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LONG-TEEM SEQUELAE OF MASSIVE DOSES OF IODINE-131 I. HISTOPATHOLOGICAL FINDINGS

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*Radiation
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OF IODINE-131

I. HISTOPATHOLOGICAL FINDINGS

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ABSTRACT

Histopathological studies have been made of a number of tissues from rats that had survived various doses (ranging from 10 to 90 μ c per gram of body weight) of radioiodine. Findings described for each tissue at each dose level include such evidence as staining reaction, degeneration and regeneration, and development of abnormal cells.

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INTRODUCTION

Histological preparations of material taken in an I¹³¹ toxicity survival study in rats (UCRL-2553, 2605, 2661, 3013) have been completed, and the slides read. Two series of control rats were utilized: (a) the major control series, consisting of nine animals that were sacrificed at 427 days of age; and (b) the Watts control series,* consisting of twelve animals that were sacrificed at from 260 to 292 days of age.

Five levels of radioiodine administration were studied: 10, 30, 50, 70, and 90 microcuries per gram of body weight of the animal. The animals were sacrificed as follows:

Dosage level	Number of animals	Age (days)	Time postinjection (days)	
10 $\mu\text{c/g}$, major series	8	571	519	
10 $\mu\text{c/g}$, Watts series	8	265	195	
30 $\mu\text{c/g}$	14	474	414	
		511	456	
		571	519	
50 $\mu\text{c/g}$	5	526	471	
		528	473	
		571	519	
		1 tumor-bearing rat	353	301
70 $\mu\text{c/g}$	6	1	356	
		4	571	
		1	511	
90 $\mu\text{c/g}$	14	403	350	
		443	385	
		474	414	
		2 tumor-bearing rats	239	179
		263	210	

* These animals were used by R.W.E. Watts for a series of metabolic rate experiments.

The sacrificed animals were of sufficient longevity that age differentials of the magnitude present in this study were considered negligible.

Histological descriptions of the material taken from the survivors of the above groups follow. The tissues to be described include liver, spleen, kidney, lung, thyroid, thymus, ovary, adrenal, mesenteric lymph node, pituitary, and tumor. The preparations were fixed in neutral formalin or Zenker's or Bouin's, and were stained with haematoxylin and eosin, with the exception of the pituitaries, which were stained with Mallory-Azan.

Liver

There were nine specimens from the major control series, and twelve from the Watts series. The nine in the major series were all recognized as normal. In the Watts series the comments defined the range of normality. Staining reaction either was uniform throughout the section, or revealed some differences in stainability; the cells in the periphery of the lobule were more deeply eosinophilic than those near the central vein. In the Watts series two out of the twelve occasionally showed small scattered clusters of dark-staining round cells, usually lying free and mostly in the sinusoids. These cells were not identifiable.

10 $\mu\text{c/g}$ level (8 specimens in standard series, 8 from Watts series). In the majority of the specimens most of the area was essentially normal. Occasionally, some variability in staining reaction and some parenchymatous degeneration were to be seen; these were found in half the specimens. In one specimen there were several places where the liver cells were arranged in rings or circles like those of a bile duct, possibly suggesting an area of regeneration.

30 $\mu\text{c/g}$ level (14 specimens). Five of the specimens were normal; seven showed rare to common incidence of clusters of small dark-staining necrotic or pyknotic cells. Two other specimens showed occasional isolated, very deeply staining liver cells with pyknotic nuclei. One specimen had several areas of very widely dilated sinusoids and atrophic epithelium. About 20% of the total of the latter section showed this change, whereas the remainder of the section was normal.

50 $\mu\text{c/g}$ and 70 $\mu\text{c/g}$ levels (5 and 6 specimens). The distribution of any changes in the liver seemed to be the same in both groups, so they were combined. Two sections, one in each group, were normal. In most of the remaining sections the majority of the area was normal, but small clusters of the dark-staining cells were found with increased frequency scattered about the section. One of the livers from the 50 $\mu\text{c/g}$ group showed sinusoids; in this specimen the possibility of some acute toxic reaction should be considered. One specimen from the 70 $\mu\text{c/g}$ group showed several areas in which there had been hepatic cell necrosis, with some scars remaining. These were small in number and in size.

90 $\mu\text{c/g}$ level (14 specimens). Two of these specimens were normal; in the remaining seven the vessels were either large or closer together, or both, leading to the suggestion that the tissue intervening between these vessels may be atrophic and degenerated; this was usually widespread. In some of the other sections there were patches of vacuolar degeneration, and in one there was substantial degeneration with only islands of healthy

cells remaining. In five of the group there seemed to be supernumerary bile ducts scattered about the tissue, not simply in the portal spaces; this bile-duct proliferation may indicate that there was an attempt at regeneration of the damaged liver. In this group only two showed the small clusters of dark-staining cells that had been so commonly encountered in previous groups.

Spleen

There were nine controls for the major series and twelve for the Watts series--a total of twenty-one. All but one of the major series were normal. Normal structure was characterized by equal distribution of white and red pulp. In the white pulp the splenic corpuscles were large and well packed with lymphocytes. Approximately 50:50 proportions of gold-brown pigment and packed red blood cells were usually seen. This proportion varied to a small extent in either direction. Connective tissue framework was inconspicuous in all the preparations. The one control that was not normal showed some drain on the lymphocyte formation, which probably was related to severe pneumonia in that animal.

10 µc/g level (major series: 8 specimens). Six specimens showed slight to appreciable depletion of lymphocytes, and reduction in the size of the splenic corpuscles. The red pulp in all these specimens appeared to be normal. Pigmentation was very heavy in some of them.

(Watts series: 8 specimens). The white pulp was always reduced to some extent. This varied from a small reduction--either fewer lymphocytes or smaller splenic corpuscles, or both--to an extreme in which the splenic corpuscles had only a thin collar of lymphocytes around their blood vessel. The red pulp was always easily seen, and usually at least half of its contents was pigment, half red cells. In some cases the red pigment was very much more in proportion. The connective tissue framework in five of the eight was very much more conspicuous than normal, probably owing to the reduction in lymphocyte content.

30 µc/g level (14 specimens). Two were almost normal; the remainder almost invariably showed reduction in the size of the splenic corpuscles and the number of lymphocytes. The red pulp in the majority of specimens was normal. Two specimens were depleted of red cells, and two were engorged. The balance of red cells and pigment was about equal, but in an appreciable number of specimens there was substantial increase in the amount of pigment. The depleted cellularity resulted in increased visibility of the connective-tissue framework in six of the fourteen specimens.

50 µc/g level (5 specimens). Although some were not badly depleted, the majority showed substantial reduction in size of the splenic corpuscles in their lymphocyte content, and even in numbers of corpuscles. The reduction in one specimen was so marked that there was only a narrow collar of lymphocytes around the blood vessel of the splenic corpuscle. The red pulp was generally normal; pigment content varied from scanty to heavy. In three of the five the connective-tissue framework became more easily visible, owing to the depletion of the cells.

70 µc/g level. The trend to smaller and fewer splenic corpuscles was increased in this group, and at times the follicles almost totally lacked lymphocytes. There was some variability even from area to area in the same slide. The red pulp continued to be normal, occasionally not heavily engorged with cells, but in other specimens showed increased vascularity. Pigmentation was also variable, sometimes substantially increased. The connective-tissue framework was more easily seen owing to the reduction of cells.

90 µc/g level (14 sections). All sections showed some damage. In four of them the white pulp was only moderately depleted in amount, and in the remaining ten it was markedly hypoplastic. In half the specimens the red pulp showed some reduction in the number of red cells, but usually the pigment was abundant, or even engorged the sinusoids. This pigment was usually in macrophages. The red pulp was virtually normal in the other half of the specimens. The connective-tissue framework in half the group was more conspicuous than normal; and in one, the greatest proportion of tissue seen was connective-tissue framework.

Kidney

There were fourteen controls, all taken from the Watts series. Glomerular counts were made at all levels in order to determine whether the number of glomeruli per low-power field was changed in the treated animals; the idea was that, if the number was appreciably increased, it might indicate tubular atrophy and generalized compression of the tissue. The glomeruli were also examined for evidence of structural damage, as were the tubules, especially in the cortex. In the controls the average number of glomeruli per low-power field was eleven. In some specimens as few as seven were found in a field, and in others as many as fifteen. Virtually all these glomeruli were well vascularized and appeared fully functional. The tubules were also normal; occasionally, some golden-brown pigment was found in convoluted tubules and, more rarely, pigment casts within the tubules.

10 µc/g level (16 specimens). Amongst these specimens, the average number of glomeruli per low-power field was thirteen, but as few as nine and as many as seventeen were seen. The majority of these glomeruli were normal, but in over half the group one could occasionally find shrunken, avascular, fibrotic glomeruli. Also, in over half the animals, golden-brown pigment was easily observed in the tubules--sometimes sparse, but often rather substantial. This was usually localized as small granules in the epithelium of the convoluted tubules. Very rarely there were areas of disrupted tubular structure.

30 µc/g level (14 specimens). The average number of glomeruli was fourteen per low-power field, but as few as eleven or as many as twenty could be found. An appreciable incidence of fibrotic, shrunken, avascular glomeruli was observed. Some of the tubules appeared damaged, particularly when the glomerular count was very high. In this group the finding of golden-brown pigment in the tubular epithelium was not as common as at the next smaller dose level.

50 $\mu\text{c/g}$ level. There were fifteen glomeruli per low-power field, with a range from fourteen to sixteen. Substantial numbers of these were damaged, varying from avascularity and fibrosis into a shriveled, scarred condition. The majority in any field, however, still appeared functional--that is, showed evidence of being well vascularized. Although there were areas of tubular scarring in the cortex, this was not a conspicuous feature of the kidney changes.

70 $\mu\text{c/g}$ level (5 specimens). There were an average of sixteen glomeruli per low-power field; as few as thirteen and as many as nineteen were found. An appreciable number of these, perhaps 20% to 25%, were avascular, fibrotic, shrunken; sometimes only a scar remained. There were limited areas of tubular degeneration; some tubules showed eosinophilic amorphous debris in their lumens. Occasional clusters of lymphocytes were seen in the perivascular spaces in one specimen; little pigment was found. The kidneys in this group appeared to be on the borderline of functional adequacy, but probably still functioning.

90 $\mu\text{c/g}$ level (12 specimens). In these there were an average of seventeen glomeruli per low-power field, with as few as thirteen and as many as nineteen. An appreciable number of these, perhaps one-third to one-half, were defective in one way or another, either in their vascularity, or in their size or the degree of content of fibrous connective tissue. In some specimens the scarring had gone to such an extent that the glomeruli became difficult to recognize, and there might actually have been more remains of glomeruli per field than the numbers shown. The amount of tubular damage, while substantial, or at least recognizable, was not as conspicuous as the glomerular damage. When it occurred, one might find areas of vascular degeneration and some casts in the lumen. Golden-brown pigment was seen in one specimen. A number of these specimens were damaged to the point where one might question their functional adequacy.

Lung

The control lungs consisted of nine specimens from the regular series and twelve from the Watts series. The two groups were quite comparable, although there was some slight difference in the incidence of mild inflammatory change, more particularly seen in the Watts series. They may have reflected the difference in the rooms and buildings in which the two groups of animals were kept. Within the range of controls we found normal, well-aerated, well-distended lungs; lungs showing slight evidence of bronchitis; and--in a small number of the animals--frank pneumonias. Two showed major consolidation, both acute and chronic lobar pneumonias. Other conspicuous changes fairly frequently encountered were the substantial lymphatic infiltrations around the bronchi, restricted areas of collapse or atelectasis, and some edema of some of the alveolar walls. In over half the group these deviations from normality probably added up to the diagnosis of a chronic subclinical pneumonitis.

10 $\mu\text{c/g}$ level (major series: 8 specimens; Watts series: 8). In both groups the incidence of normal lung tissue and of subclinical pneumonitis were completely within the range encountered in the controls.

30 $\mu\text{c/g}$ level (14 specimens). Four specimens showed acute substantial inflammatory reaction, either pneumonic or abscessed. This was a higher proportion than was encountered in the controls. The remainder usually showed substantial amounts of normally aerated and dilated lung tissue, but, with few exceptions, showed heavy collections of lymphocytes along the bronchi, which probably again represented a subclinical chronic pneumonitis which was seen in higher incidence than was found in the controls.

50 $\mu\text{c/g}$ and 70 $\mu\text{c/g}$ levels (5 and 6 specimens). The two groups had approximately the same distribution of findings, and were therefore counted together in this analysis. Normal lung tissue was found in the majority of animals in very substantial amounts. Three of the animals showed substantial acute and chronic inflammation--that is, pneumonic or abscess--and four showed peribronchial lymphatic infiltration suggesting chronic subclinical pneumonitis. The incidence of flat desquamated cells in the alveolar spaces was definitely increased in these groups.

90 $\mu\text{c/g}$ level (14 specimens). Of these, only three were completely normal. Four more showed mostly normal tissue with minimal changes suggesting small inflammatory foci. The remainder, constituting half the group, showed substantial inflammation, including collapses consolidating pneumonia, bronchitis, desquamation, and other changes as described heretofore.

Thyroid

There were nine controls in the main series and twelve in the Watts series. Of the total, parathyroid was seen in 40%.

10 $\mu\text{c/g}$ level (both series: 16 specimens). The thyroid at the 10 $\mu\text{c/g}$ level showed no residual thyroid tissue as such. Parathyroid tissue was identifiable in six specimens, and impairment of parathyroid vascularity was found in at least one. The predominant tissue was fibrous tissue, both loose and dense. Numbers of macrophages often contained golden-brown pigment, and rare degenerating isolated epithelial elements were seen. Two sections contained rosette cells, which suggested the beginnings of regeneration. In three of the sixteen there was found amorphous or fibrinous coagulated necrotic material and, very rarely, giant cells.

30 $\mu\text{c/g}$ level (14 specimens). No organized thyroid tissue was seen at this level. The majority showed replacement of thyroid with dense fibrous tissue, although loose fibrous tissue and adipose tissue were fairly common. Two of the fourteen showed fragments of parathyroid. Epithelial remnants were very scarce. Macrophages were seen but were not common. Golden-brown pigment was not conspicuous as in the previous group. Multinucleated giant cells were found in four specimens on the periphery of the granular, fibrillar, or amorphous debris. When the amorphous material was seen (in 10 of the 14 specimens) it was usually rather small in amount, well circumscribed, and enclosed by fibrous tissue, and was often being invaded and apparently replaced by the fibrous tissue.

50 $\mu\text{c/g}$ and 70 $\mu\text{c/g}$ levels (11 specimens). There were no substantial differences between these two groups. In only one of the eleven specimens could a suggestion of parathyroid tissue be found, and this was not a certain identification. In all specimens amorphous debris was the predominant material. It was usually basophilic but could have been polychromatic, or may even have lost its staining reaction in the center. This was most commonly surrounded by a layer of connective tissue like a capsule. Immediately adjacent to the amorphous tissue (in 8 of the 11 specimens), large numbers of multinucleated giant cells were usually found. A few small round cells, probably lymphocytes, were found in three of the eleven. In a small proportion of the group there were evidences that fibrous tissue was invading and possibly replacing some of the coagulated debris. In one of the specimens the debris had structure reminiscent of thyroid follicles, although it showed no epithelial material; in fact, epithelial remnants were quite rare.

90 $\mu\text{c/g}$ level (14 specimens). In almost all specimens an amorphous or necrotic material predominated. In over half the group the coagulated material retained a strong suggestion of thyroid organization in that it showed large rings and spaces reminiscent of follicles or the ghosts of follicles. The coagulum was almost always surrounded by a fibrous connective tissue which contained many multinucleated giant cells. There were minimal signs that some attempt at fibrous invasion and replacement of this necrotic tissue was taking place in almost half the groups. Macrophages were moderately common, and epithelioid single-cell remnants were seen in two of the specimens. Pigment was not conspicuous. Generally (as judged by the sparsity of small round cell infiltration), there was very little inflammatory reaction.

Thymus

There were twenty-one controls: nine in the major series, and twelve in the Watts series. Even at this advanced age, all were densely cellular and showed well-organized lymphatic tissue, and usually had a well-developed cortex and medulla. There was very little brown fat. Three of the specimens had rather large dilated cysts, usually filled with some lymphocytes and amorphous material. All slides were searched for ectopic thyroid tissue (a possibility associated with the development origin of the thymus). Of the controls, eight showed reasonably well-defined follicles resembling those of the thyroid, and even contained colloid. Four more had epithelial cords or sheets suggesting thyroidal epithelium although not arranged into follicles. The remainder showed no tissue suggesting thyroidal epithelium.

10 $\mu\text{c/g}$ level (major series: 8 specimens; Watts series: 8). The relationship between the thymic tissue and replacement tissue, consisting of adipose tissue and brown fat, varied in the group; five of the specimens were mostly lymphatic tissue. Although reduced in size, these five were apparently normal. In the remainder the incidence of brown fat varied from 10% to 90%, or more, of the area of the section. One specimen was scarcely recognizable as being thymus. One showed thyroidlike follicles; five showed cords or rosettes or sheets of epithelial cells, and the remaining ten showed no suggestion of epithelial tissue of thyroid type.

30 $\mu\text{c/g}$ level (14 specimens). In the majority, the thymic tissue was moderately depleted of lymphocytes. Brown fat predominated in four in over 80% of the section; in the remainder, depleted lymphatic tissue predominated. There were three epithelial masses or follicles containing colloid, and another had questionable epithelial tissue in it. The remainder showed no suggestion of epithelium of thyroidal type.

50 $\mu\text{c/g}$ level (5 specimens). Two specimens were predominantly lymphatic, although they were rather depleted of lymphocytes. Two of them were composed of equal parts of adipose and lymphatic tissue, and the third was predominantly brown fat. Two specimens had follicles with colloid; another two had questionable or atypical epithelial remnants; and the fifth showed no suggestion of thyroidal type of epithelium.

70 $\mu\text{c/g}$ level (5 specimens). In two specimens about one-fifth of the area was brown fat, and the remainder was depleted lymphatic tissue; the total amount of tissue was quite small. The other specimens showed almost complete replacement of the thymus by adipose tissue. Three of the group had epithelial remnants or clusters associated with droplets of colloid; the other two showed no such epithelial tissue.

90 $\mu\text{c/g}$ level (14 specimens). The proportion of lymphatic tissue to the fat was highly variable, ranging from less than 5% to more than 95%. The lymphatic tissue found in this fat was usually depleted, but occasionally it was well packed with lymphocytic tissue, and showed even lymphopoiesis. None of these specimens showed any epithelial remnants that might be related to thyroid "rests."

Ovary

There were nine specimens of controls from the major series and twelve from the Watts series--a total of twenty-one. The structure found varied depending on the cycle. The majority of animals showed a number of corpora lutea that were well vascularized, occasionally degenerating. Developing and medium-sized follicles were common, and several of the ovaries showed ripe follicles. Not all these findings were present in the same specimen, since they characterized phases of the cycle.

10 $\mu\text{c/g}$ level (major series: 7 specimens; Watts series: 8). In the major series there were occasionally small follicles, some of medium size, none in ripe condition. There were a few corpora lutea, which usually appeared to be arrested or regressing. The interstitial tissue was deficient, mostly fibrous. In the Watts series there were an appreciable number of small or developing follicles; none had become ripe. The remainder of the tissue was composed of corpora lutea shown in several stages, some almost normal or active-appearing, the remainder degenerating.

30 $\mu\text{c/g}$ level (14 specimens). Some of these showed small to medium arrested follicles, no ripe follicles. The remainder of the tissue was composed of arrested or degenerating corpora lutea. Occasionally, cystic change or some benign, possibly neoplastic, alterations were seen. The interstitial tissue was usually deficient.

50 $\mu\text{c/g}$ level (5 specimens). Four specimens showed small to medium follicles and inactive or resorbing corpora lutea with deficient interstitial tissue. One of the five showed a Graafian follicle and some well vascularized corpora lutea.

70 $\mu\text{c/g}$ level (6 specimens). All specimens were markedly atrophic and showed few or no follicles, and only rare corpora lutea which--when seen--were degenerate or atrophic.

90 $\mu\text{c/g}$ level (14 specimens). Follicles were very rare; when present, they were poorly developed or represented only primary follicles. There were no active corpora lutea. When such tissue was found, it was degenerate and appeared atrophic. Vascularity was poor; interstitial tissue was degenerate. Three of the tissues contained cysts of variable size, one large and multilocular. The cysts showed inflammatory change.

Adrenal

There were twenty-one controls: nine from the major series, and twelve from the Watts series. In all, the cortex was thick, and the three zones were well represented. Vascularity was abundant in all three. Cells of the fasciculata usually were large, and most of them had a foamy look, indicating the former presence of fat. About equal numbers of them had small, dark, or large, pale nuclei. The cells of the reticularis were similar, usually smaller and not quite so foamy looking. A small cortical adenoma was seen in one specimen. Pigment occasionally was found deep in the reticularis.

10 $\mu\text{c/g}$ level (major series: 8 specimens; Watts series: 8). Both groups showed approximately the same changes. The cortex was narrow, with the narrowing particularly marked in the fasciculata and the reticularis. The fasciculata was usually distorted in its architecture, and somewhat avascular. Few of the cells were foamy; most of them were smaller and had dark nuclei. The reticularis varied in thickness and seemed reduced in quantity. Its blood supply was usually normal, but at times some dilation of the vessels was shown. Pigment was very commonly noted in the reticularis.

30 $\mu\text{c/g}$ level (14 specimens). The glomerulosa usually appeared within normal limits. The fasciculata was disorganized, columns of cells being irregular and not straight. The vascularity was much reduced; the cells were usually smaller. There were circumscribed islands of red cells. The reticularis was narrowed, and usually increased its dimension of blood vessels to the point of engorgement. Pigment was not unusual in amount.

50 $\mu\text{c/g}$ level (5 specimens). All had a narrowed cortex, but the arrangement within it varied from specimen to specimen. Usually the cells of the glomerulosa were visible, and the zone recognizable as such. The fasciculata and reticularis were substantially distorted in their architecture. In particular, the fasciculata consisted of sheets of cells rather than cords, and were very much reduced. The cells were small, usually poorly stained. The reticularis was often conspicuously separated from the fasciculata because of its engorged sinusoids.

70 $\mu\text{c/g}$ level (5 specimens). The cortex was always narrowed; in particular, the reticularis and fasciculata were reduced in thickness. The fasciculata had atrophic cells and a poor blood supply, and its organization was completely disrupted so that the columns of cells were not easily visible. The reticularis was richly vascular and contained some degenerating cells.

90 $\mu\text{c/g}$ level (14 specimens). The cortex was always thin, sometimes extremely so. Even the glomerulosa was not infrequently reduced in thickness and showed some structural disorganization. The fasciculata and reticularis were substantially narrowed and disorganized, and sometimes inseparable from each other. The vasculature in all regions was reduced, and the cell structure was atrophic.

Mesenteric Lymph Node

There was a total of twenty-one controls: nine from the major series and twelve from the Watts series. The range of appearance of normal lymph nodes was seen. Characteristically, the cortex and the medulla comprised equal parts of the gland; the cortex was generally densely packed with lymphocytes and contained a number of follicles showing germinal centers. The cortex was commonly a continuous structure, but it was found to be interrupted in rare instances. The medulla was paler-staining than the cortex, and had fewer cells, so that the sinusoids were easily visible. Most of the lymphocytes were small. In one specimen it was seen that the plane of section could alter the appearance so that the medullary characteristics could predominate; very little cortex could be found.

10 $\mu\text{c/g}$ level (major series: 16 specimens; Watts series: 8). The cortex was variably thinned or interrupted, and only occasionally did it appear normal. The follicles were reduced in number from normal, and very often they showed no germinal centers and some lymphocyte depletion. The medulla was appreciably depleted of lymphocytes, and its framework became more visible.

30 $\mu\text{c/g}$ level (13 specimens). The degree of damage was variable, but the cortex was almost always thinned and interrupted. There could have been a normal or reduced number of follicles in the cortex, but rarely were germinal centers present. The medulla was almost always depleted of lymphocytes, and the framework apparent. As an extreme, fatty and fibrous replacement tissue took place in a large part of the gland.

50 $\mu\text{c/g}$ level (5 specimens). The picture was again variable. The cortex was always atrophied; there might be an appreciable number of follicles, but on the other hand, there might be none. When follicles were seen, there were no germinal centers. The medulla might have been slightly to markedly depleted of lymphocytes.

70 $\mu\text{c/g}$ level (6 specimens). The cortex and medulla could be distinguished in four specimens, and often somewhat separated from one another. The medulla was substantially depleted. The cortex was not distinguishable from the medulla in two specimens; the whole gland consisted of a framework of reticular tissue with sparsely scattered lymphocytes trapped in the framework.

90 $\mu\text{c/g}$ level (14 specimens). Lymphocyte content was always reduced; the cortex was usually thin or interrupted, and showed few follicles. Germinal centers were very rare except in two specimens in which they could be distinguished. For the most part, the medulla was considerably depleted or even devoid of lymphocytes. One specimen showed damage so marked that the tissue was scarcely recognizable as a lymph node, which showed little but the framework.

Pituitary

Twelve specimens of the anterior pituitary gland were examined, all from the Watts series. Chromophobe cells predominated and were usually ten to twelve times as numerous as other types. The acidophil cells were easily recognizable and were well granulated. In a single high-power field (40x objective and 12x eyepiece), they were usually too numerous for estimation of the numbers. The basophils were easily recognizable and varied from about 8 to 16 cells per high-power field. The gland showed an abundant vascularity of capillary or small sinusoidal type.

10 $\mu\text{c/g}$ level (major series: 7 specimens; Watts series: 8). Chromophobe cells were markedly in predominance. Acidophils were much reduced in number; in virtually all cases, there were 20 or fewer cells per high-power field; some specimens had as few as 5 cells per high-power field that were recognizable. These cells were generally considerably degranulated. Basophils were increased in number, most commonly about 10 to 25 cells per high-power field. The majority were quite enlarged and showed vacuoles containing a blue-staining colloid; these were the typical thyroidectomy basophils. Other basophils were found that were quite small, and probably represented new crops of proliferating basophils. Variably,

the vascularity of the gland was altered; it was slightly reduced in six of the group, normal in four, and showed dilated sinusoids in five.

30 $\mu\text{c/g}$ level (14 specimens). Chromophobes formed the great majority of cells present. Acidophils were markedly reduced, at best being fewer than 20 cells per high-power field, and sometimes rare or even unrecognizable. Difficulty of diagnosing the cells was complicated by the faint or devitalized staining appearance of many of these sections. When found, the acidophils were degranulated. The basophils were of normal or increased number; they were so abundant in some specimens that they were almost uncountable, or at least not easily estimated in a single field. Some of these were typical thyroidectomy cells--enlarged, vacuolated, and containing colloid--while others were small, and probably represented new crops of cells. The vascularity in some of these was normal, but in the majority of specimens it was increased; the sinusoids sometimes were dilated to the point where glandular tissue appeared to be crowded out.

50 $\mu\text{c/g}$ level (6 specimens). Staining reaction was poor. Chromophobes were abundant. The number of acidophils was somewhat variable, from as few as 3 to 5 cells per high-power field to as many as 25 cells per high-power field; they had scanty cytoplasm and were degranulated. Basophils were very common, sometimes increased in number. A few showed enlargement and vacuolation like thyroidectomy cells, whereas others remained normal in size and were small, but with intense staining. Vascularity was usually normal, but could show an increase of dilated sinusoids.

70 $\mu\text{c/g}$ level (5 specimens). Stainability was very poor; all of the tissue looked devitalized, and there was substantial difficulty in most sections in defining the type of cell. When cells could be defined, the number of acidophils, which were degranulated, was markedly reduced. The number of basophils were normal or increased, and some showed thyroidectomy change. Vascularity could be normal or increased; sometimes the dilation of sinusoids resulted in an appearance of compression of the gland cells.

90 $\mu\text{c/g}$ level (11 specimens). The stainability suggested uniform devitalization of the entire gland, and there was very great difficulty in differentiating between the various cell types. Certainly the acidophils were reduced, and were small in number and degranulated. Sometimes the basophils could be diagnosed as thyroidectomy cells on the basis of their morphology; their numbers, when they could be demonstrated, were normal or slightly increased. Vascularity was variable, but tended to be overabundant, with the sinusoids dilated enough to crowd out cells in some areas.

Tumor

No tumors were found in the controls on either gross or microscopic examination of these tissues, nor in any of the animals at the lowest dose level.

30 $\mu\text{c/g}$ level (14 animals): Three animals showed tumors at some point along the mammary line.

Animal 530T. Microscopic description: epithelial elements were found which were organized into ducts or alveoli, and showed some tendency to invade the surrounding connective tissue as small strands of cells. Variability in nuclear staining was seen, and mitotic figures, though rare,

could be found. Probable diagnosis: duct adenoma showing beginning malignant changes.

Animal 1082T. The tumor mass showed a dense collection of small, round, dark-staining cells, poorly vascularized, infiltrating the surrounding fatty tissue. These infiltrations showed a strong suggestion of duct formation. Nuclear staining was markedly variable; mitoses were somewhat difficult to find. The general tendency to invasiveness and to anaplastic changes in the cells suggested a diagnosis of a medullary carcinoma of the breast.

Animal 1067T. Two masses were taken, one from the main tissue suspected of being a tumor, the other from a tissue neighboring it. Histologically, the main mass showed a well-defined squamous cell carcinoma; the majority of the tissue was a Grade I type, but areas of appreciable size were found showing Grade II tissue. Duct structures were found superficially, some of which had proliferated, and some showed anaplastic changes and mitosis. The accessory mass of tissue was histologically a large fatty mass and showed some lymphatic tissue; one may suspect that it represented a lymph node near the primary tumor. It was infiltrated with clusters of duct tissue; many were well formed, and some showed anaplastic cell transformations. This was probably a metastasis into the regional lymph node.

50 $\mu\text{c/g}$ level. None of the five animals studied showed tumors.

70 $\mu\text{c/g}$ level. Three of the six studied showed tumors. Two of these were taken from mammary areas. The first had a gross description found in animal 503T. Histologically, the tissue was cystic and multilocular. The cysts contained much amorphous material. The stroma of this tumor was abundant and was widely infiltrated with epithelial cells; this infiltration suggested an invasive tendency. One area of the tissue consisted of an acinar organization, showing mitotic activity, and marked variability in the nuclear staining. The whole structure was poorly encapsulated. Probable diagnosis: cystic fibro-adenocarcinoma.

The second one was taken from the mammary region of Animal 498T. Microscopically, the main mass of tissue showed proliferated duct tissue, some showing papillary structure. It was reasonably well vascularized and contained a normal amount of stroma. For the most part, this tissue appeared benign, but one area showed some degeneration and rare mitoses, and had no basement membrane to the epithelium. Probable diagnosis: Duct adenoma of the breast with premalignant changes.

The third tumor taken in this group was an uterine tumor from Animal 523T. Microscopically, it consisted of a substantial amount of loose, fibrous tissue with an abundance of ground substance. The structural differentiation of the cells was good. There were some large cystic cavities showing an epithelial lining, which may have been endometrium. The main mass appeared to be a benign fibrous tumor, probably fibroma mole of the uterus.

90 $\mu\text{c/g}$ level. Four specimens were taken as possible tumors in the fourteen animals. Three of these were derived from the mammary-line area, and one from the uterus. The first of the mammary tumors was from Animal 1058T. Microscopically, this was a mixed tumor; most of it consisted of fibrous elements which showed substantial amounts of nuclear variability and mitosis,

and areas of dense epithelium, like sheets could be found. The diagnosis was not clear; it was either a spindle-cell sarcoma, or a sarcoma containing mixed spindle cells and giant cells. One must consider, however, the possibility that the epithelioid cells had epithelial origin, in which case it would be called an adenoma-sarcoma. No recognizable breast elements were found in the tissue except for the anaplastic fibrous structures. Whatever the subcategory, it was clearly a sarcoma of the breast region.

The second specimen was from Animal 1248T. Microscopically, this was a tumor showing an abundance of epithelial tissue. A considerable amount of it was cystic, and some of these cysts showed papillary processes. There was a substantial amount of epithelial invasion of the fibrous tissue. The epithelial cells showed mitosis and nuclear polychromasia. The diagnosis: a papillary cyst adenocarcinoma.

The third animal possessing tumors was 1190T. There were sampled tissues from the mammary region, from a growth on the stomach, and from a mass in the uterus. The tissue from the mammary region consisted of closely packed spindle-shaped cells, with some areas of small round cells. Vasculature was scanty; tumor was not encapsulated. Mitotic figures were easily found, some abnormal (i. e., tripolar, etc). The diagnosis of this tumor was fibrosarcoma. The mass from the stomach was very much like this although less anaplastic. It apparently was expanding on the surface of the stomach. Deep in the mucosa it had replaced all of the muscularis and submucosa, and at one point it had broken through the muscularis mucosae. There were numerous areas of degeneration and inflammation; the mass appeared to be a metastasis from a primary mammary tumor. The third tissue was from the uterus. The histologic section showed a dilated uterus containing a mass of fibrous tissue, and possibly some mucoid tissue. It appeared to be encapsulated, and showed no mitosis. The probable diagnosis was a benign fibromyxoma of the uterus.

The fourth animal to show suspected tumorous tissue was 1237T. In the histologic specimen of the uterus of this animal the wall was irregularly thickened, and, at one point, polypoid. The epithelium was mostly of a simple character, sometimes as ciliated and columnar, but sometimes pseudostratified. There was no apparent regular organization to the tumor; mitotic figures were sparse; there was an abundance of loose fibrous and vascular stroma and small islands of degenerative tissue. The probable diagnosis was uterine polyp.

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