 Inpatients, final Na requested	301	135.2	0.30	125–144	Negatively skewed
	270	*136.1*	*0.26*	*128–145*	*Normal*
3 Outpatients, Na requested	79	136.5	0.56	127–144	Negatively skewed
	66	*137.1*	*0.50*	*129–145*	*Normal*
4 Outpatients, Na not requested	92	139.2	0.23	135–144	Normal
5 Normal individuals	77	141.8	0.30	137–147	Normal

The figures in italics were derived from the observations according to the convention of Pryce (*6*) and Chauvenet's criterion.

to sex or age. We were unable to detect an effect of either in any of the groups.

The distribution of all sodium analysis results in Groups 1–3 were negatively skewed.

The differences between the means of results in Groups 1 and 2, 3 and 4, and 4 and 5 were all highly significant ($p < 0.001$).

The difference between Groups 2 and 3 was of marginal significance ($p = 0.04$). If a true difference exists between the populations represented by Groups 2 and 3, it is less than 1.6 mEq./L. (at $p = 0.01$). The normally distributed groups derived from Groups 2 and 3 were not significantly different ($p = 0.08$).

The distribution of Group 4 was significantly different from the distribution that would have been expected had it consisted of equal numbers from Groups 3 and 5, such a combination giving a similar mean. When the observed and calculated frequencies were compared with the χ^2 test, p was < 0.001.

Discussion

The mean serum sodium for healthy normal individuals was 141.8 mEq./L., with a 95% range of 137–147 mEq./L. (Group 5). These limits are close to those of Allen (*7*) who used the same method; are slightly narrower than those of Wootton and King (*8*) who used a chemical method; and are about 2 mEq./L. higher than those of Roberts (*9*) who used a multichannel analyzer. The difference between the means of inpatients and of normal individuals, 8.5 mEq./L., is similar to the difference reported by Van Peenen and Lindberg (*10*). We have examined sodium results for various groups of patients to try to find an explanation for this large difference.

We thought that outpatients who did not have sodium estimations requested by the clinician (Group 4) were unlikely to have symptoms of electrolyte or water disturbance, and that comparison of this group with the healthy normal group might demonstrate some general effect of illness. Hypo-osmolality, often without symptoms, is a complication of many severe illnesses (*11*), and Campbell and Dickinson (*12*) suggested that any prolonged or serious illness is likely to impair the active extrusion of sodium from cells and so result in a fall of the serum sodium concentration. The mean sodium of these patients was 2.6 mEq./L. lower than that of the healthy individuals, so it appears that less serious degrees of ill-health may also be accompanied by a fall in the serum sodium.

The division of outpatients into Groups 3 and 4 depended on whether or not the clinician requested a sodium estimation. The mean of the patients who had had sodium analyses requested was 2.7 mEq./L. lower than that of the other outpatients. The experience of Pryce and Wootton (*2*) with analyses other than sodium led us to examine the possibility that the group who had had sodium analyses requested might consist largely of a normally distributed subpopulation identical with the other outpatients combined with a minority of patients with lower values of diagnostic significance which skewed the distribution. Neither inspection of the data, nor the application of Pryce's convention supported this idea. This statistical device served merely to eliminate a number of the lower values; the "bulk population"—the group which Pryce would use as a normal range—was still significantly lower than the outpatients for whom sodium analyses had not been requested.

Thus the clinician can, and does, select for sodium requests those outpatients who, on the average, will prove to have lower values. This is perhaps not surprising, considering the characteristic histories associated with the more usual forms of sodium loss.

We may conclude that data derived from sodium requests on outpatients are heavily biased with low results, and a bulk population derived from them by statistical methods will still show a substantial bias. In this way, serum sodium differs from other biochemical determinations which were examined by Pryce and Wootton (*2*) and in which the bulk population is believed not to be biased by values of diagnostic significance.

The analyses for inpatients (Group 1) showed a wide 95% range, from 123 to 142 mEq./L.; with a mean 3.2 mEq./L. lower than that of analyses requested for outpatients (*3*). There were two possible explanations for this difference: (1) It might have been caused by the patient being hospitalized—an effect of bedrest, of some peculiarity of the food, or some other general environmental influence; or (2) it might have been caused by the inpatient group's having a greater proportion of low diagnostic values because it contained the more seriously ill patients.

As with the outpatient group, the statistical device of Pryce provided a bulk population which failed to coincide with either Group 4 or Group 5.

This device failed, therefore, to determine which of the two explanations was correct. We would have liked to study a group of inpatients for whom analyses other than of electrolytes were requested. In order to have ensured adequate volumes of serum, it would have been necessary to discuss the project with the clinical staff, thus running the risk of influencing whether or not they requested sodium analyses. (This problem did not arise with the outpatient group, as the patients were bled by technicians after the clinician had formulated his request.)

At attempt was made to measure the effects of the hospital environment by comparing the outpatient sodium values (Group 3) with those of patients for whom no further requests were made (Group 2). It may be assumed that these patients were regarded as clinically satisfactory. Inpatients in this group and outpatients in Group 3 were therefore similar in having, or having had, a history or symptoms which were an indication for electrolyte determination, and in the patients' not being sufficiently ill to require continued biochemical investigation in the hospital. Less than 1% of the patients in Group 2 paid for treatment, so financial considerations were unlikely to have curtailed their hospital stay or the number of analyses requested. The mean sodium concentrations of these 2 groups were not significantly different. This may be because no difference does exist or because the number of our samples was too small. If our assessment of these groups is correct, the effect of the hospital environment is likely to be less than 1.6 mEq./L.

Before these data can be used to derive a normal range for serum sodium, it is necessary to define this concept. To make assertions about changes in disease, a normal range is required, representing the patients' values before their illness. We consider the range derived from blood donors and university staff, 137–147 mEq./L., to be an approximation to such a normal range when considering outpatients' sodium values. As we were unable to demonstrate a significant hospital environmental effect, the same range seems appropriate for inpatients.

For biochemical determinations to be of specific diagnostic value, a different range is required. The ideal range would be derived from patients having some of the presenting signs and symptoms of the condition being considered, but not, in fact, having that condition. This ideal is rarely realized, and in some situations the range of healthy normal individuals is mentally modified according to the accumulated wisdom of clinician and chemical pathologist. The ideal may be brought nearer by using the range of Group 4 (135–144 mEq./L., which makes some allowance for nonspecific illness effects) to detect the presence of significant abnormalities of sodium concentration.

It appears to us quite unjustifiable to derive a normal range for serum sodium from the data of Groups 1–3. There is no evidence that the application of the statistical device of Pryce (*6*) will eliminate values of diagnostic significance and leave a normal bulk population; indeed, our evidence suggests otherwise.

Nevertheless, it may be argued that since the clinician is able to select patients who will prove to have low sodium concentrations (compare

Group 3 with Group 4), in asking for a sodium analysis he is anxious to judge the severity rather than the presence of sodium depletion (or overhydration). Such a view may credit the house staff with an unwarranted degree of sophistication; however, were it sustained it would support the use of a range, presumably to be derived from Groups 1–3, of "sodium levels in patients with known sodium depletion." We hesitate to specify its limits, although we note that the ranges derived from Groups 1–3 are close to the arbitrary limits of 130–145 mEq./L. suggested by Burnell *et al.* (*11*) as the range within which water disorders are unlikely to be contributing to the patient's illness. These ranges are just above the range of 115–127 mEq./L., within which symptoms commonly develop in water intoxication and sodium depletion (*13*).

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