absent. At intervals epithelial cells and leucocytes enveloped a section of the secretion giving the ducts the beaded appearance.

Summary. Large amounts of estrogenic hormone in the form of folliculin benzoate, when injected subcutaneously at weekly intervals, induced a stunted development of the mammary duct system as compared with that developed in mice receiving small amounts of theelin daily. Extensive areas of alveolar development and some areas of excessive development of the connective tissue stroma were induced. The extent and type of mammary growth induced in the male mice receiving folliculin benzoate thus differed from that observed in virgin female mice or induced experimentally in male mice receiving theelin.

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Paget's Disease: Relative Constancy of Serum Phosphatase Levels over Periods up to Two Years.

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Kay[1] and, independently, Roberts[2] were the first to point out that the phosphatase activity of the blood is increased in osteitis deformans. This observation has been confirmed and extended by subsequent investigators[3-8] whose conclusions, based upon determinations on a combined total of approximately 200 cases may be summarized as follows:

1. Increased serum (plasma) phosphatase activity is a consistent manifestation of polyostotic Paget's disease.[3-8] In localized Paget's disease, the serum phosphatase activity is usually increased[4-8] but the increase may not be marked,[4, 5, 7, 8] and in occasional cases, the values may be within normal limits.[4, 5, 8]

1 Kay, H. D., *Brit. J. Exp. Path.*, 1929, **10**, 253.
2 Roberts, W. M., *Brit. J. Exp. Path.*, 1930, **11**, 90.
3 Kay, H. D., *J. Biol. Chem.*, 1930, **89**, 249.
4 Race, J., *Arch. Med. Hydrology*, 1932, **10**, 6.
5 O'Reilly, T. J., and Race, J., *Quart. J. Med.*, 1932, **1**, 471.
6 Kay, H. D., Simpson, S. L., and Riddoch, G., *Arch. Int. Med.*, 1934, **53**, 208.
7 Bodansky, A., and Jaffe, H. L., *Arch. Int. Med.*, 1934, **54**, 88.
8 Gutman, A. B., Tyson, T. L., and Gutman, E. B., *Arch. Int. Med.* In press.

2. There is a rough proportionality between the degree of increase in blood phosphatase activity and the extent of skeletal involvement, as shown by roentgenologic examination.[3-8] In advanced cases, the serum phosphatase may be 100 Bodansky units per 100 cc. or more, as compared with the normal range of 1 to 4 Bodansky units.[9]

3. Discrepancies in this relation may occur, however, particularly in the moderately advanced polyostotic group.[3, 5, 7, 8] Disproportionately low values may be encountered, usually in cases clinically quiescent.[5, 7, 8] Some patients exhibiting disproportionately high values have been followed long enough to demonstrate unusually rapid progress of the disease in their cases.[8] It would appear, therefore, that the level of serum phosphatase activity may reflect the rate of development of the disease in some instances, and that, in this sense, the determination may be of value in prognosis.[8]

4. The value of the determination in the detection of Paget's disease in its early stages[4, 5] is limited, since the radiologic diagnosis is often obvious before the increase in serum phosphatase is unequivocal.[8]

5. The determination is of little or no value in the differentiation of Paget's disease from osteoplastic bone metastases, particularly in carcinoma of the prostate gland, since the values obtained in this condition may be as high as any seen in advanced cases of osteitis deformans.[8]

6. Increased blood phosphatase levels are encountered in certain diseases of bone other than Paget's disease[3, 7, 10] and in some disturbances of hepatic function.[2, 11] While the determination is useful in corroborating the radiologic or clinical diagnosis of Paget's disease, it is not a specific test.

7. It is probable that the increase in blood phosphatase activity in osteitis deformans is a result and not the cause of the disease;[11] in all likelihood, it is an expression of increased cellular activities leading to bone formation.[12]

It is desired here to call attention to another aspect of the phenomenon, to which no specific reference could be found in the literature, but which provides additional evidence that the increase in

9 Bodansky, A., *J. Biol. Chem.*, 1933, **101**, 93.

10 Kay, H. D., *Physiolog. Rev.*, 1932, **12**, 384.

11 Bodansky, A., and Jaffe, H. L., PROC. SOC. EXP. BIOL. AND MED., 1933, **31**, 107.

12 Robison, R., The Significance of Phosphoric Esters in Metabolism, N. Y. University Press, N. Y., 1932.

TABLE I.

Paget's Disease: Relative Constancy of Serum Phosphatase Levels in 20 Cases, Followed for Periods up to 2 Years.

				Serum		
Case*	Age	Sex	Date	Phosphatase (Bodansky units per 100 cc.)	Ca mg. %	Inorg. P mg. %
1	66	♂	2-3-34	130.3	——	3.4
			9-17-35	132.4	9.4	3.2
3	65	♂	6-22-34	109.9	9.7	3.3
			3-17-35	106.9	9.7	3.5
4	60	♀	10-3-33	88.7	10.1	2.9
			10-6-33	88.1	10.3	3.1
			5-24-34	91.9	10.1	3.5
			5-28-34	96.3	——	3.2
			5-10-35	90.5	10.2	2.5
6	51	♂	9-18-34	122.2	10.7	3.2
			3-11-35	116.0	10.2	3.4
			9-17-35	123.1	10.0	3.1
8	47	♀	6-8-34	109.5	10.0	3.8
			9-18-35	123.3	10.0	3.4
9	64	♂	6-26-34	94.3	10.7	3.7
			2-27-35	60.6	9.8	2.9
			9-17-35	60.5	10.4	2.9
12	64	♀	5-14-35	78.4	10.1	3.3
			5-21-35	70.7	——	2.8
13	69	♂	6-22-34	72.6	10.7	3.0
			3-13-35	77.6	11.0	3.2
16	45	♀	6-7-34	59.6	11.7	2.8
			6-18-34	63.9	11.5	2.9
			10-11-34	58.3	11.7	3.0
			9-18-35	57.0	11.5	2.5
24	43	♂	12-29-33	47.8	10.8	3.5
			9-17-35	61.8	9.9	3.4
34	58	♀	8-29-33	36.5	10.1	3.8
			9-21-35	33.0	10.1	3.4
36	74	♂	11-23-33	33.3	9.9	3.4
			5-31-34	34.3	10.1	3.4
			9-18-35	30.0	9.8	2.6
42	63	♀	6-9-34	29.4	10.1	5.1
			7-23-34	23.3	10.9	4.2
45	75	♀	3-25-34	24.2	9.8	3.0
			10-31-34	14.6	10.1	3.5
46	55	♀	5-18-34	23.0	10.7	3.2
			10-26-34	25.8	10.5	3.6
			9-18-35	21.1	10.5	3.2
48	63	♂	8-20-34	19.7	11.2	3.2
			12-12-34	19.3	10.2	3.4
			9-20-35	18.7	10.3	2.8
56	56	♂	4-20-33	11.5	10.9	3.8
			5-6-33	13.6	10.3	3.7
58	45	♂	1-18-34	13.1	10.6	3.2
			11-13-34	12.4	10.9	2.8
			6-4-35	13.3	10.0	2.8
67	56	♂	7-10-33	6.5	13.9	2.8
			8-3-33	8.3	17.2	3.8
			8-16-33	10.9	18.9	4.5
			8-22-33	8.7	16.4	3.9
70	34	♀	12-29-33	5.3	10.8	3.4
			1-15-34	6.9	9.8	2.9
			9-18-35	7.3	9.8	2.6

* The cases are numbered to conform with the order in Table 3, Gutman, Tyson, and Gutman[8] where the extent of bone involvement in each instance is recorded.

serum phosphatase in Paget's disease is not capricious or coincidental but significant and correlated. The data in Table I summarize the results of successive blood analyses in 20 cases of osteitis deformans,[13] the observations being made at intervals varying from several weeks to 2 years. In the majority of instances, the serum phosphatase was maintained at strikingly constant high levels. In 16 of 20 cases followed, subsequent values were within 15% of the figure obtained on the initial determination. In cases 8 and 24, there was a definite increase in serum phosphatase, in cases 9 and 45 a decrease was observed, not associated with any obvious change in the clinical picture. The serum calcium, with two exceptions, was within the range of normal variation, irrespective of the extent or stage of the Paget involvement. In case 67 (case history and necropsy findings summarized elsewhere[8]), a marked hypercalcemia was present, probably not related to the localized Paget lesion found. The serum non-protein nitrogen was essentially normal in all cases.

The phosphatase determinations were carried out in duplicate on serum from fasting patients by Bodansky's method.[9] Corrections were applied for deviations from Beer's law,[14] and for inhibition of hydrolysis by accumulation of hydrolytic products when the phosphatase activity exceeded 40 Bodansky units per 100 cc.,[15] as recommended by Bodansky.

The relative constancy of the serum phosphatase levels in Paget's disease suggests that the determination may prove useful in supplementing clinical and radiologic examination in studying the effects of various forms of therapy. It is interesting to note that in 9 of the above cases, radiotherapy was given for alleviation of pain without any apparent effect on the serum phosphatase values, whether or not the patients were benefited by treatment.

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13 Gutman, A. B., and Kasabach, H., *Am. J. Med. Sci.* In press.

14 Bodansky, A., *J. Biol. Chem.*, 1932, **99**, 197.

15 Bodansky, A., and Jaffe, H. L., *Am. J. Diseases Chil.*, 1934, **48**, 1268.