TABLE IV. Daily Fecal Creatinine Excretion.

Patient	Diagnosis	Creatinine excretion, mg/day	Serum creatinine, mg/100 ml
K	Hypogonadism	3.88 2.41 5.05	.84
D	Hodgkin's disease	6.16 3.57 5.06	.82
M	Hemochromatosis	5.68 11.24	1.2
V	Nephrosis	21.7 22.9	1.3
P	Pyelonephritis	10.72 7.15	11.8
G	Chronic glomerulonephritis	10.41 5.32	27.8
B	"	11.11	4.8

cretion of creatinine through the skin and lungs by insensible fluid loss probably can be discounted. Bass and Dobalian(9) have demonstrated a fairly large amount of creatinine and non-creatinine chromogen in the normal sweat, which may be significant in uremia, should actual sweating be sufficient in volume. Several of these possibilities merit further study.

Summary and conclusions. 1. The urinary excretion of creatinine decreases as the filtration rate falls and the serum creatinine rises in chronic renal failure. This is especially apparent when the serum creatinine exceeds 6 mg/100 ml. 2. This decrease is due to either a reduced rate of creatinine production or an alternate excretory pathway. The muscle mass is not significantly decreased, and therefore should not account entirely for decreased production. Alternative excretion in the urine as creatine, or in the feces as creatinine is excluded by the data presented. Other possible mechanisms are suggested, but have not been studied.

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Joint Disease in Mice "Thyroidectomized" with Radio-iodine I^{131}.* (20913)

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In the course of investigations on the skeletal effects of thyroid deficiency in various strains of mice, an unusual joint disease not seen in untreated animals(1) was observed in DBA mice made "athyroid" by administration of I^{131}.

Material and methods. One hundred and thirty-four mice (66 males and 68 females) of the closely inbred strain DBA raised in our laboratory and kept on a stock diet of Purina Laboratory Chow and water *ad libitum* were used. At the age of one month, the animals received a single dose of 200 μc of I^{131} corresponding to about 20 μc/g body weight. Most animals were sacrificed at the ages of 6, 8, or 12 months (age Group I), and of 15 and 18 months (age Group II); some died prematurely or were killed because of symptoms caused by hypophyseal tumors induced by the isotope(2). At necropsy, the

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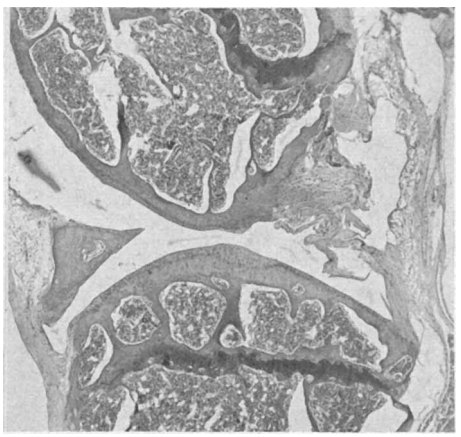
hypophyses were measured and some were fixed for sectioning. The thyroid region was inspected and in the few animals in which no hypophyseal enlargement was noted examined microscopically for remnants of thyroid tissue. The legs including the kneejoints were prepared for microscopic studies as described previously(1). The sections were stained with hematoxylin and eosin and, if desirable, with PAS.

Observations. Microscopic examination. Slight articular changes consisted of swelling of the cartilage of the menisci which contained increased amounts of Schiff positive material, but failed to undergo ossification. The ligaments were loosened, became markedly Schiff positive, and the cells assumed cartilage-like appearance. The synovialis was edematous and hyperplastic. Advanced articular changes were characterized by involvement of the articular surface and the epiphyseal bonemarrow: The cartilage cells were slightly hyperplastic and hypertrophic, the ligaments were thickened and hyalinized obliterating the articular cavity. The proliferating synovialis penetrated into the bonemarrow and underwent fibrosis (photomicrographs 1 and 2). These lesions were frequently associated with flattening and distortion of the epiphyses.

Investigations dealing with the effects of thyroid deficiency induced by I^{131} have to take into account the presence of hypophyseal



Sections through the kneejoints of male mice of strain DBA, 8 mo of age. ×20.

FIG. 1. Untreated animal. The joints show the usual architecture, the meniscus (triangle at left) is ossified.

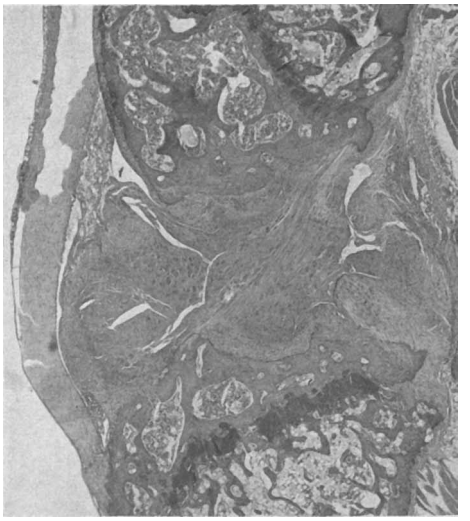


FIG. 2. Animal treated with I^{131}. The joint cavity is obliterated by thickened and degenerated ligaments, the epiphyses are flattened and distorted. The meniscus at left is ill defined, not ossified, and consists of a mass of hypertrophic and degenerating cartilage.

tumors arising under these conditions. In Table I, the findings in both, hypophyses and joints, are given, the symbols (+) and + denoting enlargement of the hypophyses up to 2 mm in diameter or hypophyseal tumors respectively. In Table II, the conditions in the hypophyses have been correlated to the presence of advanced joint disease or the absence of articular lesions. In Table III, the findings in the joints are correlated to the presence or absence of hypophyseal tumors, the symbols (+) and + denoting slight or advanced joint disease respectively.

Incidences of articular findings. 90.5% of the males of age Group I had joint disease (Table I). In mice of age Group II, neither the percentage nor the severity of the articular lesions were materially increased beyond conditions seen in the younger age group. In females, the joint disease set in at a later age than in males, but in age Group II the number of females and males showing articular lesions was similar. Still, the total incidence of joint disease was lower in females than in males indicating decreased susceptibility of the former. In addition, advanced articular changes were less frequent in females than in males.

TABLE I. Incidences and Grades of Hypophyseal and Articular Changes in Various Groups of Mice Treated with I^{131}.

Age, mo	Sex	No. of mice	Mean age at death, mo	Findings in hypophyses* 0	(+)	+	Joint disease: Total incidence No.	%	Joint disease: Advanced cases No.	% of total
7-12	♂	21	9.4	6	6	9	19	90.5	7	33.4
	♀	27	8.9	10	8	9	10	37.1	2	7.2
13-18	♂	45	15.0	12	5	28	43	95.6	16	35.6
	♀	41	13.9	3	2	36	36	87.8	15	36.6
All ages	♂	66	13.2	18	11	37	62	93.9	23	34.8
	♀	68	12.5	13	10	45	46	67.7	17	25.0

* 0, No enlargement. (+), Slight enlargement to 2 mm diameter. +, Tumor.

Correlation of articular and hypophyseal changes. There was, in males, a striking positive correlation between hypophyseal neoplasms and joint disease. In females this correlation was less conspicuous (Tables II and III). Whereas most females with advanced articular changes had hypophyseal tumors, the reverse was not true. Only a fraction of females with hypophyseal neoplasms also showed joint disease.

Discussion. The joint disease observed in DBA mice treated with I^{131} does not occur in untreated animals(1). It may, therefore, be attributed to the hypothyroid state as such or to some associated endocrine dysfunction, or to both. The latter two possibilities cannot be ruled out, since hypophyseal tumors induced by I^{131} secrete large amounts of thyrotrophin (3). In view of the positive correlation between articular lesions and hypophyseal neoplasms in males thyrotrophin given off by the hypophyseal tumors may play a role in the pathogenesis of the joint disorder. Sex differences in the incidence of articular lesions exist regardless of the fact that hypophyseal neoplasms were as frequent in males as in females. The decreased susceptibility of the female to the articular changes suggest an inhibiting role played by the ovaries. The latter may be stimulated to increased production of estrogen by the gonadotrophins reported to be secreted by the hypophyseal tumors(4).

TABLE II. Findings in Hypophyses of Mice with Advanced and without Joint Disease.

Sex	Mice showing advanced joint disease: Total No.	Findings in hypophyses* 0	(+)	+	Mice free of joint disease: Total No.	Findings in hypophyses* 0	(+)	+
♂	23	3	2	18	4	1	3	0
♀	17	0	2	15	22	12	1	9

* 0, No enlargement. (+), Slight enlargement to 2 mm diameter. +, Tumor.

TABLE III. Findings in the Joints of Mice with Hypophyseal Tumors and Grossly Unchanged Hypophyses.

Sex	Mice with hypophyseal tumors: Total No.	Findings in joints* 0	(+)	+	Mice with unchanged hypophyses: Total No.	Findings in joints* 0	(+)	+
♂	37	0	19	18	18	1	15	2
♀	45	11	21	13	13	7	4	2

* 0, No change. (+), Slight joint disease. +, Advanced joint disease.

Summary. In DBA mice "thyroidectomized" with I^{131}, articular lesions were observed which differ from the degenerative joint disease occurring spontaneously in aging mice. Males were more susceptible to the joint disease than females. In males, there was a strong positive correlation between the incidence of hypophyseal tumors induced by the isotope and the incidence of articular lesions, while in females this correlation was less obvious.

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