ENLARGEMENT OF THE PARATHYROID GLANDS IN RENAL DISEASE*

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The initial impetus to this study was given by a case of typical osteitis fibrosa with adenomatous enlargement of three parathyroid glands and associated polycystic kidneys.† The question which arose in the discussion was in regard to the relation between the kidney disease, obviously congenital in origin, and the parathyroid enlargement.

Since the report by MacCallum,[1] in 1905, of parathyroid adenoma associated with chronic glomerulonephritis, the simultaneous occurrence of renal lesions with parathyroid tumors or enlargement has been noted repeatedly. This association has been emphasized particularly in the recent study of Albright, Baird, Cope and Bloomberg,[2] who collected 83 cases of hyperparathyroidism, 43 of which showed some type of renal damage. The renal lesions are attributed to the precipitation of calcium in the tubules, with resultant sclerosis, contraction and insufficiency, or to the formation of calculi in the pelvis associated with pyelonephritis.

Thus, these authors in general regard the renal lesions as a sequel to the chronic hyperparathyroidism and stress especially the deposition of calcium in the renal tissue as the proximate cause of the kidney lesions. However, in their discussion they raise the question as to whether the parathyroid enlargement may not be secondary to the renal disease in the cases in which multiple glands are affected. They report: "It seems conceivable that a chronic renal insufficiency with phosphate retention and a high inorganic phosphorus level might likewise cause hyperplasia of all parathyroid tissue which might go on to multiple tumor formation. . . . In these cases, the kidney damage may be the cause and not the result of the parathyroid tumors."

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† This case has been reported in detail by Gutman, A. B., Swenson, Paul C., and Parsons, W. B. The differential diagnosis of hyperparathyroidism. *J.A.M.A.*, 1934, **103**, 87 (Case 4, page 90).

Bergstrand [3] in a routine study of the parathyroids in 200 autopsies found a small percentage in which the glands were "distinctly enlarged" and in most of these cases there were at the same time more or less severe changes in the kidneys. Subsequently, a series of nephritis cases was studied: in 10 of 50 cases the combined parathyroid weights exceeded 200 mg., which he regards as the upper limit of normal. We shall refer to these findings again after an analysis of our own data.

Vines [4] in his monograph states: "In chronic nephritis a somewhat similar hyperplasia (*i.e.*, as that in rickets) has been found." He gives no data or references, however.

With this suspicion of a relation between renal disease and parathyroid enlargement before us, it seemed worth while to begin a systematic study, in order to determine whether disease of the kidneys might not lead quite regularly to enlargement of the parathyroids.

Material and Methods

The parathyroid glands in a series of 27 nephritic and 72 miscellaneous cases were dissected out and weighed individually on a Roller-Smith torsion balance, sensitive to 0.2 mg. They were then fixed in Zenker's fluid and sectioned serially for identification and microscopic study. A second series of 29 nephritic and 12 control cases was obtained from neck organs which had been preserved in Klotz or Kaiserling fluid. These glands were also weighed and sectioned. The weights of these fixed specimens were found to be somewhat less than that of the fresh material, but no constant variation was found. The data obtained from this material will therefore be presented separately.

Weights of Parathyroids in Non-Nephritic Cases

In order to have a reliable standard of comparison it was necessary to obtain data on a sufficient number of control cases to show the range of biological variation in comparable groups of individuals. The ideal data for this purpose, as Bergstrand has pointed out, would include only glands from healthy persons who had died suddenly from accidental causes. Such material was not available, and we have been forced to take as controls the weights of glands from non-nephritic patients dying of various diseases. Knowing nothing of the effect which such diseases might have upon the parathyroids, it cannot be assumed that these weights represent "normal" values in a strict sense, but for the purpose of our inquiry, namely to ascertain if nephritis is commonly associated with parathyroid enlargement,

they would seem to provide a sufficiently accurate standard of comparison. So, also, a calculation of the amount of functional parenchyma would have to take into account the relative amount of interstitial fat and fibrous tissue. No attempt has been made to correct for this variable, since there seems to be no simple method for so doing, and in the comparison of fairly large numbers the error introduced by neglecting this would not appear to be significant.

The literature contains surprisingly few systematic studies of the weights of the human parathyroid. The available references to parathyroid weights in adults are given in tabular form (Table I).

TABLE I

Weights of Parathyroid Glands Cited from Literature

Author	Year	Mean weight		Combined weight
		Upper	Lower	
		gm.		*gm.*
Welch [5]	1898	0.035		
Marañon [6]	1911	0.020–0.050		0.080–0.120
Danisch [7]	1924	0.026–0.030	0.037–0.041	
Marine [8]	1928	0.020	0.035	
Aibara [9]	1931			0.067

Bergstrand,[3] 1921, gives as the upper limit of normal combined weight 200 mg., a figure which on the basis of our own data seems considerably in excess of normal. The weights which we have obtained in our series of non-nephritic control cases in which the kidneys showed no microscopic lesions of significance are presented in Table II.

These data are summarized in Table III, which gives also the standard deviation and the probable error of the mean. These figures are in close agreement with those of Danisch.

INFLUENCE OF SEX ON THE WEIGHT OF NORMAL PARATHYROIDS

It is evident from the table that the mean weights of each gland in the female exceeds that of the male. In the case of the right upper, right lower, and left upper, the difference is statistically significant.

TABLE II

Weights of Parathyroid Glands in Cases with Normal Kidneys

Autopsy No.	Age	Sex	Right upper	Right lower	Left upper	Left lower	Combined weights	Principal diagnosis
	yrs.		*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	
11,392	54	F		0.058	0.026			Bacteremia, hemolytic staphylococcus
11,393	31	F	0.035	0.032	0.025	0.031	0.123	Chorionic carcinoma
11,394	42	M		0.014				Glioblastoma
11,402	56	M	0.024	0.030	0.029			Carcinoma of rectum
11,403	64	M			0.016			Carcinoma of urethra
11,404	51	M	0.094		0.069		0.163	Lobar pneumonia, amebic colitis
11,405	55	M		0.025		0.027		Lobar pneumonia
11,406	29	F	0.021			0.031		Bacteremia, hemolytic staphylococcus
11,410	58	F	0.026		0.019	0.018		Epithelioma of uterus
11,411	60	M	0.016	0.019	0.015	0.025	0.075	Abdominal aneurysm, arteriosclerosis
11,413	41	F		0.059	0.038	0.019		Pylephlebitis
11,415	50	M	0.036		0.029	0.050		Endarteritis obliterans
11,419	25	F	0.036		0.041	0.035		Subacute bacterial endocarditis
11,423	50	F	0.022		0.041	0.016		Sepsis after hysterectomy
11,425	74	M	0.025		0.035	0.037		Arteriosclerosis
11,427	58	F	0.048	0.047				Lobar pneumonia
11,431	47	M	0.017	0.031	0.018	0.027	0.093	Emphysema
11,435	40	F	0.029	0.066	0.038	0.034	0.167	Syphilitic aneurysm of aorta
11,436	26	M	0.026	0.029		0.030		Lymphoepithelioma of pharynx
11,438	64	F	0.039					Aneurysm of abdominal aorta
11,440	44	M	0.017	0.022	0.037			Abscess of brain
11,441	67	M	0.047	0.036	0.050	0.040	0.173	Aneurysm of cerebral artery
11,447	42	F	0.062	0.058	0.031			Acute appendicitis with perforation
11,449	74	M			0.006			Carcinoma of stomach
11,450	14	M	0.012			0.013		Rheumatic heart disease
11,460	55	M	0.013	0.016				Arteriosclerosis
11,461	52	M	0.011	0.042	0.034	0.031	0.118	Rheumatic heart disease
11,463	75	F	0.026	0.027	0.020	0.034	0.107	Carcinoma of gall-bladder
11,464	40	M	0.024	0.023	0.024			Chronic ulcerative colitis
11,470	53	M	0.034		0.028	0.029		Congenital heart disease
11,471	77	F	0.021	0.022	0.015	0.021	0.079	Carcinoma of breast
11,472	13	F	0.028	0.029	0.031	0.040	0.128	Acute leukemia
11,475	74	F	0.018		0.043	0.032		Carcinoma of gall-bladder

11,476	33	M	0.017	0.010	0.014	0.007	0.048	Hodgkin's disease
11,477	38	F	0.024	0.019	0.011	0.017	0.071	Encephalomyelitis
11,479	28	M	0.021	0.037		0.015		Meningoencephalitis
11,480	64	M	0.046	0.037	0.031	0.009	0.123	Multiple myeloma
11,481	58	M	0.019	0.009	0.015	0.027	0.070	Bacterial endocarditis
11,482	40	F	0.026	0.051	0.026			Carcinoma of breast
11,487	53	M	0.029	0.044	0.023	0.035	0.131	Thrombosis of femoral veins
11,489	70	M	0.019		0.020	0.013		Carcinoma of esophagus
11,491	62	M	0.013	0.016	0.010	0.031	0.070	Rheumatic endocarditis
11,492	67	F	0.023	0.023	0.024	0.042	0.112	Sarcoma of antrum
11,494	62	M	0.030	0.035	0.031	0.022	0.118	Arteriosclerosis
11,495	64	M	0.030	0.065	0.007	0.037	0.139	Duodenal ulcer
11,500	71	M	0.015	0.014	0.008	0.022	0.059	Generalized arteriosclerosis
11,502	67	M	0.029	0.044	0.051	0.067	0.191	Duodenal ulcer
11,505	51	M	0.089		0.033	0.046	0.168	Rheumatic heart disease
11,511	34	F	0.011		0.015	0.027		Pneumonia
11,514	25	M	0.032	0.017	0.020	0.028	0.097	Abscess of brain
11,517	14	M	0.025	0.021	0.028	0.023	0.097	Generalized miliary tuberculosis
11,518	32	M	0.023	0.025	0.025	0.038	0.111	Carcinoma of sigmoid colon
11,519	50	M	0.028	0.040	0.033	0.049	0.150	Carcinoma of sigmoid colon
11,520	23	M			0.025	0.025		Lymphatic leukemia
11,523	52	M	0.022	0.026	0.014	0.040	0.102	Carcinoma of rectum
11,526	58	M	0.009		0.018	0.028		Lobular pneumonia
11,528	81	M	0.017	0.023		0.032		Carcinoma of prostate
11,529	38	F		0.035	0.017	0.055		Acute pancreatitis
11,530	42	F	0.072	0.058	0.112	0.056	0.298	Tetanus
11,533	33	F	0.038	0.040	0.048	0.020	0.146	Tuberculous meningitis
11,535	44	F	0.047	0.046	0.026	0.042	0.161	Hemolytic streptococcus sepsis
11,536	36	F	0.030	0.014	0.029	0.028	0.101	Rheumatic carditis
11,538	48	F	0.017	0.028	0.018	0.022	0.085	Lymphosarcoma of stomach
11,539	82	M	0.041			0.045		Senile arteriosclerosis
11,544	46	M	0.021	0.021		0.030		Hodgkin's disease
11,545	25	F	0.035	0.032	0.021	0.049	0.137	Cystadenoma of ovary
11,546	60	F	0.040		0.043			Carcinoma of ampulla of Vater, acute pancreatitis
11,547	56	F	0.009	0.025	0.015	0.032	0.081	Acute streptococcus sepsis following angina
11,548	33	F	0.036	0.020	0.022	0.053	0.131	Lymphogranulomatosis inguinalis (rectal)
11,557	57	M	0.014		0.011	0.021		Carcinoma of stomach
11,559	49	M	0.018	0.028	0.015	0.024	0.085	Lead poisoning, thrombosis
11,561	48	M	0.015	0.023	0.020	0.015	0.073	Rheumatic endocarditis, ulcers of duodenum

The calculated total parathyroid weight for males is 0.106 gm. and for females 0.130 gm. The glands from females are thus approximately 20 per cent heavier. If it had been possible to take into consideration the relation to total body weight the difference might have been still greater.

The explanation of this sex difference is not immediately apparent. It does not appear to be correlated with repeated pregnancies. The

TABLE III

Mean Weights of Parathyroid Glands in Non-Nephritic Cases

Gland	No. of cases	Mean weight	Standard deviation
		gm.	*gm.*
Right upper	62	0.027 ± 0.0013	0.013
Right lower	51	0.032 ± 0.0013	0.014
Left upper	59	0.027 ± 0.0013	0.015
Left lower	58	0.031 ± 0.0010	0.012
Combined weight (calculated)			0.117
Combined weight (observed, 37 cases)			0.118

mean weights of the glands in nulliparas are if anything slightly in excess of those in women who have borne children.

On the other hand, if the weights of the glands in women before and after the menopause (arbitrarily taken as 45 years) be calculated separately, the increased mean weight is found to lie entirely in the younger group. This is shown in Table V.

Although the differences in the two groups are not sufficiently great to be statistically significant, except in the case of the left lower, they are consistent for each gland and probably represent a true difference. A similar analysis of the weights of the male glands discloses no comparable difference in the two age groups. The inference which is suggested, if not proved by our data, is that the age period of sexual activity in females is marked by a definite increase in the weight of the parathyroid.

TABLE IV

Influence of Sex on Weight of Normal Parathyroids

	Right upper		Right lower		Left upper		Left lower		Combined weight (calculated)
	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	
		gm.		*gm.*		*gm.*		*gm.*	*gm.*
Males	36	0.027 ± 0.0011	30	0.027 ± 0.0015	33	0.023 ± 0.0013	35	0.029 ± 0.0010	0.106
Females	26	0.031 ± 0.0006	21	0.037 ± 0.0008	26	0.030 ± 0.0008	23	0.032 ± 0.0012	0.130
Per cent increase females over males		15		37		30		10	22

TABLE V

Mean Weights of Parathyroids in Females Under and Over 45 Years of Age

Age	Right upper		Right lower		Left upper		Left lower		Combined weight (calculated)
	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	
yrs.		*gm.*		*gm.*		*gm.*		*gm.*	*gm.*
Under 45	15	0.035 ± 0.0026	14	0.040 ± 0.0029	16	0.033 ± 0.0038	15	0.036 ± 0.0022	0.144
Over 45	11	0.026 ± 0.0027	7	0.033 ± 0.0033	10	0.026 ± 0.0023	8	0.027 ± 0.0020	0.112
Per cent increase		35		21		27		33	29

Relation of Parathyroid Weight to Age

Taking the series as a whole no correlation has been found between the weight of the parathyroids and the age. This is brought out in Table VI.

While the numbers in each group are too few to permit of statistical analysis, it is evident that there is no definite trend either toward an increase or decrease with advancing age. It should be noted that our data include no cases below the age of 10 and only 3 in the 10–19 year old group.

Weights of Parathyroids in Nephritic Cases

This group may be analyzed first from the point of view of the pathological lesions. The parathyroids were obtained from 27 cases in which at autopsy there were found significant lesions in the kidneys. The data are given in Table VII.

A summary showing in tabular form the mean weights together with the PE_M in the renal cases is given in Table VIII.

Thus, in an unselected series of cases with renal lesions there is found an increase in the weights of the parathyroid as compared with those of a control series. This applies to the individual groups as well as to the total combined weights. This difference is slightly less than three times the square root of the sums of the squares of the probable errors of the means in the cases of the right upper, right lower, and left upper, and slightly greater than three times in the cases of the left lower parathyroids. Strictly, the data are statistically significant only in this last group, according to accepted usage. But the probability that the increased weight in the renal cases is not accidental is enhanced by the fact that it is seen in each comparable group.

Since this series includes indiscriminately various types of renal lesions of various degrees of severity, without regard to duration or to clinical evidence of renal insufficiency, it is probable that the mean differences between the two groups are correspondingly reduced.

Assuming that the increased mean weight of the parathyroid is significant, the question arises as to whether it is due to the inclusion of a few glands of abnormal size or to a general tendency to enlargement. In Chart I are shown distribution curves for the weight of the

TABLE VI

Weights of the Parathyroids at Various Ages

Age	Right upper		Right lower		Left upper		Left lower		Combined weight (calculated)
	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	
yrs.		*gm.*		*gm.*		*gm.*		*gm.*	*gm.*
10–19	3	0.022	2	0.025	2	0.030	3	0.025	0.102
20–29	6	0.029	4	0.039	4	0.026	7	0.030	0.124
30–39	8	0.027	8	0.024	9	0.023	9	0.031	0.105
40–49	12	0.031	14	0.038	12	0.034	9	0.030	0.133
50–59	15	0.023	11	0.033	15	0.025	14	0.032	0.113
60–69	10	0.031	8	0.033	10	0.028	8	0.032	0.124
Over 70	8	0.026	4	0.022	7	0.021	8	0.030	0.099

TABLE VII

Weights of Parathyroid Glands in Cases with Renal Lesions

Autopsy No.	Age	Sex	Right upper	Right lower	Left upper	Left lower	Combined weight	Type of renal lesion	Marked renal insufficiency
	yrs.		*gm.*	*gm.*	*gm.*	*gm.*	*gm.*		
11,459	15	F	0.037	0.052	0.060	0.082	0.231	Chronic glomerulonephritis	+
11,456	21	M	0.077		0.041	0.040		Subacute glomerulonephritis	+
11,486	43	M	0.025	0.052	0.051	0.050	0.178	" "	+
11,378	44	F	0.022		0.013			Embolic glomerulonephritis	
11,474	27	M	0.041	0.058	0.035	0.033	0.167	" "	
11,504	35	M	0.044	0.030	0.033	0.035	0.142	" "	
11,516	40	M			0.026	0.031		Acute glomerulonephritis	+
11,399	38	M	0.038	0.196	0.051	0.148	0.433	Advanced pyelonephritis and renal calculi	+
11,485	29	F	0.042		0.031	0.035		Pyelonephritis and calculus (left)	
11,390	54	M			0.056			Arteriolar nephrosclerosis	
11,453	69	F		0.047		0.074		" "	
11,396	46	M	0.033		0.035			" "	+
11,400	37	F	0.248	0.016				" "	+
11,424	49	F	0.037		0.046			" "	
11,455	58	M				0.039		" "	
11,553	66	M	0.062	0.065	0.029	0.038	0.194	" "	+
11,556	43	F	0.043		0.040	0.027		" "	
11.462	60	F	0.025	0.013	0.035	0.020	0.093	" "	
11,398	72	F	0.053	0.034	0.010	0.056	0.153	Arteriosclerotic scars	
11,484	36	F	0.014	0.016	0.014	0.023	0.067	" "	
11,496	49	M	0.067					" "	
11,420	43	F	0.009	0.036	0.020			Slight hydronephrosis	
11,437	47	M		0.046	0.030	0.033		Marked hydronephrosis	+
11,434	59	M	0.013	0.051	0.032	0.067	0.0163	Chronic interstitial nephritis	
11,488	72	F			0.028			Infarcts of kidneys	
11,453	35	F	0.031		0.017	0.045		Healed infarcts	
11,490	54	M	0.031	0.041		0.026		Calculus, nephrectomy (right)	

TABLE VIII

Mean Weights of Parathyroids in Nephritic and Non-Nephritic Cases

Cases	Right upper		Right lower		Left upper		Left lower		Combined weight (calculated)
	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	
		gm.		*gm*		*gm.*		*gm.*	*gm.*
Nephritic	21	0.047 ± 0.0069	15	0.050 ± 0.0074	22	0.033 ± 0.0018	19	0.047 ± 0.0044	0.177
Non-nephritic	62	0.027 ± 0.0011	51	0.032 ± 0.0013	59	0.027 ± 0.0013	58	0.031 ± 0.0011	0.117
Per cent increase in nephritics		74		56		22		47	50

TABLE IX

Mean Weights of Parathyroids in Cases with Severe Renal Insufficiency

Cases	Right upper		Right lower		Left upper		Left lower		Combined weight (calculated)
	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	
		gm.		*gm.*		*gm.*		*gm.*	*gm.*
Severe nephritis	7	0.072	5	0.072	8	0.042	7	0.059	0.244
Controls	62	0.027	51	0.032	59	0.027	58	0.031	0.117
Per cent increase		166		125		56		90	109

glands in the series of nephritic and non-nephritic cases. Because of the relatively small number of nephritic cases the curves are irregular, but it is clearly seen that the greater percentage of the nephritic cases falls to the right of the mode of the controls. Of the right upper glands, 71 per cent exceed the mean weight of the controls; of the right lower, 73 per cent; of the left upper, 73 per cent; of the left lower 74 per cent. In 10 cases in which all four glands were recovered, the total weight exceeded the mean total weight of the controls (118 mg.) in 8. The 2 cases in which the total weight was lower showed only arteriosclerotic scars without clinical evidence of renal insufficiency. Of the 8 cases which were above the normal mean 4 had all glands above the mean and 4 showed enlargement of three glands, indicating that the overgrowth is not limited to one or two of the glands in a given case.

The conclusion which seems justified from this analysis is that the parathyroid enlargement is the expression of a general trend and that the increase in mean weight in the nephritic series is not due to the inclusion of a few glands of exceptional size.

In view of the fact that the female glands average heavier than the males, it should be pointed out that the nephritic series includes 14 males and 13 females. The mean of the male parathyroid is larger than that in the females. It is therefore improbable that the normal sex difference is a factor in the enlargement found in the nephritic cases.

Thus far the discussion has concerned unselected cases of renal disease without regard to the intensity of the lesions or their character. It was of interest to ascertain if there existed a correlation between the degree of parathyroid enlargement and the severity or character of the kidney disease.

Reference to Table VII shows that the maximum enlargement occurred in 2 cases of suppurative nephritis and pyelonephritis in which the combined weight of the parathyroids was approximately four times the normal. The next degree of enlargement was in the 3 cases of subacute and chronic glomerulonephritis, in 2 of which the combined weight of the four glands was approximately double the normal. Lesser increases in weight were found in the nephrosclerotic and other types. In those cases in which the renal lesions were unilateral, acute or focal in character, no enlargement of the parathyroids was found.

An attempt has been made to correlate the degree of enlargement with the severity of the clinical symptoms. From the group of 27 cases showing pathological changes in the kidneys we have selected 9 in which the clinical record gave evidence of severe renal insufficiency.

Comprised in this group are 4 cases of chronic and subacute glomerulonephritis (11,459, 11,456, 11,486), 1 of which (11,399)

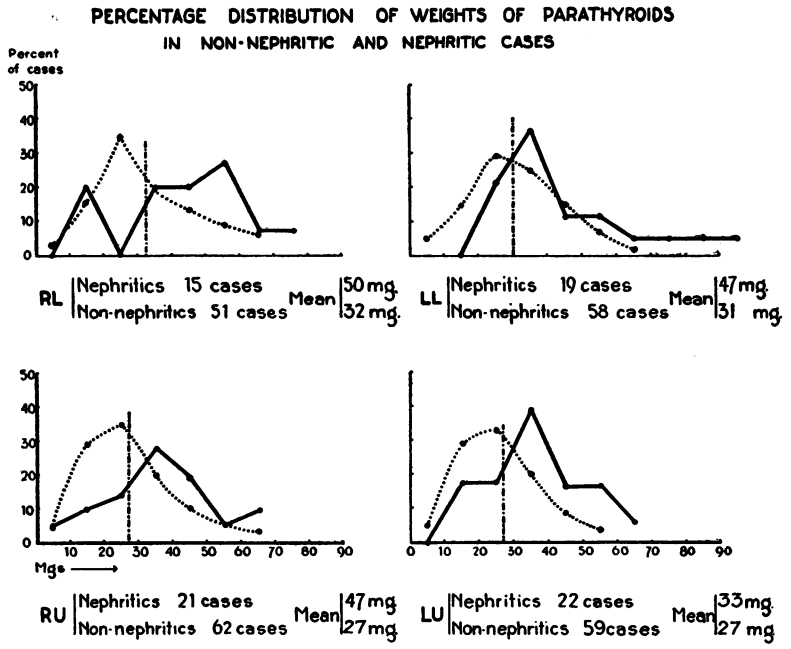

CHART 1

also had a renal calculus and pyonephrosis (all died with uremic symptoms); 3 cases of arteriolar nephrosclerosis with hypertension and terminal uremia (11,396, 11,400, 11,556); 1 marked hydronephrosis (11,437) following carcinoma of the bladder with uremia; and 1 case of acute glomerulonephritis (11,516). In spite of the smallness of the series there is rather convincing evidence that the enlargement of the parathyroids is correlated with the severity of the clinical picture. The number of cases in each group is too small and the variations too wide to justify statistical analysis.

Data on Fixed Specimens

As confirmatory evidence for the frequent association between parathyroid enlargement and renal disease we may supplement the above findings with data based on the weights of glands obtained from museum specimens. They can be presented most briefly in tabular form (Table X).

Although the actual weights of the glands are reduced by the fixation to about 70 per cent of the unfixed organs, a relative increase in weight is again found in the nephritic series, as compared with the controls. This increase is statistically significant for each group of glands in the severe cases and for the right lower and left upper in the series without clinical evidence of severe nephritis. Since these data merely confirm the observations on unfixed material, it is unnecessary to consider the cases individually.

Histological Changes

The material at hand does not lend itself to detailed cytological study. The primary purpose in sectioning glands was to make sure that no lymphatic or tissue other than parathyroid was included in the weighing. Only a few tentative statements can therefore be made in comparing the histology in the nephritic and non-nephritic cases. In spite of great variability, the impression is obtained that the glands of nephritic cases show a more compact structure and relatively less interstitial adipose tissue than those of the control series. Furthermore, the dominant cell type in most of the "nephritic" glands is the large water-clear cell in which the juxtanuclear body appears conspicuously. Oxyphile cells are not more numerous than in the control glands and indeed seem unusually sparse in some of the nephritic cases.

Definite adenomas were found three times in the nephritic series and twice in the control. They were all of the oxyphile cell type. Further study is needed to determine whether the enlargement of the glands in nephritis is due to hypertrophy of individual cells or to increase in their number.

There have been few systematic studies of the histology of the parathyroid in nephritics. Koopmann [10] examined 5 cases of chronic renal disease, including malignant nephrosclerosis, chronic glomerulonephritis, and a case of cystic disease. No histological

TABLE X

Mean Weights of Parathyroids in Nephritic and Control Cases, Based on Fixed Museum Specimens

Classification	Right upper		Right lower		Left upper		Left lower		Combined weight (calculated)
	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	No. of cases	Mean weight	
		gm.		*gm.*		*gm.*		*gm.*	*gm.*
Severe nephritis with renal insufficiency	12	0.039 ± 0.0044	8	0.052 ± 0.0070	11	0.031 ± 0.0024	9	0.042 ± 0.0036	0.164
Per cent increase over normal		77		108		72		68	82
Renal lesions without clinical nephritis	17	0.027 ± 0.0029	13	0.038 ± 0.0035	14	0.032 ± 0.0018	8	0.037 ± 0.0038	0.134
Per cent increase over normal		23		52		78		48	49
Miscellaneous controls	12	0.022 ± 0.0026	10	0.025 ± 0.0026	9	0.018 ± 0.0008	10	0.025 ± 0.0018	0.090

changes were found which could be correlated with the renal lesions or interpreted as indicating hyper- or hypofunction. No weights or measurements are given.

Radnai [11] also has studied the parathyroids in 20 nephritic cases and 20 controls of similar age groups. He believes that there is a somewhat earlier appearance of oxyphile cells and in greater number in the nephritic cases, but finds no other characteristic change. No weights or measurements are given.

Discussion

The principal facts which have emerged from this study are: (1) the mean weight of the female parathyroid glands is greater than that of males; (2) the mean weight of the parathyroids is significantly increased in any type of nephritis, if the lesions are diffuse and severe. We shall discuss briefly the possible implications of these findings.

The sex difference in the weights of the parathyroids has, so far as we are aware, not been previously observed. The first explanation that comes to mind is that the loss of calcium due to pregnancy or lactation might increase the functional demands upon the parathyroids and lead to their enlargement. Our data do not support this theory, since the enlargement was even more marked in nulliparas than in women who had borne children.

Another possibility is that the increased parathyroid weight may be in some as yet obscure way correlated with the alterations of the anterior lobe of the hypophysis which accompanies the menstrual cycle (Andersen[12]). It has been shown recently by Anselmino, Hoffmann and Herold [13] that injection of anterior pituitary lobe extract in rats is followed by a rapid hypertrophy of the parathyroids, with a characteristic change in the cytological picture. Hertz and Kranes [14] have reported similar effects in rabbits. Whether this is a reversible change or not is not known; nor has it been demonstrated yet that this activity of the anterior lobe is due to a special hormone. It is obvious that the exact explanation for the sex difference in parathyroid weights in humans must await further experimental study.

Our observations have brought out clearly the fact that most, if not all, cases of diffuse renal disease are accompanied by a significant

enlargement of the parathyroid glands. Since this occurs in such varied types of renal disorders as glomerulonephritis, arteriolar nephrosclerosis, hydronephrotic atrophy and suppurative pyelonephritis there must be some common chemical factor that stimulates the parathyroids to increased activity and growth.

It seems hardly justified to enter upon an extended discussion of the nature of this correlation on the basis of the data here presented. It is probable that the cases with severe clinical nephritis had phosphate retention, and since "any increase in PO_4 ions will decrease the amount of Ca ions in the blood" (Thomson and Collip[15]), this may incite the parathyroids to increased activity and overgrowth. Whether this simple explanation is adequate or not must be determined by further clinical and experimental studies; our data include only a few determinations of inorganic PO_4 and Ca in the nephritic series, and no conclusions as to a positive correlation can be drawn from them.

It is interesting that the group of cases in which renal lesions were found at autopsy, but in which symptoms of renal insufficiency were not recognized, nevertheless showed in most cases a certain degree of parathyroid enlargement.

It is unfortunate that the bones in this series of nephritic cases could not be carefully studied. Although in none of the cases was there any clinical or gross pathological suspicion of bone disorder, it is possible that those cases in which the parathyroid enlargement was most pronounced might have shown microscopic lesions indicating increased resorption. In renal dwarfism, in which the kidney disease leads often to extreme rickets-like deformity of the skeleton, the parathyroids have not been carefully studied. Langmead and Orr,[16] however, have reported a case in which there did occur parathyroid enlargement and they suggest that the bone changes may have been due in part to excessive parathyroid activity. It may indeed be true that excessive activity of the parathyroids during the growth period may bring about more severe skeletal deformities than in adult life.

In the series of cases which we have analyzed it seems obvious enough that the diverse renal lesions could not have resulted from excessive functional activity of the parathyroids. In the group of cases of hyperparathyroidism collected by Albright, Baird, Cope and Bloomberg [2] it is taken for granted that the renal lesions found in

over half the cases are attributable to the excessive activity of the parathyroids, and in large measure are due to calcium deposition. They hold that the precipitation of calcium phosphate in the renal parenchyma eventually leads to inflammatory changes, sclerosis and contraction, which simulate both chronic glomerular and vascular nephritis. We believe that few pathologists would accept this without question. In some of the cases cited the deposition of calcium in the renal tissues may well have been due to the hyperparathyroidism, and may have been entirely unrelated to a preëxisting nephritis. It is possible, then, that a certain proportion of cases of so-called hyperparathyroidism may be initiated by chronic renal disease.

Summary

1. The mean weights of the parathyroid glands in a series of miscellaneous non-nephritic cases over the age of 10 years is 27 mg. for the upper parathyroid and 31–32 mg. for the lower. The mean combined weight is 118 mg.

2. In the male glands there is no change correlated with advancing age.

3. In the female gland there was found an increase in weight of approximately 22 per cent during the active sexual period; after 45 years there is a decline of weight to figures corresponding with those of the series as a whole. The enlargement is not correlated with pregnancy.

4. The mean weight of the parathyroids in various types of chronic renal disease exceeds that of non-nephritic cases. In an unselected series this increase in mean weight is approximately 50 per cent; in cases with advanced renal lesions the increase amounts to more than 100 per cent.

5. The increase in weight of parathyroids is roughly proportional to the severity and extent of the renal lesions and to the intensity of the clinical signs of renal insufficiency. Usually three or four of the glands share in the enlargement.

Note: We desire to express our thanks to Dr. Walter W. Palmer and to Dr. Allen O. Whipple for permission to utilize the clinical records in these cases.

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