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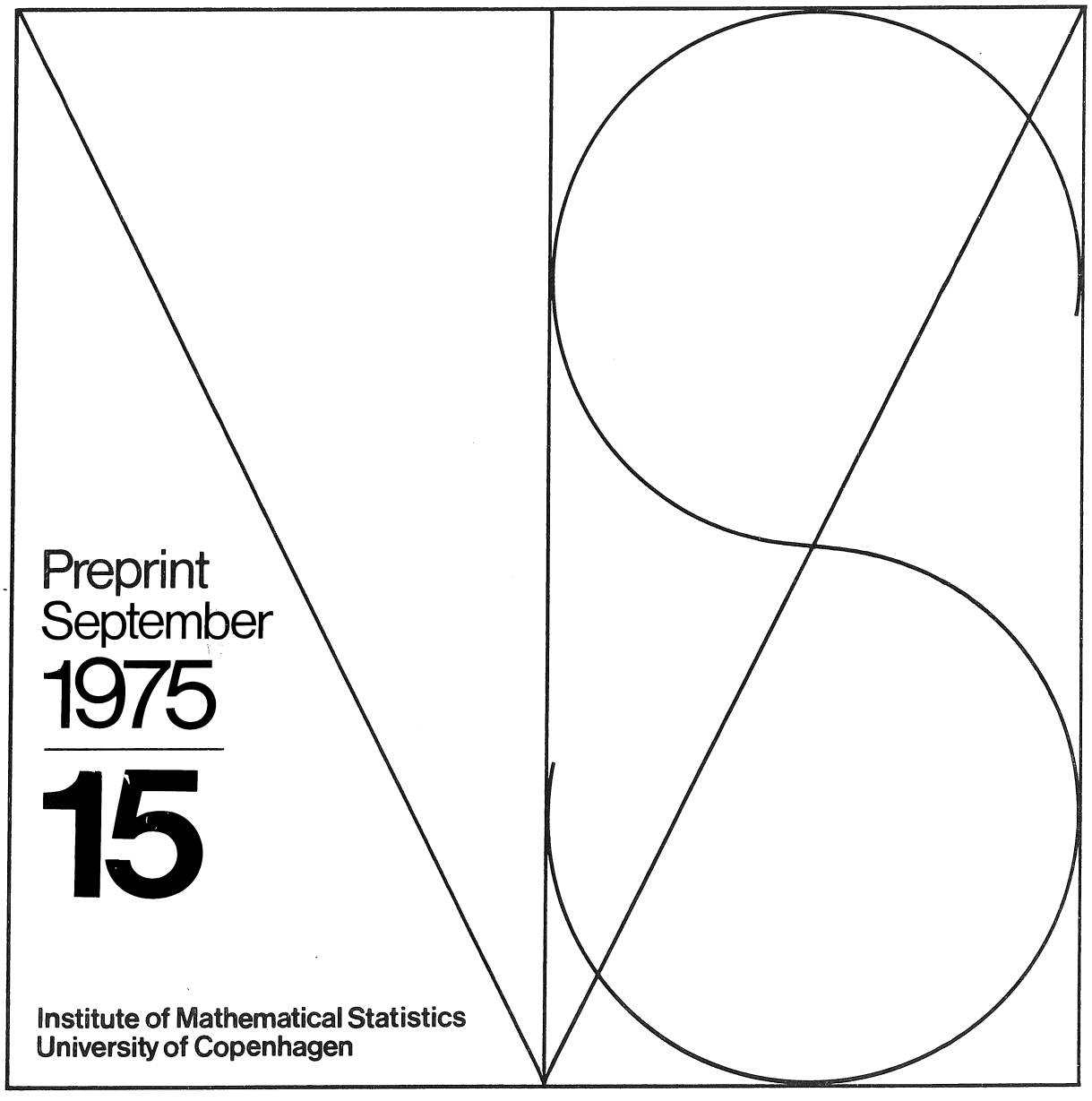

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HYPERCALCAEMIA DISCRIMINATION INDEX: A MULTIVARIATE ANALYSIS OF PARATHYROID FUNCTION IN 107 HYPERCALCAEMIC PATIENTS

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ABSTRACT

The limited usefulness of radioimmunoassays of parathyroid hormone in the differential diagnosis of hypercalcaemia invites the use of methods measuring effects of parathyroid hormone (PTH). Data derived from 4-5 day metabolic studies in 107 hypercalcaemic patients (78 retrospective and 29 prospective cases) were combined in a hypercalcaemia discrimination index (HDI). This index, HDI = (urinary calcium (mg/24 h) x 100 x serum phosphate (mg/100 ml))/(serum total-calcium (mg/100 ml) x the 24-hour clearance of creatinine (ml/min)), expresses in one figure the combined actions of PTH on the renal handling of calcium and on serum phosphate. A multivariate analysis of the retrospective data confirmed that the HDI offered optimal discrimination. An identical pattern of discrimination was observed in the prospective series. Based on the complete series HDI = 136 is found to be the optimal discrimination value. The classification of the patients as having hyperparathyroidism or pseudohyperparathyroidism (below 137) or non-parathyroid hypercalcaemia (above 136) corresponded in 100 out of 107 patients (93.5%) with the final clinical diagnosis. The effects upon the HDI of sex, age, season, large urine losses, high intakes of calcium and the use of thiazides were also evaluated.

The determination of HDI appears to be a valuable tool in the endocrine evaluation of the hypercalcaemic patient. It has served well as an alternative to the immunoassay and continues

to serve as a supplement to this assay telling something about the biological significance of the measurements of immuno-reactive PTH.

Because of the simple negative feed-back interplay between serum calcium and the secretion of parathyroid hormone (PTH) one would expect the determination of immuno-reactive parathyroid hormone (iPTH) to be an ideal tool in the differential diagnosis of hypercalcaemia. For several reasons, however, it is not so. One major reason is the immunological and biological heterogeneity of PTH metabolites in circulation (Reiss & Canterbury 1974), and another the ability of certain malignant tumors to secrete PTH-like polypeptides which may or may not behave like PTH immunologically and biologically. Certainly, the concentration of iPTH is usually raised in hyperparathyroidism (Benson et al. 1974) and low-normal to unmeasurable in non-parathyroid conditions like osteolytic metastases, sarcoidosis, vitamin D intoxication, the milk-alkali syndrome and hyperthyroidism (Buckle et al. 1969; Hawker et al. 1970; Murray et al. 1972; Cushard et al. 1972; Blair et al. 1973; Manderlier et al. 1973; Bouillon & De Moor 1974). The present status concerning measurements of iPTH in malignant disorders however, is most bewildering. Benson et al. (1974) demonstrate raised levels of iPTH in virtually all types of malignancies, myelomatosis and carcinoma of the breast inclusive, while others present patients exhibiting an identical pattern of calcium metabolism and unmeasurable iPTH levels (Powell et al. 1973; Beck-Nielsen et al. 1975). The present state of affairs invites the use of methods measuring the effects of PTH rather than the concentration of iPTH, or even better, the combined use of such technics.

PTH increases the tubular reabsorption of calcium (Kleeman et al. 1961), probably the most important biological action of this hormone and, fortunately, also one of those which can be assessed most readily. In 1966 we introduced determinations of the fractional tubular reabsorption of calcium (TRCa%) for use in the differential diagnosis of hypercalcaemia (Transbøl et al. 1967). Subsequently, the usefulness of this approach has been substantiated (Transbøl et al. 1968; Nordin & Peacock 1969; Lund et al. 1970; Transbøl et al. 1970b; Transbøl et al. 1970c; Andersen & Mosekilde 1972; Lund 1973).

In the present paper a further development is presented, the hypercalcaemia discrimination index (HDI), expressing in one figure the combined actions of PTH on the renal handling of calcium and on serum phosphate. For the purpose of statistical evaluation of the properties of HDI and in order to discuss the possibility of even better discrimination a multivariate analysis was carried out.

HDI was developed on the basis of data from a retrospective series of 78 hypercalcaemic patients and tested prospectively in 29 patients. In addition, a group of 26 healthy volunteers was included for the study of seasonal variations in HDI.

MATERIAL

The whole series comprises 107 hypercalcaemic patients referred to departments of internal medicine (Table 1). They were selected for study by not being too ill or too old to cooperate and not receiving either causal or unspecific treatment of

their hypercalcaemia. The only exceptions from this rule were the discontinuation of vitamin D ahead of the study in vitamin D intoxication and the use of propylthiouracil and glucocorticoids for adequate control of hyperthyroidism and sarcoidosis associated with hyperparathyroidism. In patients using diuretics or estrogens such treatment was discontinued 2-4 weeks ahead of the study.

The diagnostic criterion for hyperparathyroidism was a state of hypercalcaemia for which no other cause could be demonstrated, and the diagnosis was confirmed by operation in 79 out of 83 patients. In 75 patients light microscopy revealed signs of hyperplasia or adenomaformation (Table 1), while in four a lasting normalization of serum calcium resulted from the removal of histologically normal but enlarged parathyroid glands (Transbøl et al. 1970a). These glands measured: case 26: three glands, 8 x 3 x 2 mm each, case 73: two glands of which one weighed 60 mg, case 99: 12 x 4 x 4 mm and 10 x 3 x 3 mm, and case 100: 20 x 7 x 5 mm and 10 x 8 x 7 mm. Neither of these criteria of confirmation were met in case 130, who has remained hypercalcaemic for two years following the neck exploration, but without developing any signs of malignant disease. Finally, three patients fulfilling the diagnostic criterion of hyperparathyroidism have remained unexplored (case 98, 102 and 118). The final clinical diagnosis arrived at in all of the 107 patients appear from Table 1.

Seventy-eight patients from Rigshospitalet and Gentofte hospital were studied retrospectively supplying the data from which

the HDI was created in Nov. 1972, while the remaining 29 patients were studied in Gentofte hospital with the purpose of evaluating the HDI in a prospective series.

Retrospective cases (n = 78)

Rigshospital series. Thirty-eight of the hyperparathyroid patients (Nos. 1-86), including those with coexistent sarcoidosis, and 12 of the non-parathyroid patients (Nos. 137-151 and 156-162) have been presented previously, and additional information on the outcome of cortisone tests, biopsies, and so on is available from these publications (Hornum et al. 1967; Transbøl & Halver 1967; Hornum et al. 1968; Transbøl et al. 1968; Lund et al. 1970; Transbøl et al. 1970b; Transbøl et al. 1970c, Hornum & Transbøl 1973). The data used for Nos. 140 and 161 derive from previously unpublished balance studies.

Gentofte hospital series of 28 patients included 22 with hyperparathyroidism (Nos. 88-109), one with bronchogenic carcinoma without roentgenographic evidence of bone metastases (No. 134) and five with non-parathyroid hypercalcaemia (Nos. 152-154 and 164-165). By displaying a transitory normalization of serum calcium following resection of the neoplasm patient No. 134 fulfilled the second criterion of Lafferty (1966) for the diagnosis of pseudohyperparathyroidism. Furthermore, on cortisone acetate, 50 mg t.i.d. for 11 days, his serum calcium decreased just modestly from 12.9 to 11.8 mg/100 ml. Among the non-parathyroid patients Nos. 152 and 154 had the diagnosis of sarcoidosis confirmed by biopsy and responded to cortisone acetate, 50 mg t.i.d. for 10 days, with rapid normalization of serum calcium. The 3rd sarcoid patient (No. 153) had pulmonary in-

filtrates and hilar lymph node enlargements which disappeared spontaneously along with the hypercalcaemia. Finally, the diagnosis of myelomatosis was confirmed by bone marrow aspiration in Nos. 164 - 165. Their hypercalcaemia vanished in response to prednisone and cytotoxic drugs.

Prospective cases (n = 29)

This Gentofte hospital series comprised 20 cases of hyperparathyroidism, three cases of coexisting hyperparathyroidism and hyperthyroidism (Nos. 130-132) and six cases of non-parathyroid hypercalcaemia, including two with hyperthyroidism (Nos. 135-136), one with sarcoidosis (No. 155) and three patients with carcinoma of the breast metastatic to bone (Nos. 166-168).

Two patients with coexisting hyperparathyroidism and hyperthyroidism did not turn up for calciummetabolic study until their hypercalcaemia had proved resistant to adequate treatment of their hyperthyroidism (Nos. 131-132), while the third patient was studied before any treatment (No. 130a) and during adequate medical control of hyperthyroidism (No. 130b). In two further patients with hyperthyroidism (Nos. 135-136) medical treatment led to a lasting normalization of serum calcium and thyroid function. Later, along with a subtotal thyroidectomy carried out in No. 136, two normal sized parathyroid glands of normal histologic appearance were exposed. Although not confirmed histologically the diagnosis of patient No. 155 was that of chronic sarcoidosis of 10 years duration. Initially, he had displayed non-tuberculous miliary pulmonary infiltrations and hilar lymph node enlargements within the first year joined

by a relapsing and prednisone-sensitive hypercalcaemia causing renal (biopsy) and ocular metastatic calcifications. After 5 years the pulmonary changes regressed completely leaving the hypercalcaemia as the sole manifestation, probably accentuated by habitual drinking of 2-3 litres of milk daily (!). By stopping this habit and taking prednisone, 10 mg t.i.d. for 19 days, his hypercalcaemia disappeared completely. Finally, one of the patients having carcinoma of the breast metastatic to bone possibly also had hyperparathyroidism (No. 166). At least, she had a history of renal stone disease and peptic ulcer and had been given a diagnosis of hyperparathyroidism in another hospital one year prior to the actual study.

Healthy volunteers

Data on 26 healthy volunteers studied on a similar diet regimen were included for the evaluation of possible seasonal variations in HDI, since such variations might be detected more readily in individuals without endocrine or target organ diseases. This series comprised 17 males (21-29 years, average 24 years) and nine females (20-54 years, average 34 years) of whom 12 (five females) were studied from May through September and the remaining 14 from October through April.

METHODS

All subjects were studied for at least four, usually five days on a standard diet containing approximately 800 mg calcium,

900-1100 mg phosphorus and 60-140 mEq sodium per day, and 1 gram of protein/Kg body weight per day. Day 3-6 were used for daily blood sampling and day 3-5 or 4-5 for 24-hour urine collections.

The effect of high calcium intake was studied in 6 hyperparathyroid patients (Nos. 81a-86a) by the adding of 1500 mg of calcium (as 1 Calcium Sandoz effervescent tablet t.i.d.) to the diet for 2-4 days in continuation of the initial study (Nos. 81b-86b). Another 10 hyperparathyroid patients (Nos. 96a-105a) had their diet period extended for further 5 days during which bendroflumethiazide was administered in a daily dose of 10 mg. The HDI was reestimated during the last 3 days for the evaluation of the effect of thiazide diuretics (Nos. 96b-105b).

In order to assess the effect of large urine losses upon HDI one 24-hour urine was collected fractionally in 12 patients from the retrospective group (7 a.m. - 23 p.m. - 7 a.m.) and in 22 patients from the prospective group (9 a.m. - 9 p.m. - 9 a.m.). Then we calculated the "24-hour" HDI on the basis of the 24-hour urine sample and each of its fractions separately, thus permitting an estimate of the percentage change in HDI which would have occurred if 8-, 12- and 16-hour urine specimens had been lost.

Finally, the possible dependence of HDI on sex and age was assessed in the total series of 78 patients with uncomplicated hyperparathyroidism using the age of 50 years as the point of division.

Chemical methods

Serum was analyzed for total calcium (TOCa), inorganic phosphate (P) and creatinine (Cr), and urine for calcium (UCa), sodium (UNa) and Cr. The various methods used in individual patients appear from Table 2. In apparently normocalcaemic patients the presence of hypercalcaemia was ascertained by simultaneous determinations of serum ionized or ultrafiltrable calcium (Transbøl et al. 1970a; Jørgensen et al. 1973) or albumin-corrected TOCa (Jørgensen et al., unpublished).

RESULTS

Creation and statistical evaluation of HDI

In table 1 average values for TOCa, P, the 24-hour clearance of creatinine (CCr) and the 24-hour urinary excretions of calcium (UCaV) and sodium (UNaV) from each patient are presented. In fig. 1 data for the retrospective cases on TOCa, P, CCr and UCaV from uncomplicated hyperparathyroidism (Nos. 1-109, exclusive 10 and 76) and non-parathyroid hypercalcaemia (Nos. 137-165) also appear. Despite comparable levels of TOCa patients with non-parathyroid hypercalcaemia excrete more calcium than patients with hyperparathyroidism. This difference becomes much more impressive when it is realized, that non-parathyroid patients exhibit values of CCr which are on the average nearly 50% less than those found in hyperparathyroidism. Only three patients with non-parathyroid hypercalcaemia had UCaV below 300 mg/24 h, namely those with clearances of 4, 10 and 19 ml/

min, while this occurred in about 50% of the hyperparathyroid patients. Similarly, there is an obvious inter-group difference with respect to the average serum P concentrations.

Fig. 2 shows how by combining these parameters presented in Fig. 1 the differentiation between the groups becomes progressively improved. First (Fig. 2(a)) UCaV is related to the glomerular function of the individual by its expression per a standard CCr of 100 ml/min. Secondly, we include TOCa in the denominator in order to make this to represent a rough measure of the filtered load of calcium (Fig. 2(b)). Finally, HDI = (UCaV (mg/24 h) x 100 x P (mg/100 ml))/(TOCa (mg/100 ml) x CCr (ml/min)) is completed by the inclusion of the serum phosphate concentration in the numerator, resulting in a nearly complete distinction between the groups (Fig. 2(c)).

In order to assess the properties of HDI statistically and to discuss the possibility of even better discriminators, a multivariate T^2-test (Anderson 1958) was performed. By transforming the four parameters to their logarithms, the markedly skewed distributions are converted into reasonably symmetrical distributions and the HDI corresponds to a linear function of the variables: log HDI = log UCaV + log 100 + log P - log TOCa - log CCr. Considering these variables as samples from two four-dimensional normal distributions, we first test for equality of covariance matrices, obtaining for the likelihood ratio test (Anderson 1958): $\chi^2 = 31.2$, d.f. = 10, $p < 0.001$. The covariances must thus be assumed different. Since, however, the following statistical tests all give very clear answers,

we shall use the usual T^2-test as an approximation even if it presumes identical covariances. But in the further use of the results the two populations are thought of as having different variances. The T^2-test for equality of the two populations means naturally rejects ($F = 36.2$, d.f. $= (4,70)$, $p < 0.0005$). The discriminant function has the following coefficients: log TOCa: 37.0, log UCaV: -17.0, log CCr: 17.7 and log P: -16.8. It is seen that these coefficients, apart from a multiplicative constant, are very nearly -2, 1, -1 and 1, which invites the use of the index $HDI_m = (UCaV \times 100 \times P)/(TOCa^2 \times CCr)$ (fig. 2(d)). This index has the feature of being dimensionless and is the product of the dimensionless quantities $(UCaV \times 100)/(TOCa \times CCr)$ (or $((UCaV \times 100)/CCr) \times 1/TOCa$) and the ratio P/TOCa. The physiological meaning of these quantities is understandable from Fig. 3. Part A of this figure demonstrates firstly, that UCaV corrected to a standard CCr ((UCaV x 100)/CCr) increases as TOCa increases in hyperparathyroidism, and secondly, that patients with non-parathyroid hypercalcaemia excrete more (reabsorb less) calcium per standard CCr than patients with hyperparathyroidism at a given level of TOCa. Since the severity of hyperparathyroidism is roughly correlated to the degree of hypercalcaemia it is also understandable, that serum P turns out to be inversely correlated to TOCa (Fig. 3B). It appears also from this figure, that patients with non-parathyroid hypercalcaemia tends to have higher levels of P than hyperparathyroid patients at a given level of serum calcium.

The discriminatory power of any given one-dimensional discri-

minant function as opposed to the "optimal" discriminant function HDI_m (which under the assumption of equal covariance matrices is equivalent to using all four variables) may be statistically tested, see Rao (1965). For HDI we get F = 1.12, d.f. = (3,70) and $p > 0.3$, so that it may be safely assumed, that the original index, HDI, also discriminates optimally, see also Fig. 2(c) and (d). Even though the optimal discriminant function HDI_m does seem to have a valid physiological interpretation, as explained above, we shall in the following analysis mostly discuss HDI. Further we have tested whether omission of the serum phosphate concentration from HDI will affect the discrimination. Comparison of the index UCaV/(TOCa x CCr) with HDI_m yields F = 5.85, d.f. = (3,70) and $0.001 < p < 0.005$. By the analysis above HDI and HDI_m are seen to be equivalent, so we conclude that exclusion of the serum phosphate concentration from the HDI reduces the discriminatory power significantly.

Fig. 4 shows the observed and fitted logarithmically normal distributions of HDI, while fig. 5 presents the cumulative distribution of HDI plotted on probability paper for the same two groups of retrospective cases. Since the variances of log HDI differ significantly (F = 2.52, d.f. = (16, 57), p = 0.01) as might be expected from the results above, the slopes of the two theoretical lines differ. From fig. 5 it also emerges how the results may be used: The discrimination point where the same frequency (92.7%) of each population would be correctly classified according to the fitted distributions is at HDI = 144.

One might proceed using a two-step procedure, for example: 95% of the non-parathyroid population have HDI values above 107 and 95% of the hyperparathyroid population have values below 173. This approach leaves the patients having HDI's outside 105-173 as readily classified while the remaining have to be evaluated more carefully. Of course other frequencies than 95% may be used and can be directly read off from fig. 5. In practice, however, the HDI range demanding a more careful evaluation could be restricted to values slightly above the discrimination point (cf. Table 3).

Discrimination of retrospective cases

Division of the series at HDI = 144 separated all of the non-parathyroid patients (n = 17) from 58 (97%) of the patients having either hyperparathyroidism, hyperparathyroidism associated with calcium-inactive sarcoidosis (Nos. 10a and b) or pseudohyperparathyroidism. Just four (5%) of the retrospective cases, including two cases of hyperparathyroidism (Nos. 90 and 93), one of hyperparathyroidism associated with calcium-active sarcoidosis (Nos. 76a and b) and one of vitamin D intoxication (No. 140), did fall in the equivocal range of 144-173.

Discrimination of prospective cases

We first remark that the distribution of HDI for the 29 prospective cases was very much alike to that for the retrospective cases and accordingly we obtained very similar discrimination results. Eighteen of 20 cases of uncomplicated hyperparathyroidism (90%) gave values below the lines of discrimination, while values above these limits were found in five out of six cases of non-parathyroid hypercalcaemia (fig. 6).

Two unquestionable diagnostic failures were noticed: an HDI of 191 in a case of uncomplicated hyperparathyroidism (No. 122) and a value of 76 in a young boy suffering from Graves' disease (No. 136). The two patients with hyperparathyroidism associated with adequately treated hyperthyroidism gave one value below 144 and one in the questionable range. Finally, the high value of 312 noticed in a patient with untreated hyperthyroidism coexisting with hyperparathyroidism (No. 130a) was turned into a typical hyperparathyroid value of just 85 following adequate treatment of the former condition (No. 130b).

Discrimination of the complete series

For the complete series the optimal HDI and HDI_m discrimination points are 136 and 11.8, respectively. These are the points at which the same frequencies, 89.6% and 90.3%, respectively, of each population were correctly classified. The detailed information concerning the distribution of the HDI values is presented in Table 3.

Dependence on non-homeostatic factors

Hyperparathyroid females above the age of fifty had significantly higher HDI values than younger females, but did not differ from the male groups (Table 4).

Seasonal variations in HDI were observed in the healthy volunteers, who exhibited a May-September maximum of 86 ± 24 ($n = 12$) against an October-April minimum of 67 ± 20 ($n = 14$, $t = 2.148$, $p < 0.05$ (Student's t-test)). The corresponding averages

of patients with uncomplicated hyperparathyroidism, 94 ± 35 (n = 28) and 84 ± 31 (n = 50), did not differ significantly ($t = 1.391$, $p > 0.10$).

The adding of 1500 mg of calcium to the standard diet led to an increase in HDI in 5 of the 6 patients (Nos. 81b - 86b). In two patients HDI changed from hyperparathyroid to apparently non-parathyroid values (133 to 185 and 107 to 190), while the average HDI increased from 102 to 138 (Table 5). Bendroflumethiazide, on the other hand, reduced HDI drastically in hyperparathyroidism (Nos. 96b - 105b; Table 5).

The average changes in HDI caused by "losing" 8-hour (11 p.m. to 7 a.m.), 12-hour (9 p.m. to 9 a.m.), 12-hour (9 a.m. to 9 p.m.) and 16-hour (7 a.m. to 11 p.m.) urine samples from the calculation of "24-hour" HDI were the following: 5.8 ± 5.2%, 9.8 ± 5.9%, 10.4 ± 6.7% and 14.1 ± 13.6% (mean ± S.D.), respectively. Thus, the loss of one third of the 24-hour urine does not cause any appreciable change in the HDI. Just in two out of the 34 patients included in these calculations did one of the urinary "losses" referred to above cause the HDI to change from below to above 144 or vice versa.

DISCUSSION

First of all, before going on to discuss the pros and cons of the present method of discrimination, we should consider the physiologic background of HDI including the mechanisms through which homeostatic and non-homeostatic factors may influence the HDI.

Physiologic background of HDI

Homeostatic factors. Secretion of PTH in excess of normal feed-back demands increases serum calcium trough enhancements of the tubular reabsorption and intestinal absorption of calcium, and of bone resorption. Simultaneously PTH drcreases phosphate and bicarbonate reabsorption thus facilitating the rise in serum ionized calcium. If we imagine that the only effect of PTH was to increase the tubular reabsorption of calcium one would expect an initial and transitory decrease in urinary calcium excretion causing the filteres load of calcium to increase until a new steady state became established characterized by a higher filtered load of calcium and a normal urinary calcium excretion. In intact man, however, the contributions from bone and gut actions cause the filtered load of calcium to rise in excess of what is determined by the renal tubular action of PTH. Therefore urinary calcium increases, although rather modestly, in hyperparathyroidism. Since the fractional reabsorption of calcium, TRCa%, i.e. the reabsorption expressed as a percentage of the filteres load, decreases as the filtered load increases (Kleeman et al. 1961), the first part of the HDI (UCaV x 100)/(TOCa x CCr) is expected to rise in hypercalcaemic conditions, although less in hyperparathyroidism than in hypercalcaemic states characterized by suppression of PTH secretion. On the other hand, the lowering effect of PTH on serum phosphate, the second part of HDI, counteracts the rise herein, and, as a matter of fact, HDI in uncomplicated hyperparathyroidism averages 87 ± 33 ($n = 78$), which is not significantly different from that of healthy volunteers: 76 ± 22 ($n = 26$, $t = 1.589$, $p > 0.10$).

Non-homeostatic factors. Much of the scattering of the HDI values around the mean in hyperparathyroidism may be caused by variation in target organ sensitivity to PTH. Trebling of the calcium intake, for instance, makes HDI to rise considerably in some, but little in others, probably reflecting varying intestinal responses to PTH. In line herewith patients known to have or to have had pancreatitis, or to have steatorrhea, (Nos. 20, 57, 65, 73, 75 and 124) in general have rather low values of HDI. An increased sensitivity of bone to PTH secondary to lack of estrogens (Gallagher & Nordin 1972) may explain the higher HDI values observed in postmenopausal females with hyperparathyroidism. One would expect immobilization and osteolytic metastases to exert a similar action. Although alterations in HDI secondary to variations in urinary sodium excretion are undetectable in the present set-up such variations may be extremely significant in uraemic patients with non-parathyroid hypercalcaemia (Transbøl et al. 1970b).

Finally, factors such as seasonal variations in urinary calcium excretion (Robertson et al. 1974; Transbøl et al. 1975) and bendroflumethiazide (Jørgensen & Transbøl 1973), which decreases the urinary excretion of calcium, change the HDI in accordance with the effect on UCaV. For these obvious reasons, determinations of HDI have to be carried out in patients being ambulatory and taking a diet containing standard amounts of calcium, phosphate and sodium. They should not be under treatment with diuretics, estrogens or other drugs known to affect calcium metabolism.

Discriminatory power of HDI

With but very few exceptions (Raisz 1971; Massry & Coburn 1973; Parfitt 1974; Wills 1974) reviews dealing with the differential diagnosis of hypercalcaemia state, that determinations of the 24-hour urinary calcium excretion is of little or no diagnostic help. However, by relating this excretion to the product of serum total calcium and the 24-hour clearance of creatinine as a very rough approximation to the filtered load of calcium this expression gains a considerable discriminatory power. The discrimination is further improved by the inclusion of serum phosphate (fig. 2 (a-d)).

According to the fitted distributions derived from the complete series (not shown) HDI = 137 represents the point at which 89.6% of both populations would be correctly classified. In practice, where we also meet a few cases of apparent or true dual causes of hypercalcaemia (see below), this point turned out to discriminate correctly 100 (93.5%) of the total 107 patients (Table 3). It adds to the applicability of the HDI, that this degree of discrimination was obtained despite the use of a variety of routine and research methods (Table 2) in two different hospitals over a period of 10 years.

HDI values below 137 were noticed in a total of 77 patients of whom 76 (98.7%) were correctly classified, while 30 patients had values at or above 137. This group was heterogenous, comprising six cases of hyperparathyroidism, two cases of this condition associated with calciummetabolic active sarcoidosis or hyperthyroidism and 22 cases of non-parathyroid

hypercalcaemia. Since it is important therapeutically to get the true dual-cause hypercalcaemias separated from the cases of uncomplicated hyperparathyroidism, we will consider 24 patients (80.0%) of the high-HDI group as correctly identified. From a practical point of view these results imply, that values of HDI below 137 almost certainly indicate the presence of hyperparathyroidism or pseudohyperparathyroidism, while values at or above this limit necessitate a careful search for other causes of hypercalcaemia (Table 3).

Hyperparathyroidism and pseudohyperparathyroidism. Out of a total of 81 patients with uncomplicated hyperparathyroidism, including three cases of apparent dual-cause hypercalcaemia (see below), 75 patients (92.6%) had values of HDI below 137. The patient with pseudohyperparathyroidism also had his HDI in this range. The data available in the literature from studies in similar patients do not permit the calculation of HDI, but a disproportionately low urinary calcium excretion has been reported in some cases of pseudohyperparathyroidism associated with certain unspecified malignancies (Nordin & Peacock 1969) and with bronchogenic (Lafferty & Pearson 1963; Gault & Kinsella 1965; Strickland et al. 1967), renal (Case rec. MGH 1961; Goldberg et al. 1964), pancreatic (Transbøl et al. 1970c) and ovarian carcinomas (Beck-Nielsen et al. 1975). Systematic studies, however, have not been undertaken.

Dual-cause hypercalcaemia. In five patients sarcoidosis (Nos. 10 and 76) or hyperthyroidism (Nos. 130-132) was associated with hyperparathyroidism. In three patients, however, their non-parathyroid component was considered inactive at

the time of study, hence their inclusion in the preceding section. The remaining patients (Nos. 76a and 130a) had HDI values of 157 and 312 which decreased to hyperparathyroid values of 61 and 85, respectively, during therapeutic inactivation of the non-parathyroid component of their hypercalcaemia (Nos. 76b and 130b). The observations in these patients, together with the results of the high calcium intake experiments (Table 5), demonstrate that an increase in the intestinal absorption of calcium and/or in bone resorption in excess of that determined by the actual hyperparathyroidism cause the HDI to rise. Since it is important primarily to detect and to treat the non-parathyroid component in order to improve the condition of the patient ahead of parathyroidectomy and to facilitate the evaluation of the outcome of this operation, we consider HDI values above 136 as very appropriate findings in true dual-cause hypercalcaemia.

Non-parathyroid hypercalcaemia. HDI values above 136 were found in 22 (95.7%) of the 23 patients comprising this rather heterogenous group (Table 3). For the purpose of further discussion we have to divide this group into non-malignant and malignant conditions. The non-malignant group consisted of 16 patients including the single but very evident failure observed in a 16-year old boy having a typical and severe Graves' disease and an HDI of just 76. He was suspected of having hyperparathyroidism as well, but his albumin-corrected serum calcium returned to normal during propylthiouracil treatment and remained so following subtotal thyroidectomy. Explo-

ration of the parathyroids during this operation was negative, although incomplete. This hyperparathyroid value of HDI is very hard to explain unless we imagine firstly, that young bones are less sensitive to the bone-resorbing action of thyroid hormones (the normocalciuria), and secondly, that the hypersensitivity to catacholamines, which may be a feature of severe hyperthyroidism, have caused parathyroid stimulation (the hypercalcaemia). There are clinical as well as experimental evidence for catacholamine-induced parathyroid stimulation (Swinton et al. 1972; Kukreja et al. 1973; Fischer et al. 1973). The observations of Andersen & Mosekilde (1972) of hyperparathyroid TRCa% values in two adult males with hypercalcaemic hyperthyroidism and one patient with phaeochromocytoma, in all of whom a lasting normalization of serum calcium occurred postoperatively (Mosekilde, personal communication), are on line with the findings mentioned above. On the other hand, our findings of high HDI values in the other two cases of hyperthyroidism are in accordance with the depressed values of iPTH usually found in this condition (Buckle et al. 1969; Bouillon & De Moor 1974). At the present time the divergence of these results remain unclarified.

Because of the recent claim of Benson et al. (1974), that virtually all hypercalcaemias of malignancy are true cases of pseudohyperparathyroidism, the malignant part of the non-parathyroid group attracts special interest. Traditionally, patients with myelomatosis and cancer of the breast metastatic to bone are classified as being non-parathyroid because of A: their type of calciummetabolic disturbance, which certainly differs from that of hyperparathyroidism, and B: the early findings of

low-normal to unmeasurable levels of iPTH in myelomatosis as well as in metastatic malignancies (Hawker et al. 1970; Murray et al. 1972; Blair et al. 1973; Manderlier et al. 1973). On returning to the first point we find the conditions to be characterized by 1. osteolytic lesions associated with 2. hypercalcaemia, 3. normal to low intestinal absorption of calcium (Laszlo et al. 1952; Bentzel et al. 1964) and 4. excessive hypercalciuria (Gordan et al. 1962; Nordin & Peacock 1969) in spite of 5. a rapidly developing and partially reversible renal insufficiency caused by precipitation of metastatic calcifications (Arends & Mandema 1958; Jessiman et al. 1963). Furthermore, 6. cortisone-sensitivity is a feature of both conditions (Dent & Watson 1968), from the pathologic lesions of which 7. osteolytic factors other than PTH have been extracted (Gordan et al. 1966; Mundy et al. 1974). Extraction of iPTH has been unsuccessful in myelomatosis and in all but one single case of breast cancer (Mavligit 1971). In our opinion, this evidence does not form a reasonable basis for incriminating parathyroid hormone as a causative factor in the hypercalcaemia of myelomatosis or carcinoma of the breast.
A possible explanation to the often modestly raised levels of iPTH in these disorders (Benson et al. 1974) could be secondary, although not completely suppressible, hyperparathyroidism due to preexisting renal disease. Such a state of affairs is well known in renal transplant recipients (David et al. 1973). Myelomatosis often causes renal insufficiency on its own, and in metastatic cancer of the breast previous bouts of hypercalcaemia may have been followed by periods of normocalcaemia

and persisting renal insufficiency. Unfortunately, Benson et al. (1974) did not relate the levels of iPTH to renal function in their patients.

Our finding of HDI values above 136 in all of the seven malignancies is not inconsistent with a certain hypersecretion of PTH, but it certainly suggests, that this hypersecretion cannot be more than contributory to the hypercalcaemia. As in the dual-cause hypercalcaemias previously discussed, the finding of HDI values above 136 is most convenient, since it points towards the possible presence of a non-parathyroid disorder, which primarily deserves therapeutic attention.

Some years ago, in a review on the diagnosis of hyperparathyroidism, Raisz (1971) asked the question: "What to do until the immunoassay comes", suggesting that this would offer a solution to all diagnostic problems. Today we know, that the immunoassay is not going to reach the end on its own. What we need is the combined information supplied by the immunoassay and by tests measuring effects of parathyroid hormone.

Finally, somebody may ask why we have to use these tests at all, since we have to consider the possibility of malignant disease regardless of their outcome. The answer is simple. The group of malignancies causing pseudohyperparathyroidism demands one set of investigations, while another set has to be used in the search for a non-parathyroid cause of hypercalcaemia. In the case of suspected pseudohyperparathyroidism we primarily have to look for carcinomas of the lung, kidney, liver, gall bladder, pancreas, gastrointestinal and female genital tract, while in

non-parathyroid hypercalcaemia we have to evaluate the possibility of the milk-alkali syndrome, vitamin A and D intoxication and immobilization by history and to direct the attention towards the possible presence of carcinoma of the breast, osteolytic metastases, myelomatosis, leucaemia, malignant lymphomas, sarcoidosis, collagen diseases, hyperthyroidism and Addison's disease. An radiographic and scintigraphic survey of the skeleton combined with bone marrow aspiration and a biopsy program (lymph node, liver, kidney, skin, muscle) is essential in non-parathyroid hypercalcaemia as exemplified in previous reports (Lund et al. 1970; Transbøl et al. 1970b; Transbøl et al. 1970c). Thus, the most direct way to the diagnosis depends on the combination of endocrine methods to determine the course of action, followed by one of two different sets of clinical and paraclinical methods.

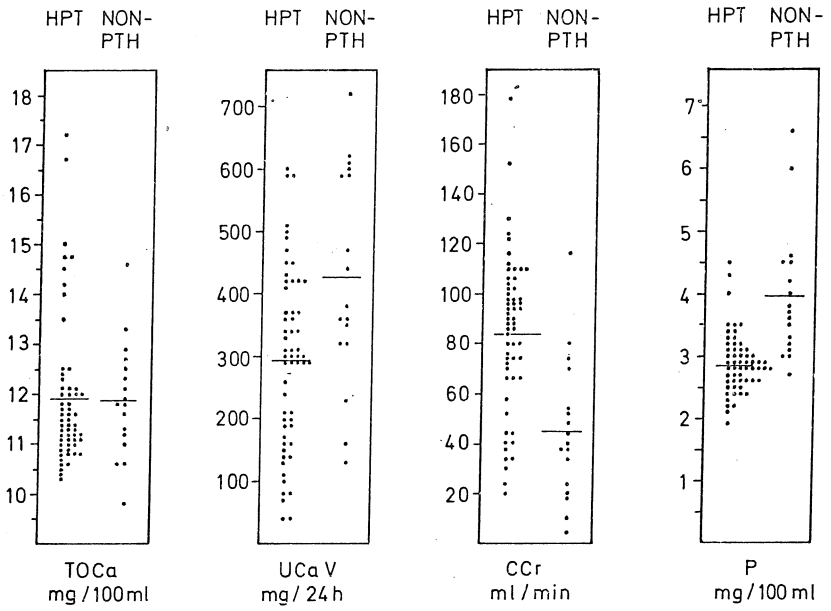
HPT
NON-PTH
18
17
16
15
14
13
12
11
10
TOCa
mg/100ml
700
600
500
400
300
200
100
UCa V
mg/24h
180
160
140
120
100
80
60
40
20
CCr
ml/min
7
6
5
4
3
2
1
P
mg/100ml

Fig. 1

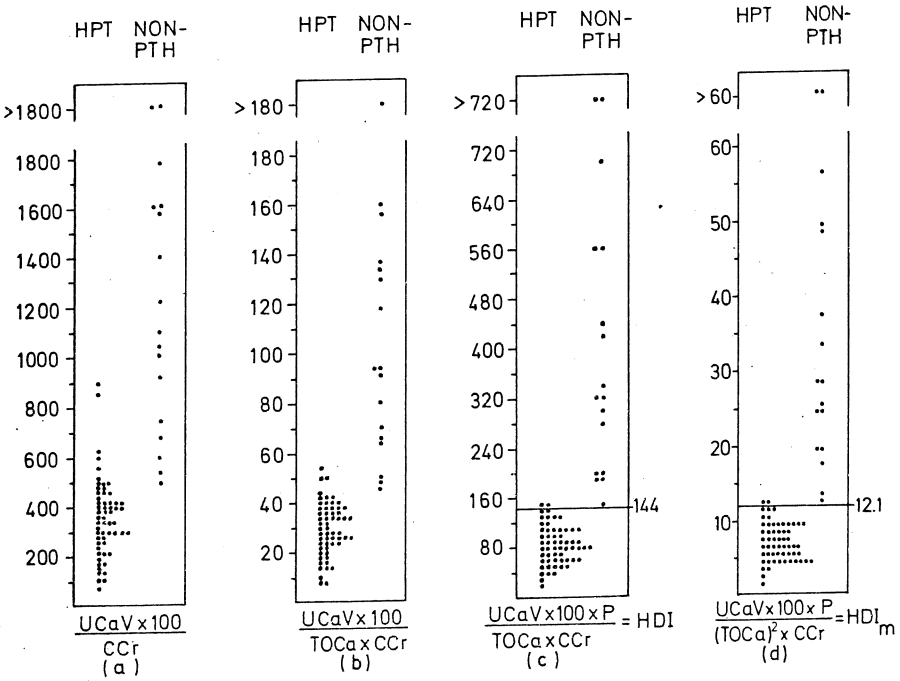
HPT
NON-PTH
>1800
1800
1600
1400
1200
1000
800
600
400
200
UCaV x 100 / CCr
(a)
>180
180
160
140
120
100
80
60
40
20
UCaV x 100 / TOCa x CCr
(b)
>720
720
640
560
480
400
320
240
160
144
80
UCaV x 100 x P / TOCa x CCr = HDI
(c)
>60
60
50
40
30
20
12.1
10
UCaV x 100 x P / (TOCa)² x CCr = HDIm
(d)

Fig. 2

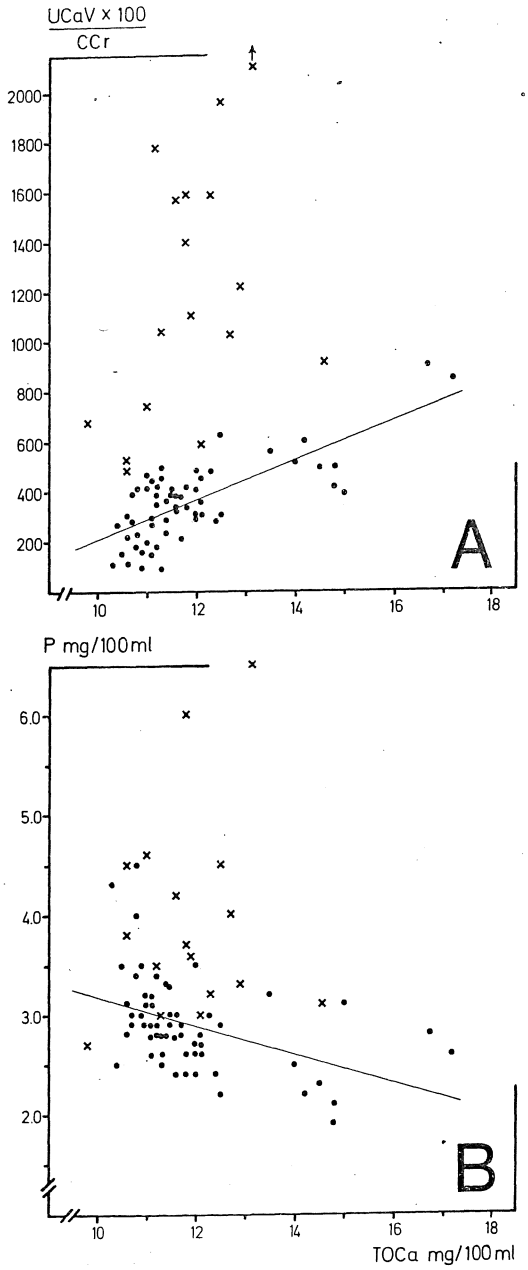
UCaV x 100
CCr
2000
1800
1600
1400
1200
1000
800
600
400
200
A
10
12
14
16
18
P mg/100ml
6.0
5.0
4.0
3.0
2.0
B
10
12
14
16
18
TOCa mg/100ml

Fig. 3

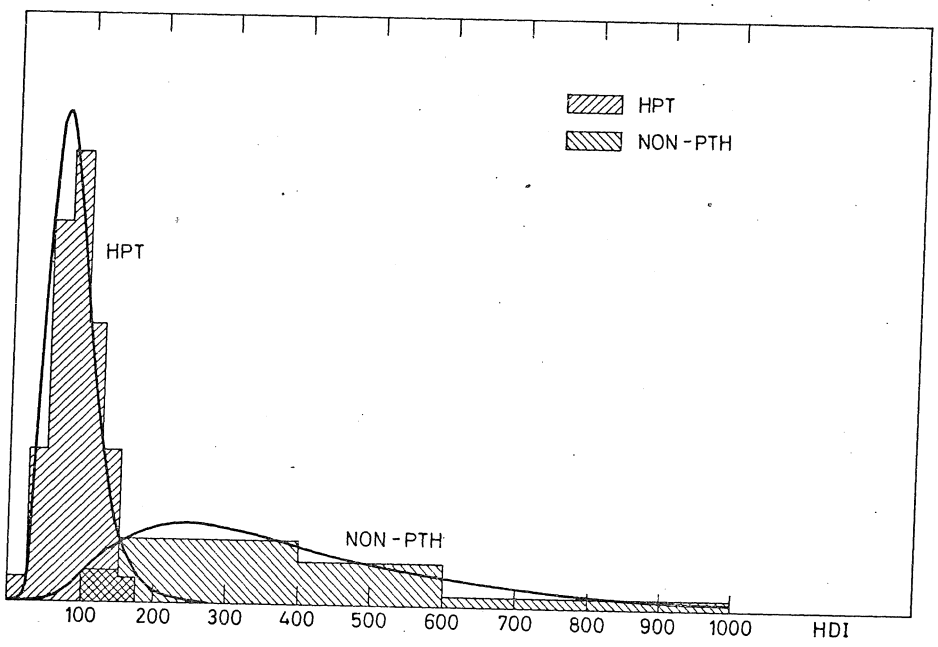
HPT
NON-PTH
HPT
NON-PTH
100
200
300
400
500
600
700
800
900
1000
HDI

Fig. 4

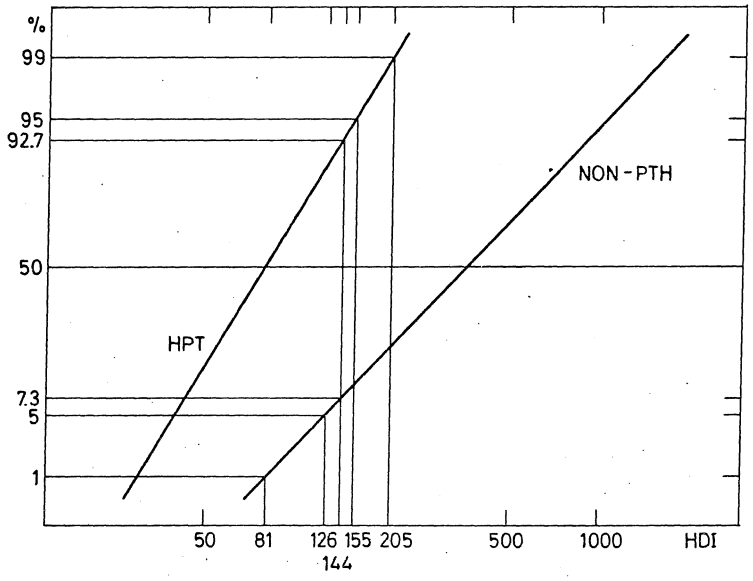
%
99
95
92.7
50
7.3
5
1
NON-PTH
HPT
50
81
126
144
155
205
500
1000
HDI

Fig. 5

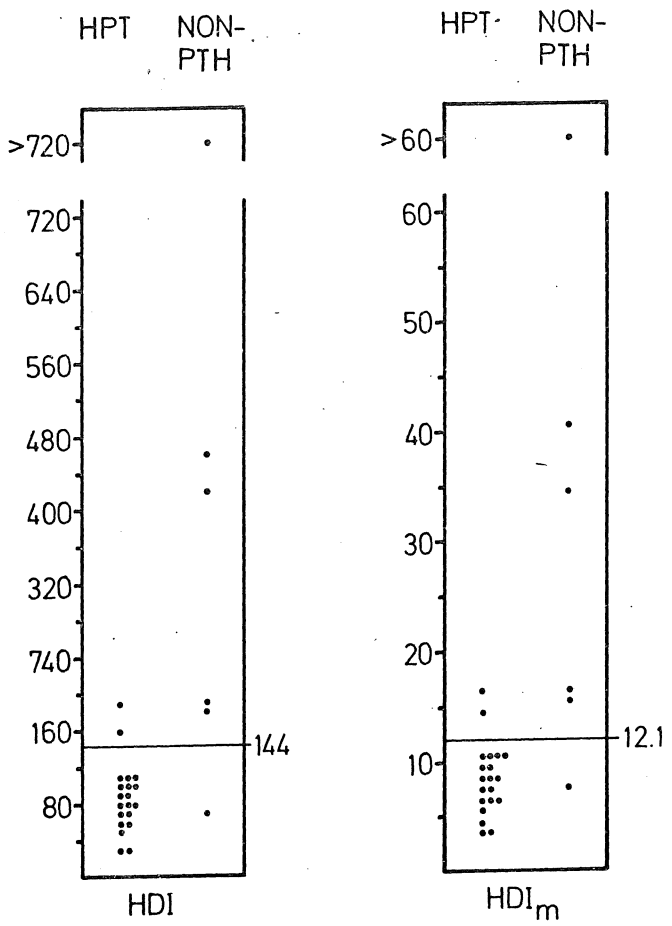
HPT
NON-PTH
>720
720
640
560
480
400
320
740
160
144
80
HDI
HPT
NON-PTH
>60
60
50
40
30
20
12.1
10
HDIm

Fig. 6

LEGENDS TO FIGURES

Fig. 1. Values for serum total calcium (TOCa), 24-hour urinary calcium excretion (UCaV), 24-hour clearance of creatinine (CCr) and serum phosphate (P) in the retrospective series comprising 58 patients with hyperparathyroidism (HPT) and 17 patients with non-parathyroid hypercalcaemia (NON-PTH).

Fig. 2. The creation step-by-step of the hypercalcaemia discrimination index (HDI) (c) from the basal parameters presented in Fig. 1. HDI_m (d) represents the index suggested by the multivariate analysis (see text). HDI as well as HDI_m yields a nearly complete distinction between hyperparathyroidism (HPT, n = 58) and non-parathyroid hypercalcaemia (NON-PTH, n = 17).

Fig. 3. (A) The relation of clearance-corrected urinary calcium excretion (UCaV x 100/CCr) to serum totalcalcium (TOCa) in hyperparathyroidism (n = 58 (•)) and non-parathyroid hypercalcaemia (n = 17 (x)). For hyperparathyroid data only: UCaV x 100/CCr = 78.4 x TOCa - 572, r = 0.73, the regression coefficient being significantly different from zero ($t = 8.09$, $p < 0.001$).

(B) The relation of serum phosphate (P) to TOCa in the same groups of patients. For hyperparathyroid data only: P = -0.146 x TOCa + 4.632, r = 0.45, the regression coefficient also differing significantly from zero ($t = 3.75$, $p < 0.001$).

Thus, for a given level of TOCa patients with non-parathyroid hypercalcaemia excrete more calcium and tend to have higher levels of serum phosphate than hyperparathyroid patients.

Fig. 4. Observed and fitted logarithmically normal distributions of HDI for the retrospective cases of hyperparathyroidism (HPT, n = 58) and non-parathyroid hypercalcaemia (NON-PTH, n = 17).

Fig. 5. Use of the estimated distributions of HDI to the determination of discrimination points. At HDI = 144 the same frequency (92.7%) of each population would be correctly classified according to the fitted distributions. More than 99% and 95% of the hyperparathyroid patients is expected to have HDI-values below the respective figures of 205 and 155, while more than 99% and 95% of the non-parathyroid patients have values above 81 and 126, respectively (see text).

Fig. 6. Determinations of HDI and HDI_m in a prospective series of hypercalcaemic patients including 20 patients with a final diagnosis of hyperparathyroidism (HPT) and 6 patients with non-parathyroid hypercalcaemia (NON-PTH).

Table 1. Information on sex, age, month of study, parathyroid pathology and the basal parameters used in the calculation of HDI in 107 hypercalcaemic patients.

(Transbøl, Jørgensen, Hornum & Keiding: Hypercalcaemia discrimination index: ....)

Pat. No.	Initials	Sex	Age	Month of study	Serum TOCa	Serum P	Urine CCr ml/min	Urine UCaV mg/24 h	Urine UNaV mEq/24 h	Urine HDI	Pathology
					RETROSPECTIVE SERIES						
	Hyperparathyroidism (n=58)										
1	AHJ	F	48	9	17.2	2.6	43	366	45	129	1 A
15	KJ	M	55	2	11.4	3.3	100	366	-	106	1 A
18	JAN	M	24	8	11.2	2.8	89	160	74	45	1 A
20	NKC	F	62	11	11.0	2.9	83	163	61	52	2 A
26	PVN	M	43	5	10.6	2.8	129	285	90	58	3 N
27	ALE	F	55	12	10.3	4.3	40	42	31	44	2 H
33	CWJ	M	51	8	15.0	3.1	38	149	57	81	1 A
37	EME	F	47	10	14.8	1.9	98	487	79	64	1 A
38	AHO	M	52	1	14.2	2.2	79	474	54	93	4 H
39	EJP	F	41	12	14.8	2.1	74	307	74	59	1 A
40	GL	F	55	4	14.0	2.5	79	408	62	92	1 A
47	JM	M	29	8	11.6	2.8	152	512	-	81	1 H
51	EHA	F	44	11	11.8	2.4	124	417	68	68	1 A
52	EAM	F	48	3	11.4	2.8	177	417	56	58	1 A
57	ECWJ	M	47	9	11.3	2.6	74	66	-	21	1 A
64	EAMJ	F	47	8	11.1	2.9	101	298	47	78	1 A
65	PS	M	59	9	12.0	2.4	106	311	67	59	1 A
66	KOS	M	50	9	12.5	2.2	96	295	66	54	1 A
67	KAEJ	F	63	9	10.8	4.0	20	36	77	67	1 A
68	NWL	F	67	10	14.5	2.3	39	193	60	78	3 H
69	BL-M	M	46	10	11.4	3.3	106	309	39	84	1 A
70	HST	F	38	10	11.6	3.0	91	303	53	86	1 A
71	PJMSK	F	64	11	11.0	3.1	72	297	66	116	1 A
72	CMF	F	57	1	12.1	2.8	101	362	67	83	1 A
73	BA	F	18	2	10.9	3.5	109	105	108	31	2 N
74	JAH	M	48	2	11.7	2.9	98	213	56	54	1 A
75	HHA	M	50	3	11.1	2.6	116	172	37	35	2 A
77	ECMH	F	48	11	10.9	3.0	65	104	136	44	1 A
78	KAM	F	55	11	11.0	3.2	73	342	30	136	1 A
79	THS	M	30	10	10.8	4.5	87	199	54	95	2 H
81a	CMN	F	59	4	12.1	2.7	69	214	72	69	1 A
- b	-	-	-	-	12.1	2.7	71	382	74	120	-
82a	KMH	F	54	4	11.2	2.9	79	334	90	110	1 A
- b	-	-	-	-	11.7	2.8	85	361	108	102	-
83a	EOA	F	65	5	13.5	3.2	23	129	56	133	1 A
- b	-	-	-	-	13.8	2.7	19	180	77	185	-
84a	RMH	F	30	5	12.0	2.6	88	263	50	65	1 A
- b	-	-	-	-	12.0	2.8	78	313	62	94	-
85a	OHWH	M	42	5	10.7	2.9	93	368	55	107	2 H
- b	-	-	-	-	10.7	2.9	85	595	81	190	-
86a	AML	F	54	5	11.1	3.2	96	427	84	128	1 A
- b	-	-	-	-	11.0	2.9	86	440	82	135	-
88	AMLP	F	51	11	12.4	2.4	66	187	-	55	1 A
89	AP	F	74	3	10.8	3.4	34	139	-	133	1 A
90	HGS	M	21	6	16.7	2.8	65	585	103	151	1 A
91	FTP	M	61	6	11.3	2.5	90	448	70	110	1 A

cont ....

(Table 1, p. 2)

92	LH	M	17	1	12.0	3.5	121	588	68	142	1 A
93	HEJ	F	70	2	12.5	2.9	95	598	115	146	2 A
94	AMJ	F	44	3	11.7	2.8	112	424	129	101	1 A
95	HMDP	F	66	10	11.3	2.8	43	195	60	112	1 A
96a	AJW-R	M	54	1	11.2	2.7	86	336	62	94	1 A
- b	-	-	-	-	12.0	2.9	77	192	46	60	-
97a	ALM	F	74	1	12.0	2.7	58	236	95	92	1 A
- b	-	-	-	-	12.7	3.1	56	100	60	44	-
98a	AHB	M	80	2	11.1	3.1	29	78	62	75	NO
- b	-	-	-	-	11.1	3.0	32	62	81	52	-
99a	NHS	M	58	2	10.5	3.5	51	76	51	50	2 N
- b	-	-	-	-	10.6	3.3	38	42	61	34	-
100a	BPM	M	49	2	12.1	2.6	110	498	67	97	2 N
- b	-	-	-	-	12.9	2.9	132	248	61	42	-
101a	HGL	M	52	3	10.7	3.0	103	286	105	78	1 A
- b	-	-	-	-	11.4	3.4	100	108	102	32	-
102a	CMSR	M	52	3	10.4	2.5	110	290	95	69	NO
- b	-	-	-	-	10.5	3.2	121	170	116	43	-
103a	IMM	F	69	4	11.5	3.0	110	452	82	107	>1 H
- b	-	-	-	-	11.9	3.2	86	170	90	53	-
104a	BEF	F	39	5	11.8	2.6	33	138	72	92	1 A
- b	-	-	-	-	12.3	3.5	33	36	93	31	-
105a	AMH	F	24	6	11.2	3.4	97	338	60	106	1 A
- b	-	-	-	-	11.8	3.5	99	172	87	52	-
106	LJRB	F	55	8	11.5	2.9	76	294	98	98	1 A
107	AMW	F	61	8	12.3	3.0	86	415	94	118	2 A
108	EAO	F	60	8	11.6	2.4	94	362	86	80	2 A
109	EJM	M	65	9	10.6	3.1	94	286	101	89	2 A
Pseudohyperparathyroidism											
134	JPEH	M	51	3	13.9	3.7	69	308	52	119	
Hyperparathyroidism and sarcoidosis											
10a	MEJ	F	67	3	12.9	2.8	73	290	-	86	>1 A
- b	-	-	-	9	12.0	3.0	62	178	63	72	-
76a	BES	F	23	4	12.5	2.7	49	356	72	157	3 H
- b	-	-	-	-	10.5	2.6	72	176	-	61	-
Non-parathyroid hypercalcaemia (n=17)											
Vitamin D intoxication											
37	PEØ	M	45	8	11.6	4.2	23	361	-	568	
38	EB	F	51	12	11.3	3.0	37	388	75	276	
40	EKT	F	29	1	12.1	3.0	54	319	61	146	
Sarcoidosis											
43	EVK	F	58	3	11.2	3.5	33	589	75	558	
46	TFS	M	26	8	10.6	4.5	73	359	33	211	
50	HEV	M	60	11	11.8	6.0	10	159	85	809	
51	HB	F	13	4	12.3	3.2	37	590	89	415	
52	EViK	F	64	8	12.5	4.5	18	353	76	706	
53	FHH	M	30	10	9.8	2.7	47	321	85	188	
54	CAL	M	73	7	12.9	3.3	19	232	62	313	
Collagen disease											
56	EMKR	F	56	1	11.9	3.6	40	443	80	335	

cont ....

(Table 1, p. 3)

157	SKI	M	61	7	11.0	4.6	81	596	88	308	
	Idiopathic intestinal hyperabsorption hypercalcaemia										
159	HOCN	M	44	10	10.6	3.8	116	616	55	190	
	Malignant lymphomas										
161	BSH	M	28	8	11.8	3.7	44	614	53	437	
162	AFL	M	62	1	14.6	3.1	51	471	67	196	
	Myelomatosis										
164	EKC	F	50	12	12.7	4.0	70	718	66	323	
165	OTK	F	50	12	13.3	6.6	4	133	74	1850	

PROSPECTIVE SERIES

Hyperparathyroidism (n=20)

110	IJVJ	F	57	12	10.5	3.8	125	173	91	50	1 A
111	JHKM	F	61	12	10.9	3.3	92	287	101	94	1 A
112	KS	F	73	3	12.2	2.7	79	227	74	64	1 A
113	EMC	F	65	4	10.6	2.2	97	179	119	38	1 A
114	TNH	F	41	4	11.5	2.5	139	491	75	77	1 A
115	EKjJ	F	53	4	11.3	2.3	63	354	80	114	1 A
116	ILBJ	F	39	8	10.3	3.7	94	281	95	107	1 A
117	JA	M	21	10	9.5	3.6	118	255	104	82	1 A
118	LJP	F	30	12	10.7	3.4	127	296	62	74	NO
119	HRJ	M	58	2	10.6	2.4	67	95	118	32	1 A
120	TELM	M	58	2	10.6	3.3	99	370	165	116	4 H
121	BH	F	65	3	11.6	3.3	75	254	72	96	1 A
122	ACDL	M	69	5	11.3	3.2	76	514	85	191	1 A
123	HH	M	33	5	10.3	3.6	78	244	129	102	1 A
124	HAGN	F	67	6	11.3	2.9	103	408	116	102	1 A
125	KRC	F	47	8	11.1	3.1	72	174	73	68	>1 A
126	EKN	F	70	9	11.0	3.4	69	264	42	118	1 A
127	CPC	F	79	10	12.1	2.8	52	201	73	89	1 A
128	EKaJ	F	46	11	10.7	3.3	98	253	45	80	1 A
129	HTAA	F	68	12	11.4	3.5	65	352	32	166	>2 H

Hyperparathyroidism and hyperthyroidism

130a	ES	F	62	1	11.5	6.0	11	566	90	312	OU
- b	-	-	-	10	11.9	4.1	25	62	83	85	-
131	GTR	F	51	11	11.1	3.0	76	441	120	157	1 A
132	LKMP	F	52	1	11.2	3.0	99	303	92	82	1 A

Non-parathyroid hypercalcaemia (n=6)

	Hyperthyroidism										
135	OLG	M	26	8	12.7	2.8	60	525	-	193	
136	MFB	M	16	12	10.7	5.3	151	233	146	76	2 N
	Sarcoidosis										
155	NPMN	M	32	9	12.3	4.8	28	301	93	420	
	Cancer of the breast metastatic to bone										
166	EBA	F	55	9	11.3	3.5	61	367	28	186	

cont ....

(Table 1, p. 4)

167	EMPS	F	65	9	16.0	6.0	14	652	27	1746
168	ET	F	63	9	11.4	5.3	45	450	25	465

Abbreviations:

A = adenoma, H = hyperplasia, N = large but histologically normal glands, see section on MATERIAL, OU = operation unsuccessful, NO = not operated

Table 2. Review of chemical methods used in the individual patients.

Analysis	Literature	Reference range (mean ± 2 S.D.)	Patients Case Nos. in Table 1.
TOCa	Transbøl et al. 1970a	9.2 - 10.6	1-86, 137-151, 156-162
-	Jordal, unpublished[1]	9.3 - 10.4	88-95, 112-117, 130, 135, 152-154, 164-165
-	Jørgensen et al. 1973	8.7 - 10.3	96-111, 134
-	Jørgensen et al. unpublished	9.5 - 10.7	118-129, 131-132, 155, 166-168
P	Transbøl et al. 1968	2.5 - 4.6	1-86, 137-151, 156-162
-	Jørgensen et al. 1973	2.5 - 4.6	88-136, 152-155, 164-168
Creatinine	Transbøl et al. 1968		1-86, 137-151, 156-162
-	Jørgensen & Transbøl 1973		88-95, 112-117, 130, 135, 152-154, 164-165
-	Bonsnes & Taussky 1945		118-129, 131-132, 155, 166-168
Urine Ca	Transbøl et al. 1968		1-86, 137-151, 156-162
-	Jordal, unpublished[1]		88-95, 112-117, 130, 135, 152-154, 164-165
-	Jørgensen et al. 1973		96-111, 118-129, 131-132, 134, 155, 166-168
Urine Na	Transbøl et al. 1968		1-86, 137-151, 156-162
-	Jørgensen et al. 1973		88-136, 152-155, 164-168

[1]EDTA-titration using calcon-carbonic acid as indicator

(Transbøl, Jørgensen, Hornum & Keiding: Hypercalcaemia discrimination index: ...)

Table 3. Correspondence between the HDI-based classification and the final clinical diagnosis in 107 hypercalcaemic patients.

Patients		Hypercalcaemia discrimination index							
Final clinical diagnosis	Total No.	99% range of HPT / 99% range of NON-PTH						Correct diagnosis (89.6% limit)	
		95% range of HPT / 95% range of NON-PTH							
		89.6% range of HPT / 89.6% range of NON-PTH							
		< 60	61-101	102-136	137-159	160-211	> 211	No.	%
HPT	78	18	35	20	3	2	-	73	93.6
Pseudo-HPT	1	-	-	1	-	-	-	1	-
HPT + NON-PTH[1]	5	-	2[2]	-	1[2]+1[3]	-	1[3]	4	-
NON-PTH	23	-	1	-	1	6	15	22	95.7
Total	107	18	38	21	6	8	16	100	93.5

[1] Sarcoidosis or hyperthyroidism

[2] NON-PTH condition judged to be calciummetabolic inactive, see text

[3] NON-PTH condition judged to be calciummetabolic active, see text

(Transbøl, Jørgensen, Hornum & Keiding: Hypercalcaemia discrimination index: ...)

Table 4. Dependence of HDI (mean ± S.D.) upon sex and age in hyperparathyroidism (n = 78).

	Years	
Age	< 50	≥ 50
Females	77 ± 24[1] (n=18)	96 ± 32[1] (n=31)
Males	86 ± 37 (n=13)	81 ± 39 (n=16)

[1] $p < 0.05$ (Student's t-test)

(Transbøl, Jørgensen, Hornum & Keiding: Hypercalcaemia discrimination index: ...)

Table 5. Effects of high calcium intake and of thiazide administration upon HDI in hyperparathyroidism.

Change of regimen	Number of patients	HDI before	HDI during
High calcium intake[1]	6	102[2]	138[2]
Bendroflumethiazide[1]	10	86[3]	44[3]

[1] See methods

[2] $p < 0.05$

[3] $p < 0.001$ (Method of paired comparisons)

(Transbøl, Jørgensen, Hornum & Keiding: Hypercalcaemia discrimination index: ...)

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