BODY POTASSIUM MEASUREMENTS

BY WHOLE-BODY COUNTING:

SCREENING OF PATIENT POPULATIONS

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A statistical study of body potassium measurements in the disease groups was undertaken with correlations between repetitive measurements and the course of the disease.

Total-body potassium was measured in 750 patients with a whole-body counter equipped with 4π plastifluor scintillators. Preliminary studies on control subjects yielded reference norms based on regression equations as a function of age and weight and demonstrated an excellent correlation, in healthy subjects, between total-body potassium and total-body water or lean body mass. Results obtained in the patients were expressed as a percentage of maximally individualized reference norms, thus enabling comparisons to be made despite the heterogeneity of the data. Screening of patients in ten disease groups showed that total-body potassium was frequently lowered. At least insofar as mean values are concerned, low potassium levels were characteristic not only of patients with cirrhosis, amyotrophy, and obesity but also of those with heart failure, high blood pressure, renal failure, and even stabilized diabetes and treated hyperthyroidism. Longitudinal studies in cirrhotic patients also disclosed a marked instability of body potassium over time. Depletion is not necessarily irreversible but fatal issues were preceded by a drastic fall. The system responsible for this potassium deficit appears to be the skeletal musculature where the losses seem to be a general and relatively nonspecific response.

The introduction of whole-body counting techniques into hospital use has facilitated the measurement of total-body potassium, a parameter of body composition which is as significant in human pathology as in human physiology. Total-body potassium shows a clear-cut tendency to be low in many disease states, including uncontrolled diabetes, hepatic, cardiac, renal, and neuromuscular diseases, and the measurement conditions are such that one is in practice determining intracellular potassium. The data obtained can thus add significantly to our knowledge concerning the intracellular compartment. However, the wide range of absolute values of body potassium in normals, the scatter of results even in homogeneous subject groups, the difficulty of finding a wholly satisfactory reference index for expressing the values, and the nonspecificity of the perturbations observed in a variety of diseases, all tend to complicate the issue. In particular, the distinction between "normal" and "pathologic" values is often a subtle one in individual cases. It was thus felt that a statistical approach to the problem might prove useful. In the present study, 750 subjects in ten disease groups were screened. An attempt was made to bring out the particular characteristics of each group or condition without being too concerned with distinguishing on an individual basis between "normal" and "pathologic". Also investigated was the possibility of doing longitudinal studies of clinical course with the same whole-body counting technique.

MATERIALS AND METHODS

The whole-body counter used at the University of Liège has been described previously [1]. Its 4π plastifluor detector is one of the few of its kind in the world [2]. Efficiency and reproducibility are excellent, although to the detriment of resolution. As a result, the counting time can be reduced to 200 sec, but calibration must rely not on spectrometry but on an algebraic technique based on the ratio between two channels [1]. The counter's technical characteristics (background, geometry, resolution,

and efficiency) are comparable to those of the more widely used detectors with liquid scintillators (3). Accuracy has been verified using the double calibration method with a tracer dose of ^{42}K. The effect of the subject's body build on his results has been studied with phantoms of increasing weight and variable potassium concentrations; the use of several types of phantoms, simulating individual somatotype more closely, proved to be essential for good precision and has been adapted for routine use. The calibration technique as a whole is regularly subjected to quality control procedures based on daily measurements of the main parameters that serve to establish formulas: background, potassium standard (saturated solution of $KHCO_3$), phantom (Grey and Marten, Ltd.) containing 140 gm of potassium and 3 nCi of ^{137}Cs, and reference subjects. These procedures guarantee a technical reproducibility of 5% over time, which is better than that obtainable with isotopic dilution methods (4).

The problem of "reference norms" is a complex one. To evaluate this complexity, 1,000 controls of various ages and weights in good health were counted and distributed into cells based on sex, age, and weight. (Computations showed that height is not an independent factor.) Computer processing of these data disclosed that the expression of results in terms of body weight (gm/kg or mEq/kg) was the most appropriate method, making it possible to derive the following linear regression equations:

For male subjects, $Y = 3.396 - 0.012\,x_1$
$$- 0.014\,x_2; \tag{1}$$

For female subjects, $Y = 2.707 - 0.010\,x_1$
$$- 0.011\,x_2, \tag{2}$$

where Y is the total potassium (gm/kg), x_1 the age (years), and x_2 the weight (kg).

The 5% confidence limits within homogeneous cells varied with the cell, ranging from 5 to 15% of the value estimated. Repeated counts on the same subjects (ten men and ten women each measured 20 times within 1 month) confirmed that inter-individual variations are greater than intra-individual variations and thus that the total-body potassium value can be considered as a relative "constant" with respect to individual subjects. These equations thus allow the prediction of individually fitted reference norms for each patient. Recently, total potassium was very accurately measured with a highly sophisticated body counter (5), yielding mean values slightly lower than ours (6). However, this divergence is probably due to the selection of the control population which had higher mean body weights (6) than our subjects. As our body counter and calibration methods provide an invariant response

relating to body size it was not thought necessary to relate the body potassium to an index of body thickness, such as (weight/height)$^{1/2}$, useful for other types of body counter (7).

In healthy adult subjects there is an excellent correlation between total potassium and the values of both lean body mass as calculated from anthropometric measurements (8) and total-body water as measured by isotopic dilution. (Isotopic dilution also yields an estimate of lean body mass which is in excellent agreement with anthropometric measurements.)

Figure 1 shows the correlations of body potassium, with (A) lean body mass and (B) with body water (75 young adult subjects). However, it should be stressed that these correlations were established in subjects in good health and thus presuppose that the potassium level in the lean body mass is a constant, or, in other words, that there are no potassium abnormalities. Since this presupposition does not necessarily hold under pathologic conditions, the application of such relationships to the ill requires great caution. Although the reference to body weight alone is open to some criticism from a physiologic standpoint (9), it can be used for clinical purposes to establish "reference norms" in the absence of other criteria of demonstrably greater value. This approach yields norms individualized for the age and body build of the patients according to Eqs. 1 and 2. The values obtained in pathologic cases may thus be expressed as a percentage of the predicted value.

In a number of cases total-body water and exchangeable sodium were measured by the classic isotope-dilution techniques. These results have also been expressed as a percentage of reference norms drawn from tables in the literature (10). Lately there is an important restriction on potassium measurements made by low-resolution whole-body counters: once the subject has been administered a radioisotope emitting gamma rays of energy greater than 0.3 MeV, no counts can be made as long as the istope remains active.

A total of 750 patients were screened for body potassium; their distribution by disease groups is shown in Table 1 with the age and weight ranges. The choice of these disease groups was oriented by reports from the literature, based often on isotopic dilution of ^{42}K but also on whole-body counting, that total potassium diminishes in diabetes (11,12), cirrhosis of the liver (13,14), heart failure (13,15), hyperthyroidism (16), and neuromuscular diseases accompanied by wasting (13,17). The question of potassium deficit in uncomplicated hypertension (18) and renal failure is more controversial. For
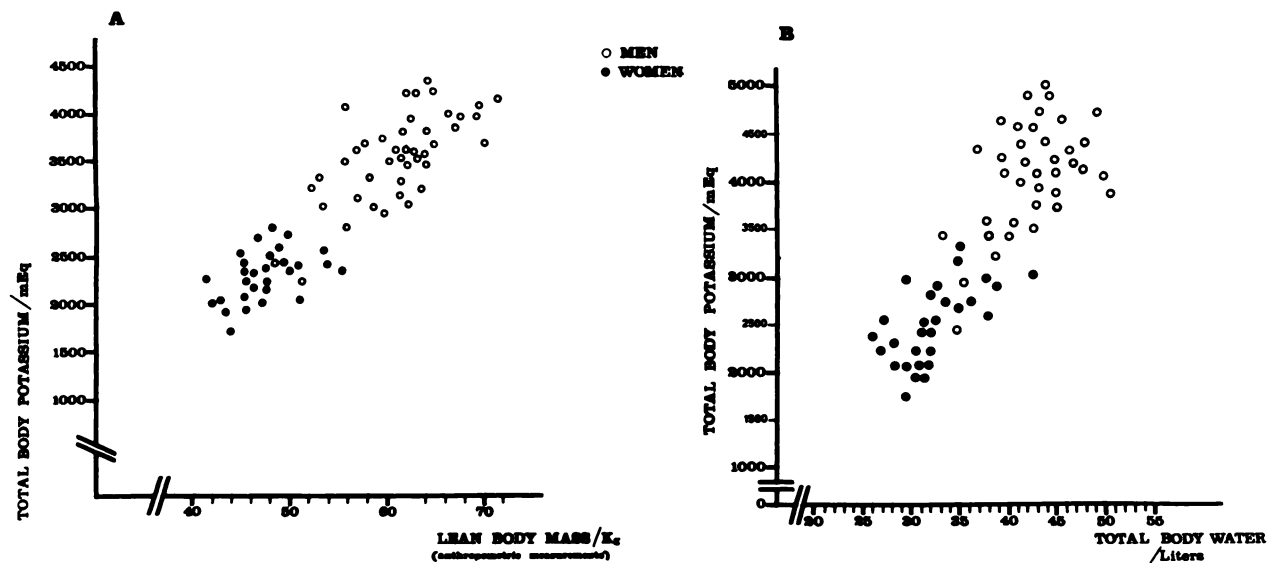
FIG. 1. Correlations between total-body potassium (mEq) and (A) lean body mass (kg) as calculated from anthropometric measurements (men : r : 0.7786, p < 0.001; women : r : 0.6307, p < 0.001) and (B) total water (liters) measured by tritiated water dilution (men : r : 0.6030, p < 0.001; women : r : 0.4959, p < 0.01) (healthy young adults).

purposes of comparison, patients with angina pectoris or myocardial infarction without decompensation, neuromuscular diseases without atrophy, and dermatologic conditions were counted. Screening was limited to patients in a generally satisfactory condition, most of them ambulatory and able to come to the counting room, generally unassisted, from inpatient or outpatient services. The diabetic patients were stabilized with either insulin or oral hypoglycemic agents; the hypertensives showed no major cardiac or renal complications; the hyperthyroid patients had been treated at least 1 year earlier with ^{131}I and appeared clinically cured; and the heart-

disease patients had no clinically apparent edema. By excluding bedridden, cachectic, and very weakened subjects, we attempted to avoid the influence of nonspecific factors such as severe dietary restriction, overall marasmus and the results of chronic immobilization.

RESULTS

Table 2 provides some examples of our manner of expressing results. It can be seen that the only significant values are those which are based on individualized reference norms, computed from Eqs.

TABLE 1. CLASSIFICATION OF PATIENTS SCREENED FOR TOTAL-BODY POTASSIUM

Groups based on diagnosis	No. of cases		Range of ages (yr)	Range of weights	Remarks
1. Diabetes	115	(58M; 57F)	16–72	40–96	27 treated with insulin
2. Essential hypertension	80	(39M; 41F)	20–70	50–100	10 treated with diuretics, slight mean overweight
3. Renal failure	80	(38M; 42F)	18–77	37–88	Severe failure in need of dialysis
4. Cirrhosis	75	(50M; 25F)	34–75	40–94	
5. Obesity	60	(15M; 45F)	16–67	60–105	
6. Heart disease with decompensation	55	(22M; 33F)	33–80	41–97	
Angina or infarction without decompensation	45	(23M; 22F)	30–79	44–84	
7. Hyperthyroidism	40	(12M; 28F)	17–67	44–81	Treated with [131]I 1 yr earlier
8. Neuromusmular diseases without atrophy	35	(15M; 20F)	18–75	45–92	
Neuromuscular diseases with atrophy	30	(18M; 12F)	18–78	43–80	
9. Adrenal insufficiency	20	(11M; 9F)	35–65	44–87	
10. Misc. skin diseases	115	(62M; 53F)	17–88	41–100	
Total	750	(363M; 387F)			

TABLE 2. DATA PROCESSING OF SOME INDIVIDUAL VALUES OF TOTAL-BODY POTASSIUM

Diagnosis	Sex	Age	Weight (kg)	Reference values from Eqs. 1 and 2 (mEq/kg)	mEq	Measured values (mEq/kg)	% ref. value
Virilism	F	22	77	42.1	2215	47.1	112
Anorexia nervosa	F	18	41	53.2	2397	59.0	111
Gastric ulcer	M	67	48	49.2	2495	51.8	105
Incipient pulmonary carcinoma	M	67	69	41.7	2949	43.0	103
Ulcerative colitis	M	42	84	44.1	3806	45.3	103
Gastric ulcer	F	33	54	45.7	2244	42.0	92
Spasmophilia	F	22	40	52.5	1895	47.2	90
Hyperadrenocorticism	M	32	72	51.4	3190	44.3	86
Advanced pulmonary carcinoma	M	40	61	52.9	2692	44.1	83
Regional ileitis	F	40	50	45.1	1876	37.5	83
Ulcerative colitis	M	66	58	45.9	2172	37.5	82
Ulcerative colitis	M	65	72	41.2	2374	32.9	80
Toxemia of pregnancy	F	32	90	35.8	2322	25.6	72
Prostatic carcinoma with metastases	M	63	68	43.3	2070	30.5	70
Severe malnutrition	F	24	41	51.7	1222	29.1	56

These cases do not belong to disease groups studied in Tables 1 and 3.

1 and 2. One of the advantages of this procedure is to permit intergroup comparison despite the heterogeneity of individual data.

In this light, Table 3 gives the mean values obtained for the groups of Table 1. It will be observed from Table 3 that only by expressing the recorded values as a percentage of the reference norms (short-circuiting sex differences), were we able to demonstrate that the overall characteristic of most of the groups was a reduction in total-body potassium. Mean potassium was very clearly lowered in cases of amyotrophy, cirrhosis, obesity, and heart failure. The mean deficit was less marked but still significant in patients with hypertension, diabetes, renal failure, and hyperthyroidism. In the diabetic patients, there was a minimal difference between the insulin-treated and noninsulin-treated patients. Scatter was not appreciably greater in the patients than in the pre-

viously measured controls. Hence, the changes in potassium, expressed in terms of a common index, do appear to be a characteristic of the disease groups studied and not an artifact of patient selection. Without having to introduce the difficult distinction between "normal" and "pathologic" values of body potassium, we found that each group was characterized by a definite pattern insofar as mean potassium value was concerned.

In Fig. 2A, the individual values (expressed as a percentage of the reference norms) are listed for the most significant disease groups studied. Figure 2B gives the frequency distribution of total potassium losses as a function of magnitude expressed as a percentage of the reference norm. While the potassium loss is invariably present in amyotrophy, its frequency decreases as the mean values rise. This part of the figure demonstrates that the means ob-

TABLE 3. MEAN VALUES OF TOTAL-BODY POTASSIUM

|	Mean values in mEq/kg Men	Mean values in mEq/kg Women	Mean values as % of reference norm
1. Neuromuscular diseases with atrophy	43.3 ± 10.0	27.7 ± 11.6	71.4
2. Cirrhosis	38.5 ± 7.7	34.4 ± 8.3	73.5
3. Obesity	40.2 ± 7.1	31.4 ± 4.8	78.6
4. Heart diseases with decompensation	44.1 ± 11.5	34.6 ± 8.2	80.4
5. Essential hypertension	42.8 ± 9.3	35.6 ± 6.5	86.4
6. Diabetes (without insulin)	44.1 ± 8.2	34.9 ± 9.0	88.6
7. Diabetes (with insulin)	46.2 ± 9.4	39.2 ± 10.9	89.9
8. Renal failure	46.4 ± 9.6	39.7 ± 9.2	88.6
9. Hyperthyroidism (treated)	45.6 ± 11.7	37.2 ± 8.1	88.8
10. Misc. skin diseases	42.3 ± 8.9	32.6 ± 9.5	91.6
11. Neuromuscular diseases without atrophy	49.7 ± 8.4	37.7 ± 7.4	94.2
12. Angina or myocardial infarction without decompensation	46.7 ± 7.8	38.2 ± 8.2	94.7
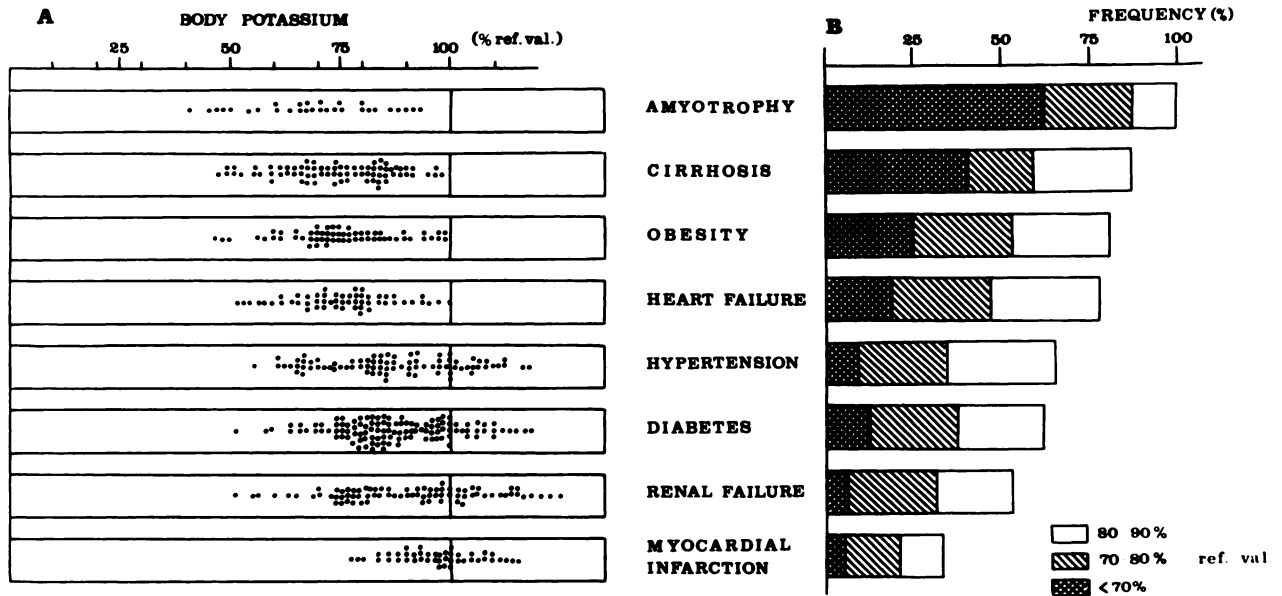
FIG. 2. (A) individual values of total-body potassium, expressed as percentage of reference norms, in various disease groups. (B) frequency distribution, in these groups, of total-body potassium values as function of relative degree of kaliopenia (expressed as percentage of reference norms). While potassium loss is present in amyotrophy, its frequency decreases as mean values rise.

tained are associated with a general shift of the frequency distribution and not due to certain aberrant or discordant individual values. It will also be noted that the renal failure group contains a small number of significantly increased values, which are exceptions to the general rule that all potassium changes

are negative: these patients constituted a homogeneous subgroup with severe renal failure of pyelonephritic origin (*19*).

It is well known that there is no correlation between serum potassium and total-body potassium. Figure 3 shows that this is true regardless of how
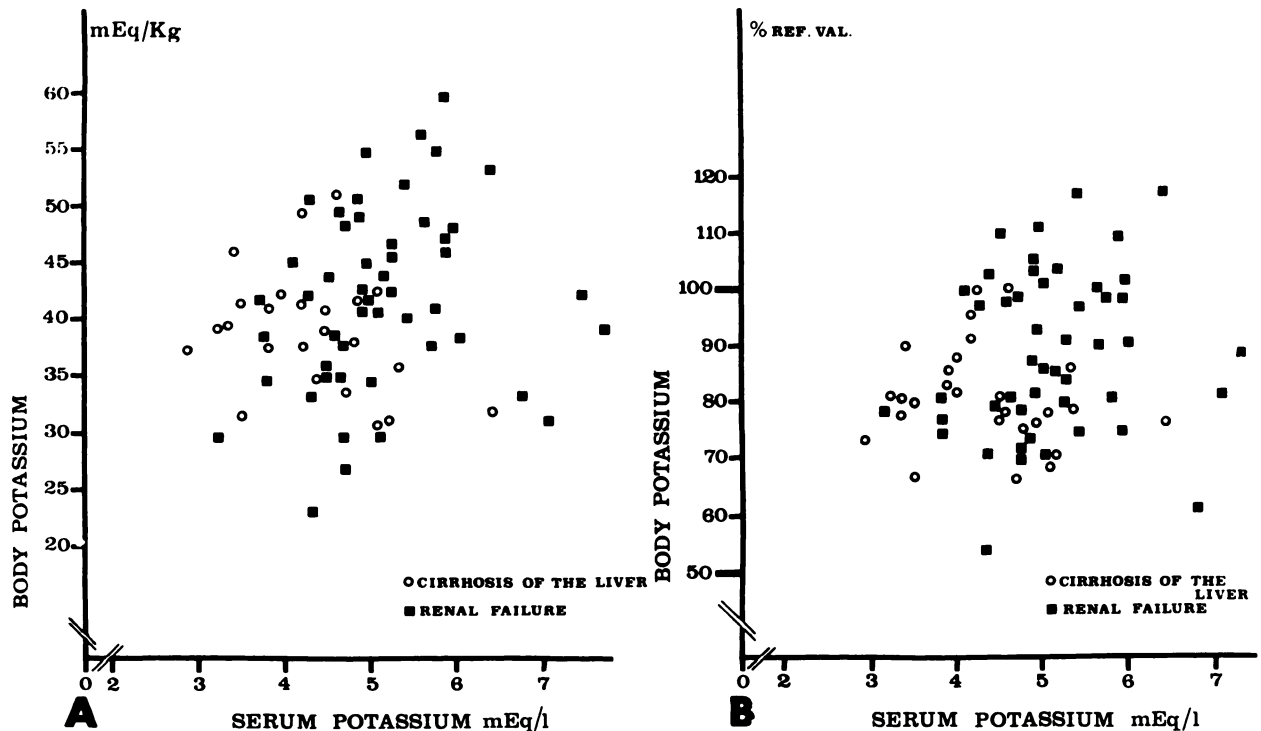
FIG. 3. Absence of correlation between serum potassium (mEq/l) and total-body potassium in disease states: (A) expressed in absolute values (mEq/kg), and (B) expressed in relative values (percentage of reference norms).

total potassium is expressed (mEq/kg or relative to reference norm), notably in two diseases where serum potassium levels are known to vary in both directions: cirrhosis and severe renal failure.

Simultaneous determinations of total water and exchangeable sodium by isotopic dilution were also performed in some of the patients subjected to whole-body counting. Figure 4 attests to the complete absence of correlation between the results of total water and total potassium in the patients tested in contrast with the excellent correlation obtained in healthy subjects (Fig. 1B). Figure 5 similarly confirms the lack of correlation between total potassium and exchangeable sodium. It does thus appear that knowledge of one of the parameters of water and mineral composition in no way helps to deduce, in individual cases, the other parameters or even to predict in what direction they will be shifted.

The inter-individual variability of total-body potassium is greater, in healthy subjects, then the intra-individual variability over short periods of time; this is a recognized feature (20,21). In patients also, longitudinal measurements are thus the logical complement·of the statistical approach which, although valuable for the information it provides about mean body potassium, furnishes essentially static data. In chronic disease states, such data provide an "instantaneous" view at some point in a pathologic process where the stage of the disease may be of great importance. Cirrhosis with its course marked by successive exacerbations and remissions is a good case in point. A total of 25 cirrhotic patients were subjected to longitudinal measurements for as long as 24 months. Figure 6 shows the results obtained in ten typical cases expressed as a percentage of the reference norms and compared to the potassium

changes occurring during the same time period in a healthy reference subject. The short-term fluctuations were even more marked than those previously described (14). Over the long term, the fluctuations were also very great and correlated with the overall clinical course of the patient as determined by hospital admission and discharges. However there was no correlation with serum potassium. Thus, in addition to the fact that body potassium is lowered in cirrhotic patients, this parameter is also highly labile and subject to appreciable short-term variations, as opposed to its stability in the normal subject. It is particularly interesting to note that the courses with a fatal outcome were preceded by a drastic fall in potassium. However, even when the depletion is profound it is not necessarily irreversible, even though during remissions potassium never reaches completely normal levels.

DISCUSSION

The results of whole-body counting of potassium in healthy and ill subjects show that this technique is suited rather for studies of populations than to individual determinations. However, there are relatively few reports of mass screenings in the literature (22,23), and it was felt that a global approach could clarify a host of questions. Some of the deviations found in the present study were confirmations of data in the literature (11,17); others were either unexpected or of unexpected magnitude. Aside from the subgroup discussed above (19), characterized by a relative potassium excess, the deviations are always negative. Another striking finding is that an appreciable number of patients, distributed in the various disease groups, had deficits of considerable magnitude (Fig. 2A): values as low as 50% of the
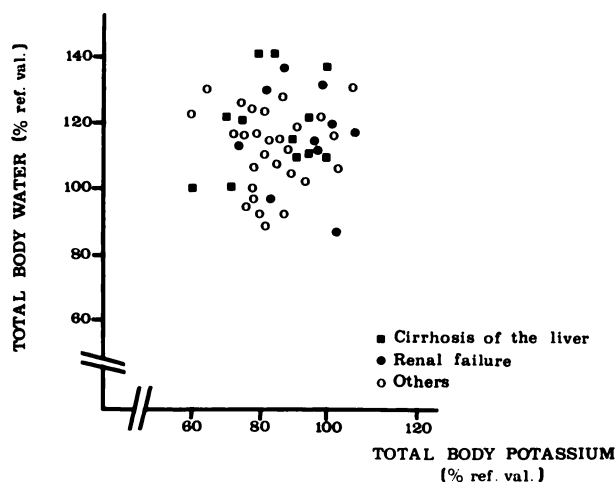

FIG. 4. Absence of correlation between total-body potassium and total water in disease states (values expressed as a percentage of reference norms).
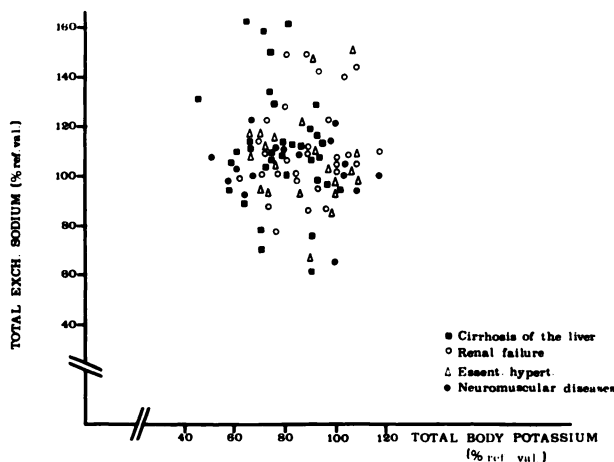

FIG. 5. Absence of correlation between total-body potassium and exchangeable sodium (values expressed as percentage of reference norms).
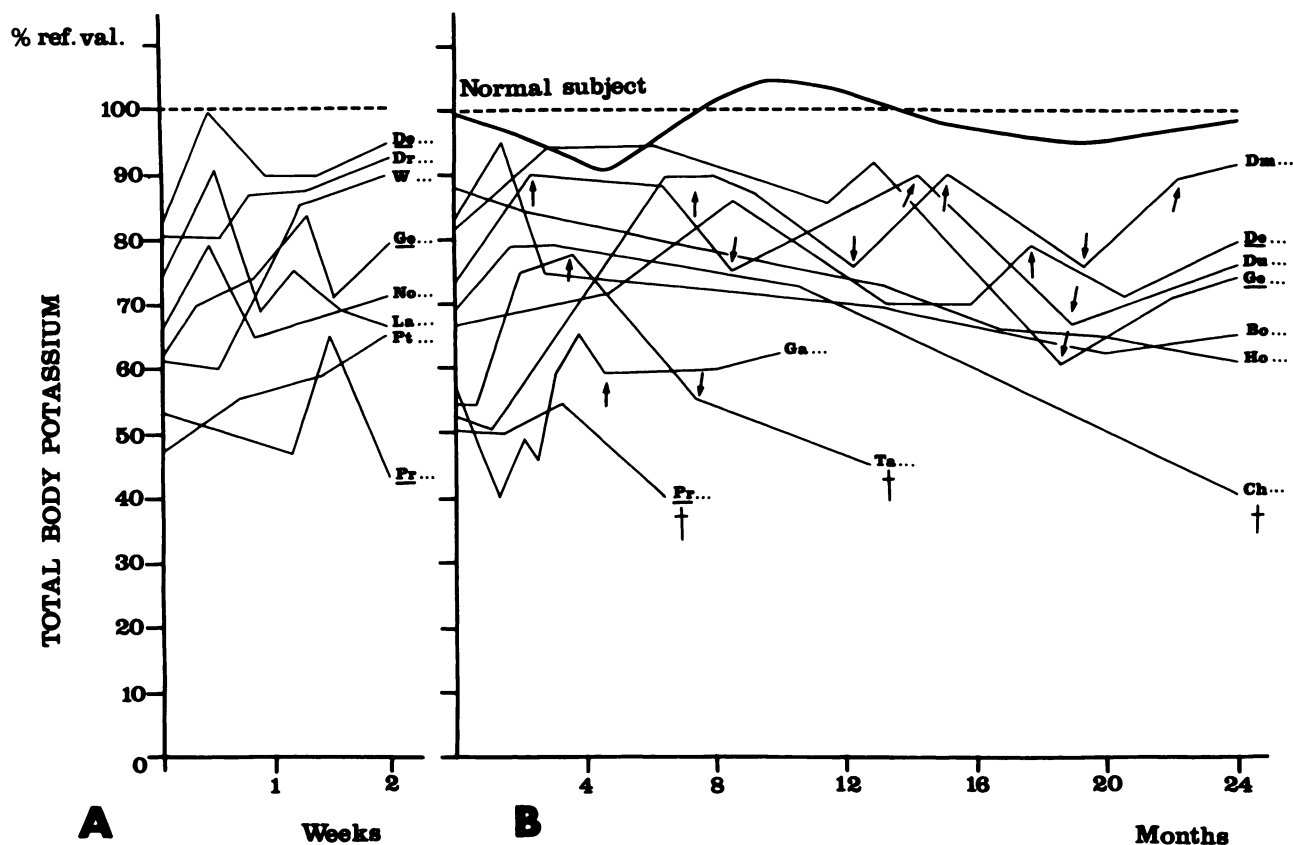
FIG. 6. Longitudinal studies of total-body potassium in patients with cirrhosis: (A) short-term study, and (B) long-term study (values expressed as a percentage of reference norms). †—death. ↑—hospital discharge. ↓—hospital readmission.

norm are not exceptional. This statistical approach thus established an unequivocal decrease in total-body potassium whose relative magnitude seems to be characteristic of the diseases in question and not merely a reflection of their chronicity. In contrast, certain conditions similar to the preceding diseases (e.g., myocardial infarction without decompensation, neuromuscular diseases without wasting) show barely any change in total potassium. [The group of patients with "neuromuscular diseases without wasting" deliberately did not include patients with myasthenia gravis during the phase of exacerbation; in a previous study (24), 15 such patients proved to have a significantly depressed mean value.] Some cases deserve a further comment. In obese patients, the decrease in potassium is clear-cut and cannot be explained simply by the excess body weight since the individual results are expressed in terms of norms derived from equations where weight is a negative factor. In diabetes, insulin treatment was expected to be a factor, since this hormone seems involved in protein anabolism (25). In our series there was a slight but statistically insignificant difference between the insulin-treated patients and those stabilized without insulin. In renal failure, studies of patients similar

to ours (26) have attributed the decrease of body potassium to a reduction in the intracellular compartment. Nevertheless a drop in total-body potassium thus appears to be a rather nonspecific condition, which might almost be called "commonplace"; however, it is compensated for by the characteristic patterns reflected in Fig. 2B, permitting the diseases studied to be rated on a well-defined scale in terms of their effects on body potassium. Total-body potassium disturbances are thus of unquestionable value in nosologic descriptions: kaliopenia should be added to the usual symptoms of diseases such as cirrhosis, heart failure, obesity, and even hypertension, diabetes, and renal failure.

Longitudinal studies carried out in patients with cirrhosis and, as previously studied and reported elsewhere, renal failure (19) and myasthenia gravis (24), reveal that, in addition to being generally low, total potassium in these disease states is markedly unstable.

Repeated measurements of whole-body potassium not only provides a valuable index that parallels the clinical course (for the potassium depletion even when profound is not necessarily irreversible) but also draws attention to possible disturbances of the

regulation of intracellular potassium stores and suggests that further studies may be of value.

However, it appears difficult to prove in these cases a real "decrease in intracellular potassium concentration," as distinct from a "reduction of lean body mass" (main potassium store) (13,27). As a matter of fact, the methods of determination of lean body mass are subject to caution in severely ill persons and it seems dangerous to use this concept as a reference for potassium in our cases. Indeed the system primarily responsible for the decrease in total potassium seems to be the skeletal musculature, since it contains 70% of body potassium (28), as compared with 3% for the liver (14), and an even smaller percentage for the kidneys and heart. The total potassium loss observed in most disease states is not a direct result of organic lesions but rather a general type of disturbance. The pathogenesis of this disturbance is still unclear, but it is thought to consist of a distant metabolic repercussion, particularly visible in organs having the largest potassium stores. ["Metabolic myopathy" has been described (29) as existing with certainty in endocrine diseases and with great probability in heart, liver, and kidney conditions.] Whole-body counting would thus provide a rapid, precise, and easy method of detecting the magnitude of these repercussions. It should also be recalled that the courses ending fatally in our series were preceded by a drastic fall in total potassium.

CONCLUSION

The determination of total potassium by whole-body counting is especially useful when investigating homogeneous patient groups or performing longitudinal studies. This technique makes it possible to bring out the pattern characteristic of each disease despite the heterogeneity of the individual data. One thus has a "marker" of the intracellular compartment, providing information about the body as a whole. This is an investigational tool of particularly great value in this field, where there are few techniques available for the study of the intracellular compartment. For the clinician, the measurement of whole-body potassium is a highly useful approach to the pathophysiology of many diseases.

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