THE METABOLIC EFFECTS OF STEROID HORMONES IN OSTEOPOROSIS

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In a previous communication from this clinic (1), three metabolic studies on the effect of estradiol benzoate on the calcium and phosphorus metabolisms of patients with post-menopausal osteoporosis were published in abstract form. The first objective of the present paper is to report these studies in detail, supplemented by 2 additional studies: one in which testosterone propionate by itself, and in combination with estradiol benzoate, was used; and another in which diethylstilbestrol by itself, and in combination with progesterone, was employed. The subject of the last investigation had, in addition to post-menopausal osteoporosis, Paget's disease.

The second objective is to publish metabolic studies on the effect of testosterone propionate alone and in combination with estradiol benzoate in a male patient with senile osteoporosis.

The third objective is to present studies on 3 patients with the acute osteoporotic process which follows orthopedic operations, and the effect of estradiol benzoate on this process in 2 of these subjects.

In another previous communication from this clinic (2), metabolic studies of the effect of estradiol benzoate, testosterone propionate, and progesterone on 3 patients with Cushing's syndrome were reported. The fourth objective is to present these data more completely in graphic form, and especially to rectify an unwarranted conclusion as to the effect of estrogen on the calcium balance.

DEFINITION OF OSTEOPOROSIS

Osteoporosis is not synonymous with demineralization of bone; it is that category of too-little-bone where the primary disturbance is lack of bone matrix formation. It is not to be confused with osteomalacia, where the primary disturbance is failure of mineralization of bone, or with osteitis fibrosa generalisata, where the primary disturbance is increased bone destruction. For further discussion, see (1, 3, 4).

CONDITIONS ASSOCIATED WITH OSTEOPOROSIS

In clinical medicine one encounters the following conditions associated with osteoporosis: (*1*) disuse atrophy, where the normal stimulus to osteoblastic activity is absent (4, 5); (*2*) old age, where the bone tissue like other tissue (*cf.* hair, skin, muscles) atrophies; (*3*) malnutrition, where the protein requirements are not fulfilled, and the bone matrix, like other tissues, is depleted; (*4*)

[1] The expense of these studies was defrayed by grants from the Josiah Macy, Jr. Foundation, from the Rockefeller Foundation, and from the National Research Council (Committee for Research in the Problems of Sex). A bed supported by the Mallinckrodt Chemical Company on the Metabolic Ward was used for part of these studies.

[2] Presented in part at the twenty-sixth annual meeting of the Association for the Study of Internal Secretions, Atlantic City, New Jersey, June 8, 1942, in connection with a symposium on "Relation of Endocrines to Skeletal Development"; an outline of this presentation may be found in: Reifenstein, E. C., Jr.; Albright, F.; Parson, W.; and Bloomberg, E.: The effect of estradiol benzoate and of testosterone propionate and of combinations of both on post-menopausal osteoporosis and senile osteoporosis, Endocrinology, 30: S1024 (1942). Also presented in part at the first annual meeting of the American Federation for Clinical Research, Minneapolis, Minn., April 20, 1942. Preliminary reports of part of these data may be found in: Albright, F.; Reifenstein, E. C., Jr.; and Forbes, A. P.: Conferences on the Metabolic Aspects of Convalescence (Including Bone and Wound Healing), Transactions of the First Meeting, Sept. 11–12, 1942, pages 5–7, 37–38; Transactions of the Second Meeting, December 11–12, 1942, pages 69, 96–98; Transactions of the Third Meeting, March 12–13, 1943, pages 63–65; and Transactions of the Fourth Meeting, June 11–12, 1943, pages 77–85. Transactions distributed by the Josiah Macy, Jr. Foundation, New York, N. Y.

[3] The work described in this paper was done in part under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Massachusetts General Hospital.

TABLE I

Data for case 1 (F.F., M.G.H. 156453)

Period number	Date	Calcium				Phosphorus				Nitrogen				Body weight		Serum				Treatment		
		Urinary	Fecal	Intake	Balance	Urinary	Fecal	Intake	Balance	Urinary	Intake	Balance	Theoretical balance	Measured*	Theoretical	Day of period	Calcium	Phosphorus	Alkaline phosphatase	Estradiol benzoate (i.m.)	Estradiol dipropionate (i.m.)	Progesterone (i.m.)
		mgm. per 24 hr.				*mgm. per 24 hr.*				*grams per 24 hr.*				*kgm.*			*mgm. per 100 ml.*		*B.U.*			
1	11/14 to 18/38	289	620	735	−174	371	288	606	− 53	6.99	7.69	−0.07	+0.51	51.03	51.12	I	9.7	4.0		None	None	
2	11/19 to 23/38	286	514	735	− 65	386	225	606	− 5	6.80	7.69	+0.12	+0.43	51.13	51.13							
3	11/24 to 28/38	278	412	735	+ 45	364	171	606	+ 71	6.74	7.69	+0.18	+0.72	51.13	51.15							
4	11/29 to 12/2/38	259	455	735	+ 21	312	235	606	+ 59	6.60	7.69	+0.32	+0.72	51.37	51.18	I	9.3	4.5	3.3	1.66 mgm. every third day		None
5	12/ 3 to 7/38	249	349	735	+137	237	170	606	+199	6.14	7.69	+0.78	+1.95	51.47	51.28	III	9.4	3.8				
6	12/ 8 to 12/38	210	486	735	+ 39	276	268	606	+ 62	5.95	7.69	+0.97	+0.65	51.74	51.41							
7	12/13 to 17/38	187	323	735	+225	262	194	606	+150	6.39	7.69	+0.53	+0.55	51.90	51.48	II	9.7	4.4				
8	12/18 to 22/38	182	527	735	+ 26	226	282	606	+ 98	6.14	7.69	+0.78	+1.27	51.97	51.58							
	No collections for 23 days													51.97	51.58							
9	1/16 to 20/39	180	395	735	+160	217	229	606	+160	6.18	7.69	+0.74	+1.20	52.23	51.67	I	9.4	3.6	2.3			
10	1/21 to 25/39	161	430	735	+144	226	254	606	+126	5.95	7.69	+0.97	+0.81	52.28	51.80							
11	1/26 to 30/39	178	418	735	+139	213	237	606	+156	6.93	7.69	−0.01	+1.31	52.06	51.79	I	10.4	4.4	3.1			10 mgm. daily
12	1/31 to 2/4/39	149	418	735	+168	227	259	606	+120	6.38	7.69	+0.54	+0.54	52.68	51.86	V	9.0	3.7	3.4			10 mgm. daily
13	2/ 5 to 9/39	181	615	735	− 61	156	315	606	+135	5.62	7.69	+1.30	+2.49	53.40	52.03					None	None	None
14	2/10 to 14/39	147	198	735	+390	258	113	606	+235	5.97	7.69	+0.95	+0.60	52.47	52.16							
15	2/15 to 19/39	138	432	735	+165	288	245	606	+ 73	7.33	7.69	−0.41	−0.15	52.04	52.09							
16	2/20 to 24/39	163	472	735	+100	269	263	606	+ 74	7.06	7.69	−0.14	+0.36	52.42	52.06	I	10.0	3.9	3.4			
17	2/25 to 3/1/39	153	431	735	+151	269	244	606	+ 93	6.52	7.69	+0.40	+0.25	52.40	52.11							
18	3/ 2 to 6/39	171	717	735	−153	298	378	606	− 70	6.59	7.69	+0.33	+0.11	52.19	52.15							
19	3/ 7 to 11/39	192	295	735	+248	286	158	606	+162	6.01	7.69	+0.91	+0.57	52.36	52.27	I	9.9	4.5	2.1			
20	3/12 to 16/39	207	555	735	− 27	293	258	606	+ 55	6.17	7.69	+0.75	+1.03	52.09	52.37							
21	3/17 to 21/39	219	695	735	−179	296	296	606	+ 14	6.21	7.69	+0.71	+1.55	52.37	52.46	IV	10.0	4.4	2.8			
22	3/22 to 26/39	234	485	735	+ 16	309	210	606	+ 87	6.86	7.69	+0.06	+1.19	52.31	52.46	I	9.6	4.7	3.1			
23	3/27 to 31/39	237	610	735	−112	292	260	606	+ 54	6.61	7.69	+0.31	+1.65	52.77	52.49	I	10.7	4.6	2.5			
24	4/ 1 to 5/39	231	677	735	−173	207	260	606	+139	6.07	7.69	+0.85	+3.39	52.60	52.60	V	9.8	4.6	3.0			
	No collections for 79 days													51.85						1.66 mgm. every third day		
25	6/25 to 29/39	197	417	735	+121	256	207	606	+143	6.22	7.69	+0.70	+1.17	52.19						1.66 mgm. every third day		
	No collections for 297 days													49.60						1.66 mgm. every fifth day		
26	4/22 to 26/40	226	692	735	−183	246	345	606	+ 15	8.13	7.69	−1.21	+1.61	49.70						1.66 mgm. every third day		
27	4/27 to 5/1/40	207	865	735	−337	287	392	606	− 73	6.46	7.69	+0.46	+2.22	49.60						1.66 mgm. every third day		
	No collections for 602 days													47.13		12/23/41	10.0	3.8	2.0	Pellets 195 mgm.	5 mgm. every 10 days**	
28	12/25 to 29/41	216	441	735	+ 78	231	219	606	+156	6.39	7.69	+0.53	+1.77	48.33						1.66 mgm. every third day	None	
29	12/30 to 1/3/42	244	513	735	− 22	245	272	606	+ 89	6.37	7.69	+0.55	+1.51	48.27						1.66 mgm. every third day	None	
30	1/ 4 to 8/42	256	513	735	− 34	273	272	606	+ 61	6.56	7.69	+0.36	+1.19	48.07						1.66 mgm. every third day	None	
	1/9/42																8.5	4.4	1.7			

Dietary intake of periods 1 to 30 in amounts per 24 hours: protein (analyzed nitrogen × 6.25) = 48.1 grams, fat (estimated from tables) = 85.0 grams, carbohydrate (estimated from tables) = 212.8 grams, calories (calculated from the values 4 for 1 gram of protein, 9 for 1 gram of fat, and 4 for 1 gram of carbohydrate) = 1,809. In addition sugar was given *ad lib*, with an average intake of 30 grams (120 calories).

* Initial weight 51.14 kgm.

** Continued for 6 months.

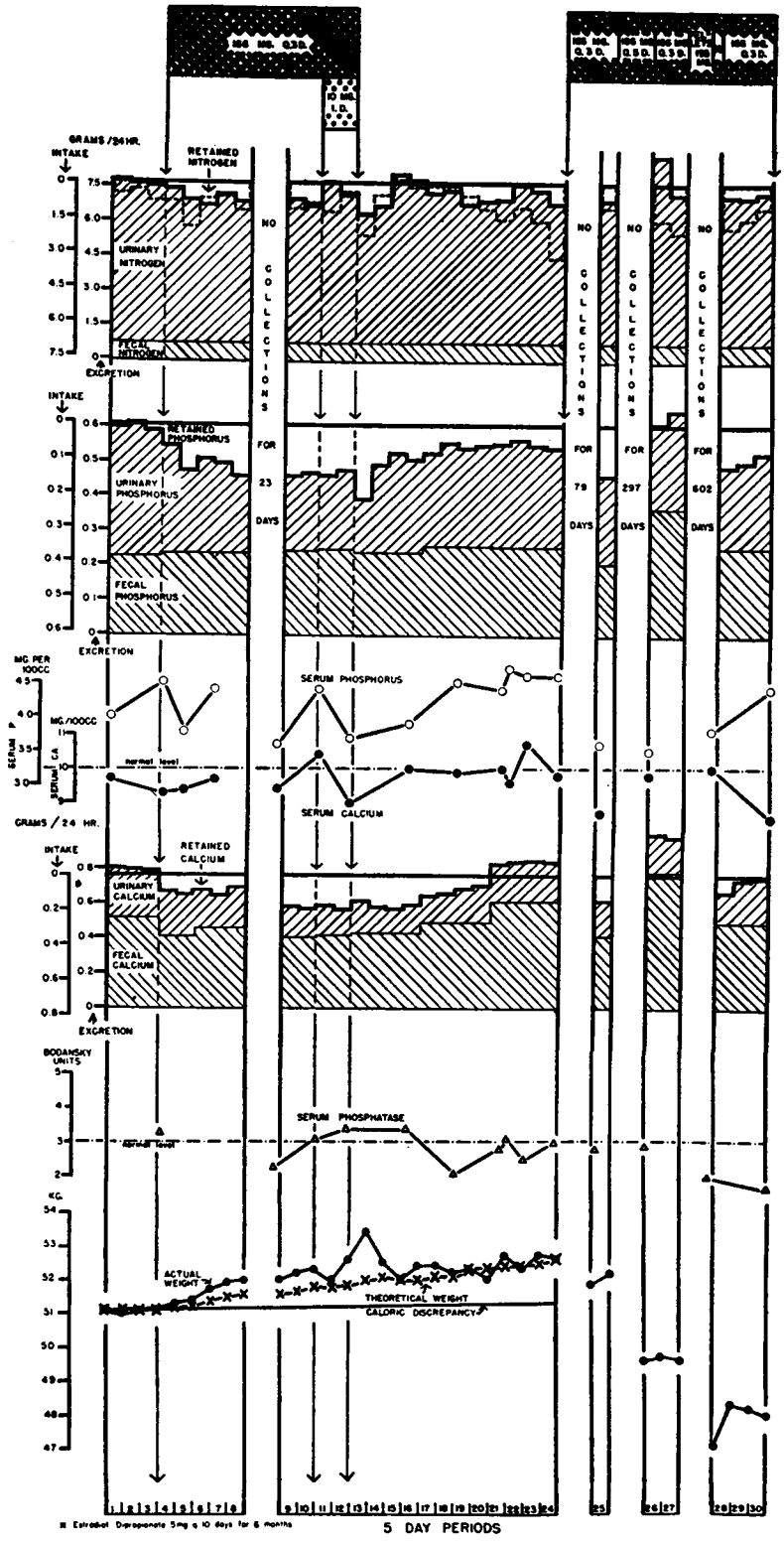

FIG. 1. CASE 1 (F. F., M.G.H. 156453): EFFECT OF ESTRADIOL BENZOATE ON NITROGEN, PHOSPHORUS, AND CALCIUM BALANCES, ON SERUM

Cushing's syndrome where, we believe, an excess of the adrenal cortical "sugar" or "S" hormone inhibits anabolism of protoplasm including bone matrix (2, 6); (5) adaptation syndrome of Selye (7), where, we believe, the pathological physiology is the same as in Cushing's syndrome; (6) idiopathic osteoporosis, where the cause of the condition remains obscure; (7) acromegaly, where the cause may be the increase of pituitary hormone(s), or the secondary lack of gonadal hormones (8); and (8) the post-menopausal state, the commonest of all forms, where the difficulty is a deficiency in estrogen to stimulate the osteoblasts. Frequently 2 or more factors combine in one individual; thus, after an orthopedic operation (see Cases 7, 8, and 9, below) factors (1) and (5) probably both play a part.

METABOLIC STUDIES

For the methods employed in the accumulation, interpretation and presentation of these data, see (9). Case histories are abstracted in the appendix.

A. Post-menopausal osteoporosis

Case 1. Post-Menopausal Osteoporosis; Artificial Menopause; Estradiol Benzoate Therapy.

The metabolic data of Case 1 are shown in Figure 1 and Table I. The first part of the study, conducted in 5-day periods, consisted of: (1) three control periods; (2) five periods with estradiol benzoate 1.66 mgm. intramuscularly every 3 days; (3) twenty-three days with the same therapy at home; (4) two periods with the same therapy; (5) two periods with progesterone 10 mgm. intramuscularly daily in addition to the estradiol; and (6) twelve periods after the cessation of both medications. The patient was then discharged on estrogen therapy which was given continuously in varied dosage during the next 3 years; during this interval she was brought back to the metabolic ward for study (1 to 3 five-day periods) on 3 occasions.

The data (Figure 1) are self-explanatory. Attention should be called to: (1) nitrogen, phosphorus, and calcium equilibria during the control periods (1 to 3); (2) the high serum phosphorus level which tended to fall under estrogen therapy (less marked in this case than in the others [*vide infra*]); (3) the slight improvement in nitrogen balance under estrogen therapy; (4) the striking and growing decrease in calcium excretion, both fecal and urinary, with estrogen treatment and the gradual return (40 days) in calcium excretion to pre-treatment levels following cessation of estrogen therapy; (5) a decrease with estrogen treatment in the phosphorus excretion almost entirely confined to the urinary component, and reasonably proportional to the changes in the calcium and nitrogen metabolisms (see "Theoretical Nitrogen Balance"); (6) failure of the serum phosphatase level, the index of osteoblastic activity, to rise under estrogen therapy; (7) an increase in nitrogen, but not in calcium and phosphorus, excretions in periods 11 and 12 with progesterone therapy; and (8) the tendency to retain extracellular fluids with estradiol therapy, as suggested by the increase in the actual weight above the theoretical weight.

The apparent discrepancy in the effect of estrogen on the calcium and phosphorus balances during periods 26 and 27 is probably to be explained by erroneously high fecal excretions resulting from too short a period of observation (9).

Case 2. Post-Menopausal Osteoporosis; Physiological Menopause; Question of Superimposed Atrophy of Disuse; Estradiol Benzoate Therapy.

The metabolic data of Case 2 are shown in Figure 2 and Table II. The study, conducted in 5-day periods, consisted of: (1) five control periods; (2) thirteen periods during which the patient received estradiol benzoate 3.32 mgm. intramuscularly every other day. In addition, during the 3 periods 14, 15, and 16, testosterone propionate 25 mgm. were administered intramuscularly every other day.

The data in Case 2 confirm the main observations made on Case 1. The fall in the serum phosphorus level after estradiol medication was more pronounced than in Case 1, and in addition there was a fall in the serum calcium level. Again the serum phosphatase level failed to rise with the improvement in the calcium balance. The duration of the testosterone propionate therapy was too short to judge its effect on the calcium balance; it brought about the expected increase in the nitrogen retention and rise in the urinary 17-ketosteroid excretion. The theoretical nitrogen balance based on the phosphorus balance after it had been corrected for the calcium balance agrees quite well with the measured nitrogen balance.

CALCIUM, PHOSPHORUS, AND ALKALINE PHOSPHATASE LEVELS, AND ON BODY WEIGHT IN A FEMALE PATIENT WITH POST-MENOPAUSAL OSTEOPOROSIS

For discussion, see text.

The dotted line in the nitrogen metabolism data represents the "theoretical nitrogen balance." The fecal nitrogen was estimated as 10 per cent of the intake. The fecal calcium and phosphorus values as charted are averages of 1, 2, 3, or 4 five-day periods as follows: 1 through 3, 4 through 5, 6 through 8, 9 through 10, 11 through 12, 13 through 16, 17 through 20, 21 through 24, 25, 26 through 27, 28 through 30; the individual values are given in Table I.

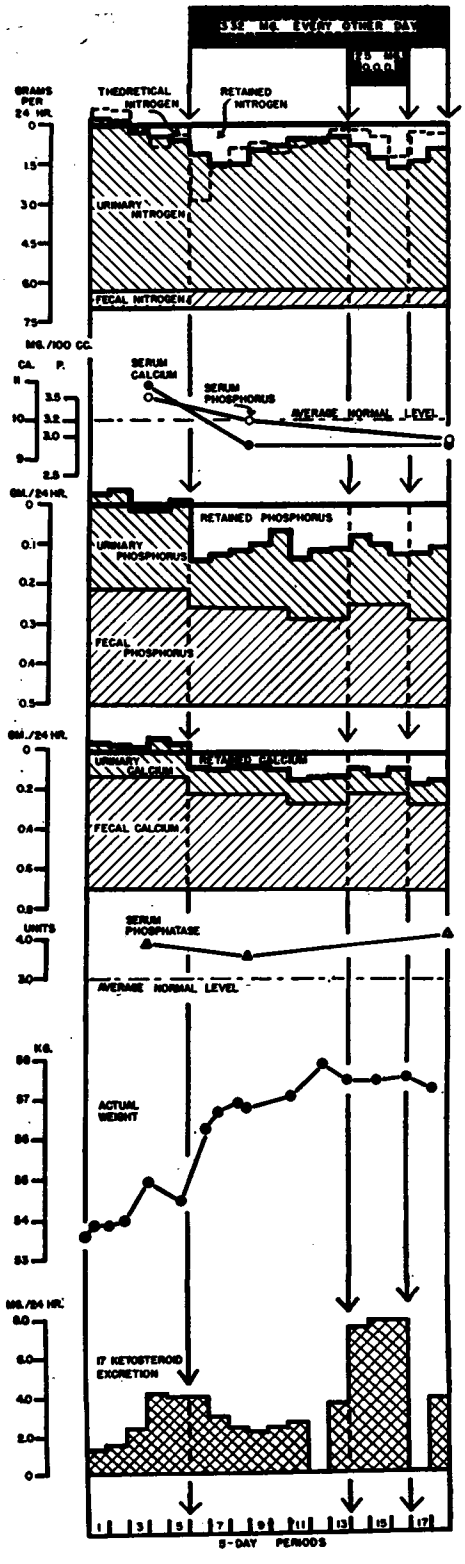

FIG. 2. CASE 2 (E. P., M.G.H. 203540): EFFECT OF ESTRADIOL BENZOATE AND TESTOSTERONE PROPIONATE ON NITROGEN, PHOSPHORUS, AND CALCIUM BALANCES, ON SERUM CALCIUM, PHOSPHORUS, AND ALKALINE PHOSPHATASE LEVELS, ON BODY WEIGHT AND ON URINARY 17-KETOSTEROID EXCRETION

For discussion, see text.

The fecal nitrogen was estimated as 10 per cent of the intake. The fecal phosphorus and calcium values as charted are averages of 2, 3, 4, or 5 five-day periods as follows: 1 through 5, 6 through 9, 10 through 13, 14 through 16, 17 through 18; the individual values are given in Table II.

Case 3. Post-Menopausal Osteoporosis; Artificial Menopause; Estradiol Benzoate Therapy.

The metabolic data of Case 3 are shown in Figure 3 and Table III. The study, conducted in 5-day periods, consisted of: (*1*) four control periods; (*2*) nine periods in which 1.66 mgm. of estradiol benzoate were administered intramuscularly every 3 days; (*3*) ninety-three days at home on the same medication; (*4*) five periods on the same medication; (*5*) seven periods during which the estradiol dosage was doubled; and (*6*) five control periods of medication. During period 10 the patient was given in addition 10 mgm. of progesterone intramuscularly each day.

It will be noted in Figure 3 that the improvement in the calcium balance in this case following estradiol therapy was almost entirely due to the fall in the urinary calcium excretion. It is further suggested that the positive calcium balance tends to diminish with time (compare periods 14 to 18 with periods 11 to 13). Note, furthermore, that the calcium balance was not improved, and possibly reduced, when estradiol therapy was doubled in periods 19 through 25. The fall in the serum phosphorus level with medication was especially striking in this case. The actual weight was greater than the theoretical weight during the therapy, which suggests retention of extracellular fluids.

Case 4. Post-Menopausal Osteoporosis; Artificial Menopause; Methyl Testosterone, Estradiol Benzoate and Pregnenolone Therapy.

The metabolic data of Case 4 are given in Figure 4 and Table IV. The study, conducted in 6-day periods, consisted of: (*1*) four control periods; (*2*) four periods on methyl testosterone, 40 mgm. by mouth daily; (*3*) five periods in which 1.66 mgm. of estradiol benzoate daily by injection were added to the methyl testosterone therapy; (*4*) five periods back on the methyl testosterone therapy alone; (*5*) four more control periods off medication; (*6*) three periods on pregnenolone, 30 mgm. intramuscularly daily; (*7*) four more control periods off medication; (*8*) five periods back on methyl testosterone, 40 mgm. by mouth daily with a change in the nitrogen and phosphorus intakes during the last 3 of these; and (*9*) one final period where the methyl testosterone therapy was increased to 100 mgm. by mouth daily. The urinary determinations were made on 3-day periods throughout.

In Figure 4 it should be noted first that the theoretical nitrogen balance is consistently less than the actual

TABLE II

Data for case 2 (E.P., M.G.H. 203540)

Period number	Date	Calcium				Phosphorus				Nitrogen				Body weight		Urinary 17-ketosteroids		Serum				Treatment	
		Urinary	Fecal	Intake	Balance	Urinary	Fecal	Intake	Balance	Urinary	Intake	Balance	Theoretical balance	Measured*	Theoretical	Day of period		Day of period	Calcium	Phosphorus	Alkaline phosphatase	Estradiol benzoate (i.m.)	Testosterone propionate (i.m.)
		mgm. per 24 hr.				*mgm. per 24 hr.*				*grams per 24 hr.*				*kgm.*			*mgm. per 24 hr.*		*mgm. per 100 ml.*		*B.U.*		
	9/18/39															IV	1.5		10.1	3.5	3.7		
1	9/23 to 27/39	183	428	708	+ 97	238	256	506	+ 12	6.47	6.93	−0.23	−0.57	53.90	53.71	V	2.4						
2	9/28 to 10/2/39	177	594	708	− 63	255	314	506	− 63	6.39	6.93	−0.15	−0.48	53.86	53.77								
3	10/ 3 to 7/39	146	624	708	− 62	198	329	506	− 21	5.92	6.93	+0.32	+0.15	54.02	53.90			II	10.9	3.5	3.9	None	
4	10/ 8 to 12/39	187	581	708	− 60	197	284	506	+ 25	5.78	6.93	+0.46	+0.79	54.96	54.06	II	4.2						
5	10/13 to 17/39	162	589	708	− 43	223	278	506	+ 5	5.64	6.93	+0.60	+0.37	54.48	54.23	IV	4.0						None
6	10/18 to 22/39	133	377	708	+198	118	193	506	+195	5.12	6.93	+1.12	+2.95	56.38	54.48	IV	4.0						
7	10/23 to 27/39	129	671	708	− 92	127	322	506	+ 57	4.74	6.93	+1.50	+1.51	56.70	54.79	IV	3.0						
8	10/28 to 11/1/39	139	471	708	+ 98	146	249	506	+111	4.72	6.93	+1.52	+0.91	56.83	55.10	IV	2.4	V	9.4	3.2	3.5		
9	11/ 2 to 6/39	142	404	708	+162	160	215	506	+131	5.27	6.93	+0.97	+0.73		55.34	IV	2.2						
10	11/ 7 to 11/39	131	407	708	+170	195	178	506	+133	5.45	6.93	+0.79	+1.21		55.54	II	2.4						
11	11/12 to 16/39	125	427	708	+156	162	238	506	+106	5.69	6.93	+0.55	+0.71	57.11	55.70	IV	2.6						
12	11/17 to 21/39	136	471	708	+101	175	236	506	+ 95	5.71	6.93	+0.53	+0.65	57.89	55.86								
13	11/22 to 26/39	141	431	708	+136	178	244	506	+ 84	5.73	6.93	+0.51	+0.23		56.02	IV	3.6					3.32 mgm. every other day	
14	11/27 to 12/1/39	127	481	708	+100	173	267	506	+ 66	5.47	6.93	+0.77	+0.21	57.49	56.22	V	7.5						25 mgm. every other day
15	12/ 2 to 6/39	91	367	708	+250	151	205	506	+150	4.95	6.93	+1.29	+0.51	57.52	56.50	IV	7.8						25 mgm. every other day
16	12/ 7 to 11/39	122	595	708	− 9	129	297	506	+ 80	4.61	6.93	+1.63	+1.25	57.64	56.81	IV	7.8						25 mgm. every other day
17	12/12 to 16/39	106	407	708	+195	168	202	506	+136	4.79	6.93	+1.45	+0.39	57.34	57.11								None
18	12/17 to 21/39	124	446	708	+138	185	222	506	+ 99	5.24	6.93	+1.00	+0.43	57.34	57.34	II	3.8						None
	12/22/39																		9.4	2.9	4.1		

Dietary intake of periods 1 to 18 in amounts per 24 hours: protein (analyzed nitrogen × 6.25) = 43.3 grams, fat (estimated from tables) = 75.8 grams, carbohydrate (estimated from tables) = 213.3 grams, calories (calculated from the values 4 for 1 gram of protein, 9 for 1 gram of fat, and 4 for 1 gram of carbohydrate) = 1,609. In addition sugar was given *ad lib*, with an average intake of 30 grams (120 calories).

* Initial weight (9/23/39) 53.66 kgm.

** Urinary 17-ketosteroid on 9/20/39 1.3 mgm. per 24 hours.

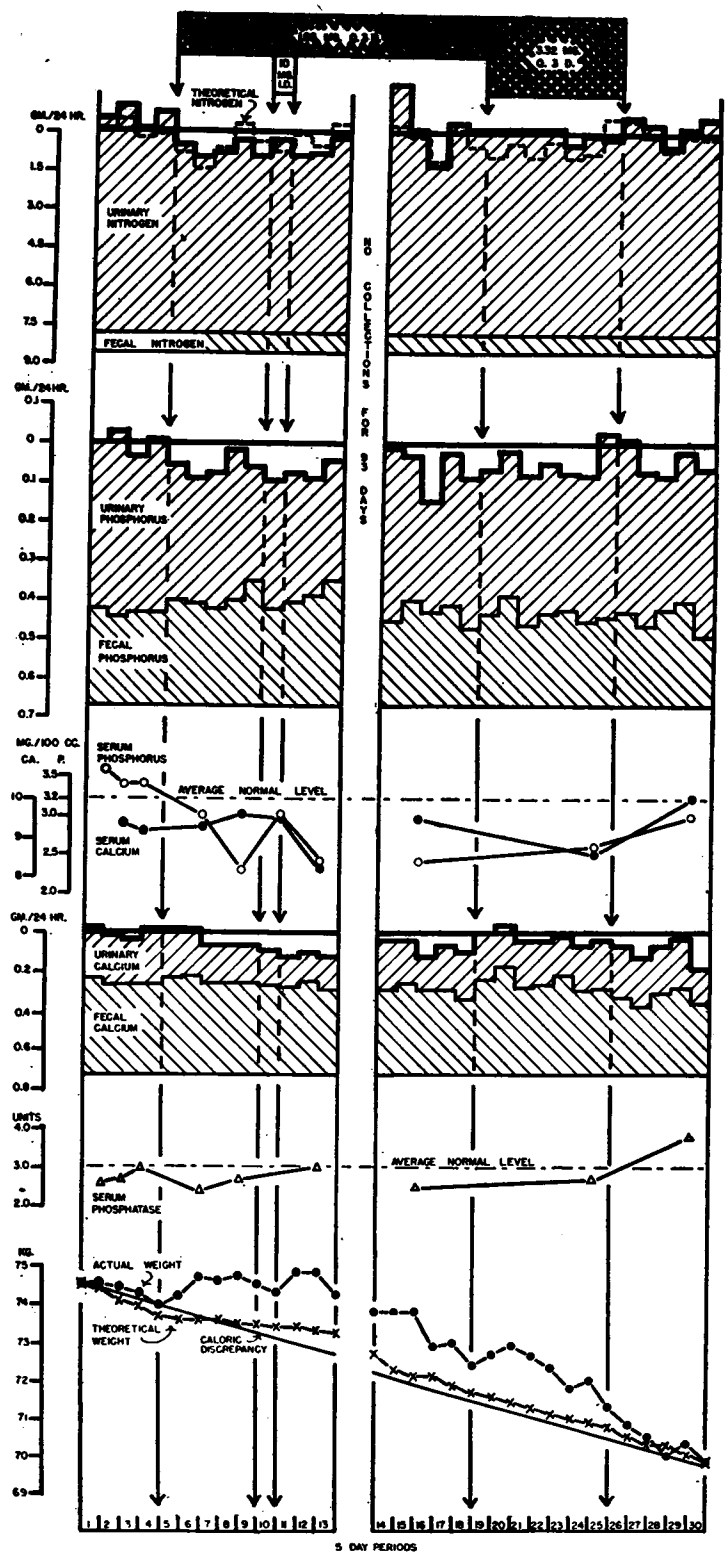

FIG. 3. CASE 3 (A. M. R., M.G.H. 29358): EFFECT OF ESTRADIOL BENZOATE ON NITROGEN, PHOSPHORUS, AND CALCIUM BALANCES, ON SERUM CALCIUM, PHOSPHORUS, AND ALKALINE PHOSPHATASE LEVELS, AND ON BODY WEIGHT IN A FEMALE PATIENT WITH POST-MENOPAUSAL OSTEOPOROSIS

For discussion, see text.

TABLE III

Data for case 3 (A.M.R., M.G.H. 29358)

Period number	Date	Calcium				Phosphorus				Nitrogen				Body weight		Serum				Treatment	
		Urinary	Fecal	Intake	Balance	Urinary	Fecal	Intake	Balance	Urinary	Intake	Balance	Theoretical balance	Measured*	Theoretical	Day of period	Calcium	Phosphorus	Alkaline phosphatase	Estradiol benzoate (i.m.)	Progesterone (i.m.)
		mgm. per 24 hr.				*mgm. per 24 hr.*				*grams per 24 hr.*				*kgm.*			*mgm. per 100 ml.*		*B.U.*		
1	4/23 to 27/39	251	505	739	− 17	412	255	667	0	8.21	8.56	−0.51	−0.13	74.53	74.50						
2	4/28 to 5/2/39	276	460	739	++ 3	467	234	667	− 34	8.69	8.56	−0.99	−0.53	74.37	74.27	I		3.6	2.5	None	
3	5/ 3 to 7/39	251	460	739	++ 28	389	246	667	+ 32	7.72	8.56	−0.02	+0.27	74.28	74.21	I	9.4	3.4	2.6		
4	5/ 8 to 12/39	292	460	739	− 13	428	244	667	− 5	8.44	8.56	−0.74	+0.03	74.00	74.03	I	9.2	3.4	2,9		None
5	5/13 to 17/39	246	499	739	− 6	342	274	667	+ 51	7.14	8.56	+0.56	+0.81	74.23	74.04						
6	5/18 to 22/39	251	510	739	− 22	313	267	667	+ 87	6.77	8.56	+0.93	+1.47	74.76	74.10						
7	5/23 to 27/39	201	475	739	++ 63	343	251	667	+ 73	6.91	8.56	+0.79	+0.63	74.66	74.15	I	9.3	3.0	2.3		
8	5/28 to 6/1/39	199	477	739	++ 63	385	270	667	+ 12	7.32	8.56	+0.38	−0.29	74.76	74.13						
9	6/ 2 to 6/39	193	479	739	+ 67	294	319	667	+ 54	6.80	8.56	+0.90	+0.31	74.55	74.19	I	9.6	2.3	2.6		
10	6/ 7 to 11/39	187	466	739	+ 86	320	253	667	+ 94	7.38	8.56	+0.32	+0.77	74.34	74.16						10 mgm. daily
11	6/12 to 16/39	151	455	739	+133	328	267	667	+ 72	6.83	8.56	+0.87	+0.09	74.80	74.22	I	9.5	3.0			
12	6/17 to 21/39	163	481	739	+ 95	303	279	667	+ 85	6.92	8.56	+0.78	+0.57	74.81	74.26						
13	6/22 to 26/39	181	438	739	+120	308	321	667	+ 38	7.41	8.56	+0.29	−0.33	74.23		I	8.3	2.4	2.9		
	No collections for 93 days													73.73	73.73						
14	9/23 to 27/39	263	437	739	+ 39	447	219	667	+ 1	9.64	8.56	−1.94	−0.27	73.68	73.23						
15	9/28 to 10/2/39	231	478	739	+ 30	372	268	667	+ 27	7.80	8.56	−0.10	+0.18	73.73	73.01						
16	10/ 3 to 7/39	173	431	739	+135	277	245	667	+145	6.50	8.56	+1.20	+1.17	72.94	72.98	I	9.5	2.4	2.4		
17	10/ 8 to 12/39	254	428	739	+ 57	385	263	667	+ 19	8.10	8.56	−0.40	−0.15	72.98	72.71						
18	10/13 to 17/39	255	387	739	+ 97	376	206	667	+ 85	7.76	8.56	−0.06	+0.54	72.37	72.49					1.66 kgm. every third day	
19	10/18 to 22/39	246	493	739	0	371	237	667	+ 59	7.85	8.56	−0.15	+0.89	72.67	72.26						
20	10/23 to 27/39	214	564	739	− 39	375	278	667	+ 14	7.80	8.56	−0.10	+0.49	72.95	72.04						
21	10/28 to 11/1/39	253	451	739	++ 35	378	215	667	+ 74	7.86	8.56	−0.16	+0.85	72.62	71.81						
22	11/ 2 to 6/39	238	465	739	++ 36	382	242	667	+ 43	7.81	8.56	−0.11	+0.37	72.27	71.58						
23	11/ 7 to 11/39	219	513	739	+ 7	346	253	667	+ 68	7.22	8.56	+0.48	+0.97	71.88	71.44						
24	11/12 to 16/39	247	433	739	+ 59	370	220	667	+ 77	7.68	8.56	+0.02	+0.72	72.06	71.24						
25	11/17 to 21/39	266	446	739	+ 27	466	231	667	− 30	7.50	8.56	+0.20	−0.65	71.28	71.06	I	8.6	2.6	2.6	3.32 mgm. every third day	
26	11/22 to 26/39	277	401	739	+ 61	432	245	667	− 10	8.36	8.56	−0.66	−0.61	70.80	70.75						
27	11/27 to 12/1/39	263	357	739	+119	389	213	667	+ 65	8.13	8.56	−0.43	+0.09	70.54	70.48						
28	12/ 2 to 6/39	256	428	739	+ 55	338	250	667	+ 79	7.11	8.56	+0.59	+0.63	69.98	70.36						
29	12/ 7 to 11/39	261	455	739	+ 23	384	269	667	+ 14	7.93	8.56	−0.23	+0.05	70.32	70.12						
30	12/12 to 16/39	263	373	739	+103	420	188	667	+ 59	8.24	8.56	−0.54	+0.12	69.83	69.83	I	10.0	3.0	3.7	None	None

Dietary intake of periods 1 to 30 in amounts per 24 hours: protein (analyzed nitrogen × 6.25) = 53.5 grams, fat (estimated from tables) = 95.2 grams, carbohydrate (estimated from tables) = 241.6 grams, calories (calculated from the values 4 for 1 gram of protein, 9 for 1 gram of fat, and 4 for 1 gram of carbohydrate) = 2,037. In addition sugar was given *ad lib*, with an average intake of 30 grams (120 calories).

* Initial weight 74.65 kgm.

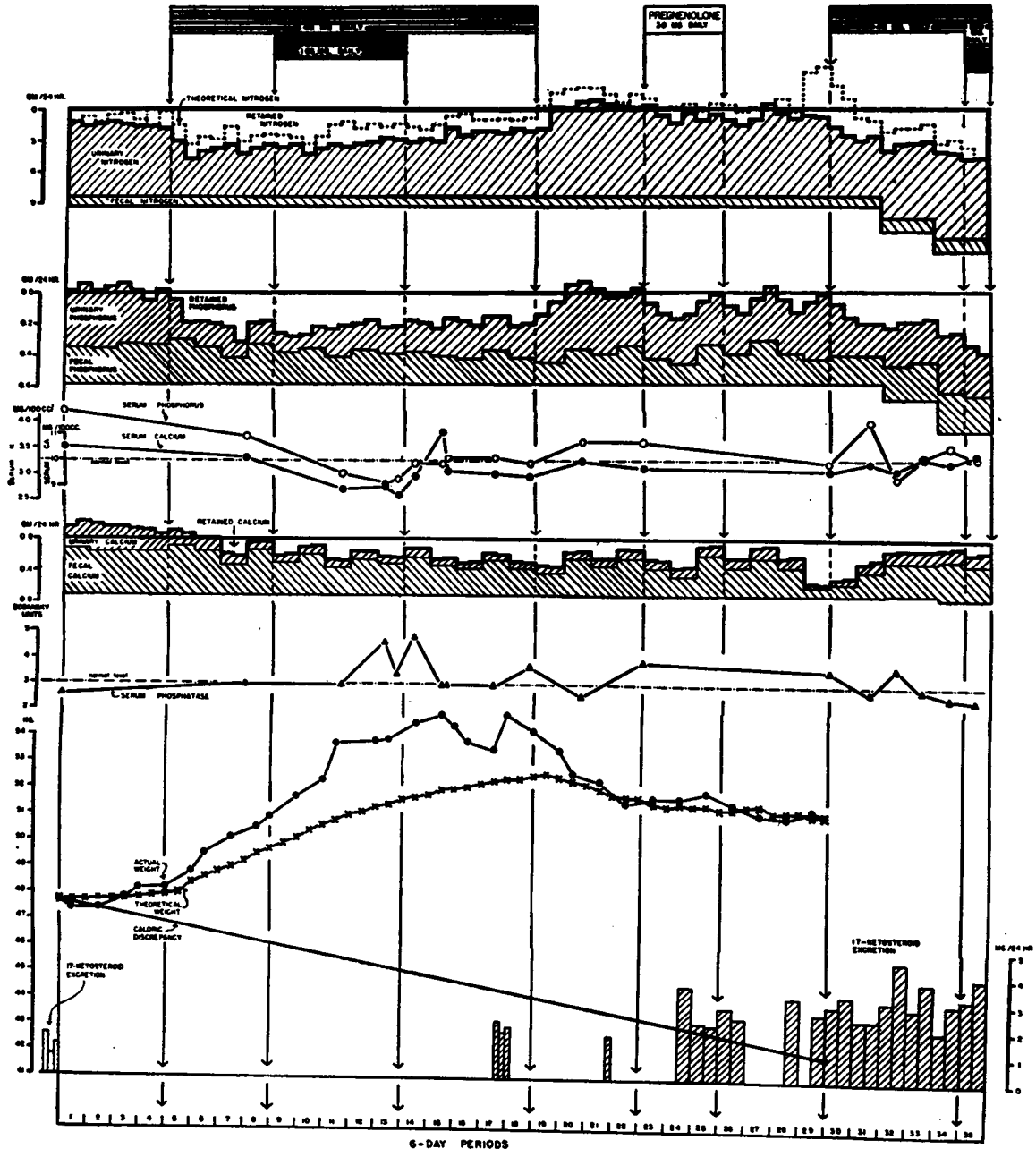

FIG. 4. CASE 4 (R. W., M.G.H. 319940): EFFECT OF METHYL TESTOSTERONE ALONE AND IN COMBINATION WITH ESTRADIOL BENZOATE, AND OF PREGNENOLONE ON NITROGEN, PHOSPHORUS, AND CALCIUM BALANCES, ON SERUM CALCIUM, PHOSPHORUS, AND ALKALINE PHOSPHATASE LEVELS, ON BODY WEIGHT, AND ON URINARY 17-KETOSTEROID EXCRETION IN A FEMALE PATIENT WITH POST-MENOPAUSAL OSTEOPOROSIS

For discussion, see text.

nitrogen balance, which indicates that there is some constant error throughout. Part of the error may be in the fecal nitrogen excretion which was not analyzed, but taken as 10 per cent of the nitrogen intake. In the absence of analyzed values, it would have been preferable, and the discrepancy would have been cut down, had we used the value of 1.283 grams per 24 hours, the average fecal nitrogen value for adults regardless of intake (9). The major part of the discrepancy is probably to be attributed to errors in the intakes. The daily diet was

TABLE IV

Data for case 4 (R.W., M.G.H. 319940)

Period number	Date	Calcium				Phosphorus				Nitrogen				Body weight		Urinary 17-ketosteroids	Serum				Treatment		
		Urinary	Fecal	Intake	Balance	Urinary	Fecal	Intake	Balance	Urinary	Intake	Balance	Theoretical balance	Measured	Theoretical		Day of Period	Calcium	Phosphorus	Alkaline Phosphates	Methyl testosterone (p.o.)	Estradiol benzoate (i.m.)	Pregnenolone (i.m.)
		mgm. per 24 hr.				*mgm. per 24 hr.*				*grams per 24 hr.*				*kgm.*		*mgm. per 24 hr.*		*mgm. per 100 ml.*		*B.U.*			
	9/17/41																	10.6	3.1	3.7			
	10/15 to 16/41															1.6							
	10/16 to 17/41															0.8							
	10/17 to 18/41													47.70		1.2							
1	10/18 to 20/41	271	581	708	−144	347	240	584	− 3	7.15	9.31	+1.23	+1.0	47.37	47.70		III	10.5	4.2	2.4	None	None	None
	10/21 to 23/41	339	581	708	−212	405	240	584	− 61	6.86	9.31	+1.52	+0.6		47.73								
2	10/24 to 26/41	343	547	708	−182	358	234	584	− 8	6.99	9.31	+1.39	+1.2	47.40	47.76								
	10/27 to 29/41	316	547	708	−155	398	234	584	− 48	7.03	9.31	+1.35	+0.4		47.77								
3	10/30 to 11/1/41	315	554	708	−161	385	258	584	− 59	7.26	9.31	+1.12	+0.3	47.83	47.80								
	11/ 2 to 4/41	284	554	708	−130	327	258	584	− 1	6.78	9.31	+1.60	+0.9	48.16	47.84								
4	11/ 5 to 7/41	279	552	708	−123	289	254	584	+ 41	6.80	9.31	+1.58	+1.5		47.88								
	11/ 8 to 10/41	215	552	708	− 59	347	254	584	− 17	6.67	9.31	+1.71	+0.18	48.26	47.93								
5	11/11 to 13/41	207	623	708	−122	254	288	584	+ 42	5.39	9.31	+2.99	+1.5		48.09						40 mgm. daily	1.66 mgm. daily	None
	11/14 to 16/41	162	623	708	− 77	111	288	584	+185	3.77	9.31	+4.61	+3.3	48.79	48.39								
6	11/17 to 19/41	156	563	708	− 11	169	240	584	+175	4.49	9.31	+3.89	+2.7	49.55	48.63								
	11/20 to 22/41	150	563	708	− 5	153	240	584	+191	5.00	9.31	+3.38	+2.9		48.83								
7	11/23 to 25/41	142	380	708	+186	198	172	584	+214	5.30	9.31	+3.08	+1.7	50.14	49.00								
	11/26 to 28/41	112	380	708	+216	100	172	584	+312	4.16	9.31	+4.22	+3.1		49.27								
8	11/29 to 12/1/41	99	583	708	+ 26	140	257	584	+187	4.77	9.31	+3.61	+2.6	50.53	49.48								
	12/ 2 to 4/41	94	583	708	+ 31	150	257	584	+177	5.14	9.31	+3.24	+2.4	50.86	49.67								
9	12/ 5 to 7/41	92	420	708	+196	121	201	584	+262	4.50	9.31	+3.87	+2.5		49.91								
	12/ 8 to 10/41	100	420	708	+188	108	201	584	+275	4.82	9.31	+3.56	+2.7	51.70	50.12								
10	12/11 to 13/41	96	528	708	+ 84	90	230	584	+264	4.24	9.31	+4.14	+3.3		50.38								
	12/14 to 16/41	102	528	708	+ 78	138	230	584	+216	4.76	9.31	+3.62	+2.6	52.34	50.59								
11	12/17 to 19/41	103	356	708	+249	183	174	584	+227	5.12	9.31	+3.26	+1.5	53.73	50.78								
	12/20 to 22/41	97	356	708	+255	204	174	584	+206	5.00	9.31	+3.28	+1.2		50.98								
12	12/23 to 25/41	105	465	708	+138	173	222	584	+189	5.30	9.31	+3.10	+1.8		51.15								
	12/26 to 28/41	100	465	708	+143	195	222	584	+167	5.44	9.31	+2.94	+1.4	53.83	51.31								
13	12/29 to 31/41	92	402	708	+214	168	195	584	+221	5.83	9.31	+2.55	+1.7	53.94	51.43		III	8.9	3.0	2.9			
	1/ 1 to 3/42	85	402	708	+221	187	195	584	+202	5.67	9.31	+2.71	+1.4		51.57		II	9.0	2.8	4.5			
14	1/ 4 to 6/42	111	473	708	+124	201	209	584	+174	5.47	9.31	+2.91	+1.7	54.48	51.72		II	8.7	2.9	3.3			
	1/ 7 to 9/42	111	473	708	+124	188	209	584	+187	5.71	9.31	+2.67	+1.9		51.85		III	9.4	3.2	4.7			
15	1/10 to 12/32	88	388	708	+232	179	182	584	+223	5.33	9.31	+2.85	+1.5	54.82	52.00								
	1/13 to 15/42	94	388	708	+226	246	182	584	+156	6.81	9.31	+1.57	+0.64	54.44	52.04								
16	1/16 to 18/42	78	342	708	+288	246	164	584	+174	6.04	9.31	+2.34	+0.45		52.14		I	9.6	3.3	2.9			
	1/19 to 21/42	90	342	708	+276	218	164	584	+202	6.40	9.31	+1.98	+0.96	53.86	52.22								
17	1/22 to 24/42	85	451	708	+172	214	219	584	+151	6.21	9.31	+2.17	+0.97		52.29								
	1/25 to 27/42	78	451	708	+179	213	219	584	+152	6.37	9.31	+2.01	+0.94	53.52	52.37	{2.2 {1.8	III	9.5	3.3	2.9			
18	1/28 to 30/42	95	342	708	+271	210	171	584	+203	6.57	9.31	+1.81	+1.0	54.83	52.42	2.0							
	1/31 to 2/2/42	86	342	708	+280	220	171	584	+193	6.33	9.31	+2.05	+0.8		52.50								

TABLE IV—*Continued*

Period number	Date	Calcium				Phosphorus				Nitrogen				Body weight		Urinary 17-ketosteroids	Serum				Treatment		
		Urinary	Fecal	Intake	Balance	Urinary	Fecal	Intake	Balance	Urinary	Intake	Balance	Theoretical balance	Measured	Theoretical		Day of Period	Calcium	Phosphorus	Alkaline Phosphates	Methyl testosterone (p.o.)	Estradiol benzoate (i.m.)	Pregnenolone (i.m.)
		mgm. per 24 hr.				*mgm. per 24 hr.*				*grams per 24 hr.*				*kgm.*		*mgm. per 24 hr.*		*mgm. per 100 ml.*		*B.U.*			
19	2/ 3 to 5/42	98	298	708	+312	308	141	584	+135	6.59	9.31	+1.79	−0.31	54.20	52.56		II	9.4	3.2	3.6	None	None	None
	2/ 6 to 8/42	84	298	708	+326	391	141	584	+ 52	8.39	9.31	−0.01	−1.6		52.46								
20	2/ 9 to 11/42	82	466	708	+160	412	224	584	− 52	8.40	9.31	−0.02	−1.9	53.47	52.35								
	2/12 to 14/42	97	466	708	+145	428	224	584	− 68	9.19	9.31	−0.81	−2.1	52.61	52.18								
21	2/15 to 17/42	92	379	708	+237	409	195	584	− 20	9.35	9.31	−0.97	−2.0		52.00		II	10.0	3.6	2.5			
	2/18 to 20/42	94	379	708	+235	369	195	584	+ 20	8.87	9.31	−0.49	−1.4	52.31	51.86	1.7							
22	2/21 to 23/42	106	470	708	+132	324	247	584	+ 13	8.63	9.31	−0.25	−0.8		51.73								
	2/24 to 26/42	102	470	708	+136	366	247	584	− 29	8.51	9.31	−0.13	−1.4	51.52	51.62								
23	2/27 to 3/1/42	101	350	708	+257	362	166	584	+ 56	8.81	9.31	−0.43	−1.1	51.69	51.48		I	9.8	3.6	3.8			
	3/ 2 to 4/42	100	350	708	+258	289	166	584	+129	7.77	9.31	+0.60	0		51.43								
24	3/ 5 to 7/42	110	238	708	+360	287	126	584	+171	7.03	9.31	+1.35	−0.13	50.60	51.45								
	3/ 8 to 10/42	123	238	708	+347	318	126	584	+140	7.92	9.31	+0.46	−0.49	51.59	51.39	3.6							
25	3/11 to 13/42	117	506	708	+ 85	280	251	584	+ 53	7.25	9.31	+1.13	+0.61	51.99	51.39	2.2							
	3/14 to 16/42	129	506	708	+ 73	329	251	584	+ 4	7.82	9.31	+0.56	−0.48	51.35	51.34	2.1							
26	3/17 to 19/42	122	357	708	+229	311	189	584	+ 84	7.18	9.31	+1.20	−0.45	51.48	51.34	2.8							
	3/20 to 22/42	127	357	708	+224	263	189	584	+132	6.65	9.31	+1.73	+0.3	51.37	51.39	2.4							
27	3/23 to 25/42	144	472	708	+ 92	272	274	584	+ 38	7.34	9.31	+1.04	−0.1	51.12	51.38								
	3/26 to 28/42	163	472	708	+ 73	346	274	584	− 36	8.71	9.31	−0.33	0	51.15	51.26								
28	3/29 to 31/42	126	365	708	+217	348	193	584	+ 43	7.86	9.31	+0.52	−0.97	51.06	51.20								
	4/ 1 to 3/42	132	365	708	+211	266	193	584	+125	7.45	9.31	+0.93	+0.3	51.06	51.18	3.2							
29	4/ 4 to 6/42	58	141	708	+509	375	187	584	+ 22	7.83	9.31	+0.55	−3.5	51.35	51.13								
	4/ 7 to 9/42	50	141	708	+517	419	187	584	− 22	7.64	9.31	+0.74	−4.0	51.10	51.10	2.6							
30	4/10 to 12/42	56	115	708	+537	320	151	584	+113	6.67	9.31	+1.70	−2.3	50.86		2.9	I	9.6	3.2	3.5			
	4/13 to 15/42	71	115	708	+522	240	151	584	+193	5.69	9.31	+2.69	−1.0	51.10		3.3							
31	4/16 to 18/42	119	297	708	+292	205	180	584	+199	5.41	9.31	+2.97	+0.79	51.81		2.4							
	4/19 to 21/42	161	297	708	+250	204	180	584	+200	5.75	9.31	+2.63	+1.1	52.26		2.4	III	9.9	4.0	2.7			
32	4/22 to 24/42	150	412	700	+138	246	216	682	+220	6.53	11.80	+4.09	+2.2	52.31		3.1							
	4/25 to 27/42	163	412	700	+125	282	216	682	+184	7.16	11.80	+3.46	+1.8	52.27		4.6							
33	4/28 to 30/42	159	405	700	+136	255	238	682	+189	7.30	11.80	+3.32	+1.8	52.38		2.8	I	9.6	2.9	3.6			
	5/ 1 to 3/42	161	405	700	+134	273	238	682	+171	7.35	11.80	+3.27	+1.5	52.84		3.8							
34	5/ 4 to 6/42	166	478	745	+101	365	255	890	+270	8.29	13.9	+4.22	+3.3	52.67		2.0	I	10.1	3.3	2.8			
	5/ 7 to 9/42	157	478	745	+110	379	255	890	+256	8.42	13.9	+4.09	+3.0	52.49		3.0							
35	5/10 to 12/42	160	431	745	+154	329	232	890	+329	7.66	13.9	+4.85	+3.7	52.56		3.2	I	9.9	3.5	2.5	100 mgm. daily		
	5/13 to 15/42	170	431	745	+144	279	232	890	+379	7.71	13.9	+4.80	+4.6	52.95		4.0					100 mgm. daily		
	5/16/42																	10.2	3.3	2.4			

Dietary intake of periods 1 to 31 in amounts per 24 hours: protein (analyzed nitrogen × 6.25) = 52.5 grams, fat (estimated from tables) = 63.5 grams, carbohydrate (estimated from tables) = 207.5 grams, calories (calculated from the values 4 for 1 gram of protein, 9 for 1 gram of fat, and 4 for 1 gram of carbohydrate) = 1,611; periods 32 to 33: protein = 63.7 grams, fat = 51.3 gram, carbohydrate = 197.9 gram, calories = 1,508; periods 34 to 35; protein 86.9 grams, fat = 61.1 grams, carbohydrate = 178.7 grams, calories = 1,612. In addition throughout sugar was given *ad lib*, with an average intake of 30 grams (120 calories).

analyzed twice with the following results: analysis October 1941: calcium 71 mgm., phosphorus 584 mgm., and nitrogen 9.31 grams; analysis February 2, 1944: calcium 64 mgm., phosphorus 611 mgm., and nitrogen 8.40 grams. Figure 4 was constructed from the analysis of 1941; had it been constructed from the analysis of 1944, the discrepancy would have been almost eliminated. Thus, if one recalculates on the basis of the 1944 analysis the theoretical nitrogen balance of period 4b, and in addition uses the value of 1.283 grams for the fecal nitrogen instead of 10 per cent of the intake, one obtains the values + 0.65 and + 0.45 grams for the theoretical and actual nitrogen balances, respectively, in contrast to the values of + 0.18 and + 1.71 grams. Since the above discrepancy is fairly constant, it does not affect the trends induced by treatment.

Figure 4 is self-explanatory. To be noted are: (*1*) the decrease in the nitrogen, phosphorus, and calcium excretions with methyl testosterone therapy, and the rebound of nitrogen and phosphorus excretions on cessation of therapy; (*2*) the fact that the fecal, as well as the urinary, excretions of both calcium and phosphorus were reduced under methyl testosterone therapy; (*3*) the fact that there was not an immediate rebound of the calcium excretion following cessation of methyl testosterone therapy; (*4*) the further improvement in the calcium balance, but not in the nitrogen balance, when estradiol benzoate therapy was added to the methyl testosterone therapy (periods 9 to 13); (*5*) the fall in serum phosphorus level with methyl testosterone and especially with estradiol benzoate therapy; (*6*) the definite tendency of the serum calcium level to parallel the serum phosphorus level (see also Figure 2); and (*7*) the failure of the serum phosphatase level to show a significant change. The effect of the pregnenolone therapy is inconclusive; it did not significantly affect the very low 17-ketosteroid excretion. No explanation is forthcoming in periods 29 and 30 for the low fecal calcium excretions not associated with low nitrogen and phosphorus excretions; as a result, the data during periods 30 through 36 are difficult to interpret. The actual and theoretical weight curves suggest that there was retention of extracellular fluid with methyl testosterone therapy which was augmented when estradiol benzoate therapy was added. Pregnenolone therapy had a minimal effect on extracellular fluid retention.

Case 5. Post-Menopausal Osteoporosis; Artificial Menopause; Paget's Disease; Diethylstilbestrol and Progesterone Therapy.

The metabolic data of Case 5 are given in Figure 5 and Table V. The study, conducted in 6-day periods, consisted of: (*1*) three control periods; (*2*) five periods on 1 mgm. of diethylstilbestrol by mouth daily; (*3*) seven periods on 15 mgm. of diethylstilbestrol by mouth daily, with an increase in the diet in the last 3 of these; (*4*) six periods with the same dosage of diethylstilbestrol in which progesterone by injection was given in addition (25 mgm. daily for the first 4 of these periods, and 100 mgm. daily for the last 2); and (*5*) three periods on 15 mgm. of diethylstilbestrol daily alone.

This patient was selected for the study not only because she had marked osteoporosis from an artificial menopause 30 years before, but because she had, in addition, Paget's disease. The primary pathologic process of the Paget's disease, bone destruction, was not being responded to with the usual amount of increased bone formation because of the menopause (4). Therefore, it was thought that any action of estrogen to stimulate bone formation would be magnified in this patient.

Figure 5 is self-explanatory. To be noted are: (*1*) the markedly negative calcium and phosphorus balances during the control periods; (*2*) the marked improvement of these balances with 1 mgm. of diethylstilbestrol daily; (*3*) the further improvement with 15 mgm. of diethylstilbestrol daily; (*4*) the lack of effect of progesterone on the calcium and phosphorus balances; (*5*) the high serum phosphorus before treatment; (*6*) the tendency of the serum phosphorus to fall during treatment; (*7*) the failure of the serum phosphatase to rise with improvement of the calcium balance; (*8*) the tendency of the 17-ketosteroid excretion to rise with progesterone; (*9*) the failure of the "11-oxysteroid" excretion [4] to fluctuate outside of the normal range with therapy; (*10*) the striking fall [5] in the urinary follicle-stimulating hormone (FSH) excretion with diethylstilbestrol therapy; and (*11*) the subsequent rise in the FSH excretion when progesterone therapy was superimposed on the diethylstilbestrol therapy. The increase in the positive nitrogen balance and the increase in weight during periods 22 to 24 may be indications that progesterone was acting unfavorably on the nitrogen balance (12). Not explained is the rise in FSH excretion in periods 23 and 24.

B. Senile osteoporosis

Case 6. Senile Osteoporosis in a Male of 72; Testosterone Propionate and Estradiol Benzoate Therapy.

The metabolic data of Case 6, which comprise studies done on 290 of 530 consecutive days, are shown in Figure 6 and Table VI. The study, conducted in 5-day periods, consisted of: (*1*) five control periods; (*2*) five periods on testosterone propionate, 25 mgm. by injection daily; (*3*) five periods in which estradiol benzoate 1.66 mgm. by injection on alternate days was added to the testosterone propionate therapy; (*4*) five periods back on testosterone propionate alone; (*5*) seven control periods off all medication; (*6*) five periods on estradiol benzoate 1.66 mgm. by injection twice daily; (*7*) ten days without collections on the same medication; (*8*) two more periods on the same medication; (*9*) ninety-three days at home on estradiol benzoate 3.32 mgm. by injection 3 times

[4] These observations were carried out by Dr. Nathan B. Talbot with his method (10). The normal range is 0.10 to 0.35 mgm. per 24 hours.

[5] The level fell from 200–300 units per day to less than 6 units per day. Normal range of FSH excretion is 6 to 50 mouse units per day (11).

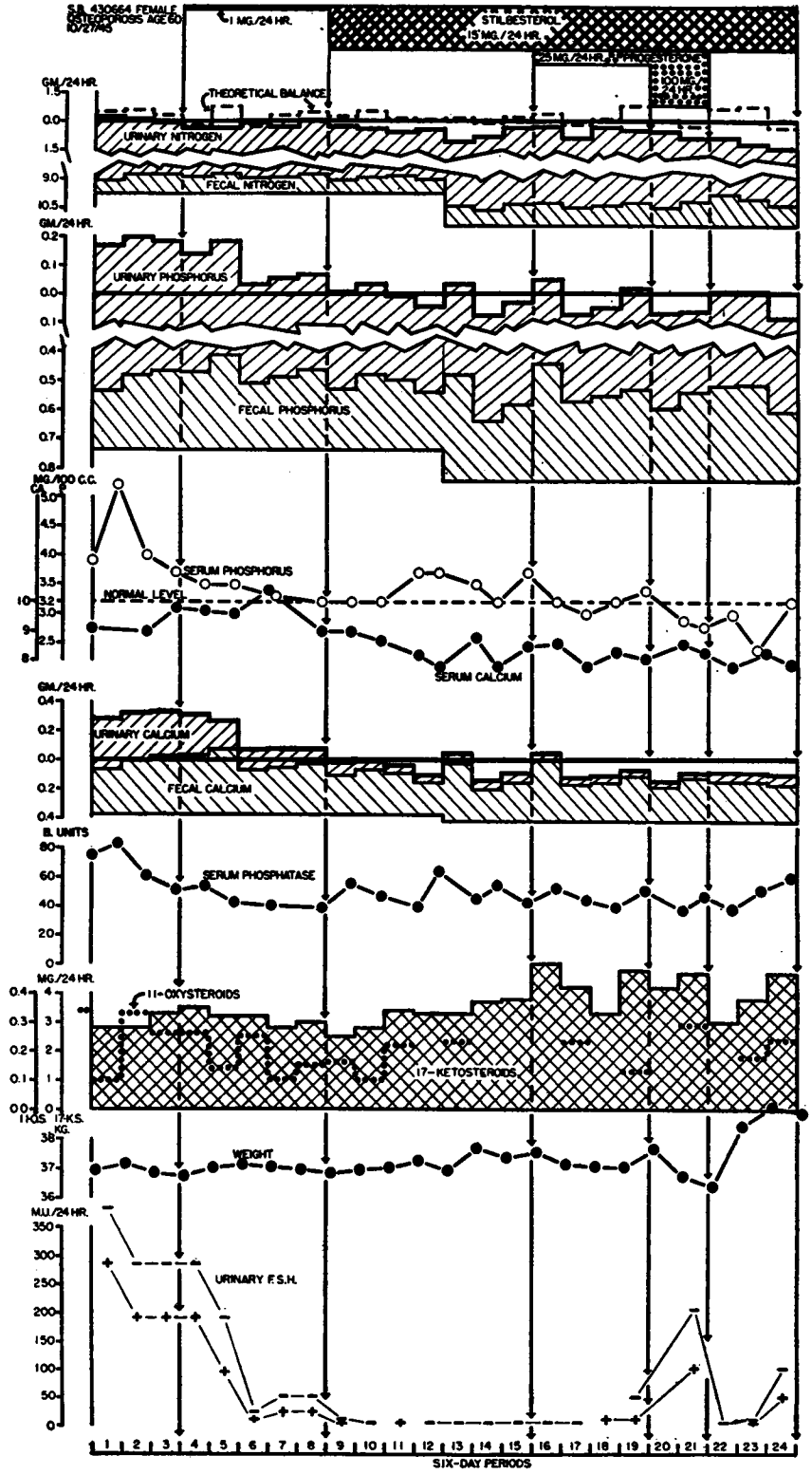

FIG. 5. CASE 5 (S. B., M.G.H. 430664) : EFFECT OF DIETHYLSTILBESTROL ALONE AND IN COMBINATION WITH PROGESTERONE ON NITROGEN, PHOSPHORUS, AND CALCIUM BALANCES, ON SERUM CALCIUM, PHOSPHORUS, AND ALKALINE PHOSPHATASE LEVELS, ON BODY WEIGHT, AND ON URINARY 17-KETOSTEROID, "11-OXYSTEROID," AND FOLLICLE-STIMULATING HORMONE EXCRETION IN A FEMALE PATIENT WITH POST-MENOPAUSAL OSTEOPOROSIS AND PAGET'S DISEASE

For discussion, see text.

TABLE V

Data for case 5 (S.B., M.G.H. 430664)

Period number	Date	Calcium				Phosphorus				Nitrogen					Body weight	Urinary 17-ketosteroids	Urinary 11-oxysteroids	Follicle stimulating hormone excretion in urine		Serum				Treatment	
		Urinary	Fecal	Intake	Balance	Urinary	Fecal	Intake	Balance	Urinary	Fecal	Intake	Balance	Theoretical balance	Measured	Urinary 17-ketosteroids	Urinary 11-oxysteroids	Positive	Negative	Day of period	Calcium	Phosphorus	Alkaline phosphatase	Diethylstilbestrol (p.o.)	Progesterone (i.m.)
		mgm. per 24 hr.				*mgm. per 24 hr.*				*grams per 24 hr.*					*kgm.*	*mgm. per 24 hr.*		*mouse units per 24 hr.*			*mgm. per 100 ml.*		*B.U.*		
	10/23/45																				8.8	3.7	61.5		
	10/24/45															3.4	0.34								
	10/27/45														36.9									None	
1	10/27 to 11/1/45	341	315	377	−279	696	212	737	−171	9.29	0.74	9.83	−0.20	−0.44	37.1	2.8	0.10	+288	−384	I	9.1	3.9	75.7		
2	11/ 2 to 7/45	324	373	377	−320	678	257	737	−198	8.91	1.03	9.83	−0.11	−0.56	36.9	2.8	0.33	+192	−288	I		5.2	82.8		
3	11/ 8 to 13/45	296	406	377	−325	646	275	737	−184	8.72	1.03	9.83	+0.08	−0.32	36.7	3.3	0.26	+192	−288	I	9.0	4.0	61.2		
4	11/14 to 19/45	277	413	377	−313	607	271	737	−141	8.53	0.94	9.83	+0.36	+0.22	37.0	3.5	0.26	+192	−288	I	9.8	3.7	51.5		
5	11/20 to 25/45	188	454	377	−265	592	329	737	−184	8.44	1.03	9.83	+0.36	−0.76	37.1	3.2	0.14	+ 96	−192	I	9.7	3.5	53.7		
6	11/26 to 12/1/45	140	306	377	− 69	539	230	737	− 32	8.94	0.80	9.83	+0.09	+0.03	37.1	3.2	0.25	+ 13	− 26	I	9.6	3.5	42.1		
7	12/ 2 to 7/45	127	324	377	− 74	542	251	737	− 56	8.70	0.86	9.83	+0.27	−0.28	37.0	2.8	0.10	+ 26	− 52	II	10.4	3.3	39.9	1 mgm. daily	
8	12/ 8 to 13/45	101	351	377	− 75	527	277	737	− 67	8.84	1.01	9.83	−0.02	−0.44	36.8	3.0	0.15	+ 26	− 52						None
9	12/14 to 19/45	88	275	377	+ 14	535	209	737	− 7	8.74	0.77	9.83	+0.31	−0.21	36.9	2.5	0.16	+ 6.5	− 13	I	9.0	3.2	39.4		
10	12/20 to 25/45	64	308	377	+ 5	510	261	737	− 34	8.53	0.88	9.83	+0.42	−0.53	37.0	2.8	0.10		− 6.5	I	9.0	3.2	55.6		
11	12/26 to 31/45	54	287	377	+ 36	486	243	737	+ 8	8.31	0.95	9.83	+0.57	−0.15	37.3	3.4	0.22	+ 6.5		I	8.7	3.2	46.8		
12	1/ 1 to 6/46	54	221	377	+102	496	196	737	+ 45	8.63	0.75	9.83	+0.45	−0.09	36.9	3.3			− 6.5	II	8.2	3.7	39.7		
13	1/ 7 to 12/46	68	393	417	− 44	513	361	842	− 32	9.34	1.02	11.46	+1.10	−0.15	37.7	3.3	0.23		− 6.5	I	7.8	3.7	63.7		
14	1/13 to 18/46	59	218	417	+140	562	202	842	+ 78	9.78	0.84	11.46	+0.84	+0.12	37.3	3.7			− 6.5	II	8.8	3.5	44.9		
15	1/19 to 24/46	62	269	417	+ 86	552	260	842	+ 30	9.50	1.14	11.46	+0.37	−0.19	37.5	3.8			− 6.5	I	7.8	3.2	54.0		
16	1/25 to 30/46	52	415	417	− 50	492	398	842	− 48	9.95	1.19	11.46	+0.32	−0.34	37.1	5.0			− 6.5	I	8.5	3.7	41.9		25 mgm. daily
17	1/31 to 2/5/46	41	254	417	+122	495	273	842	+ 74	9.59	0.97	11.46	+0.90	+0.19	37.1	4.2	0.23		− 6.5	I	8.6	3.2	52.4		25 mgm. daily
18	2/ 6 to 11/46	42	264	417	+111	506	288	842	+ 48	10.07	1.06	11.46	+0.33	−0.10	37.1	3.3		+ 13		I	7.8	3.0	44.0		25 mgm. daily
19	2/12 to 17/46	48	300	417	+ 69	546	314	842	− 18	9.86	1.11	11.46	+0.48	−0.76	37.7	4.8	0.13	+ 13	− 52	I	8.3	3.2	38.8		25 mgm. daily
20	2/18 to 23/46	41	229	417	+147	526	246	842	+ 70	9.97	0.97	11.46	+0.53	−0.04	36.7	4.2				I	8.1	3.4	50.2		100 mgm. daily
21	2/24 to 3/1/46	38	289	417	+ 90	479	299	842	+ 64	9.28	1.25	11.46	+0.93	+0.28	36.4	4.7	0.29	+104	−208	II	8.6	2.9	37.7	15 mgm. daily	100 mgm. daily
22	3/ 2 to 7/46	62	269	417	+ 86	526	323	842	− 7	8.93	1.63	11.46	+0.89	−0.73	38.5	3.0			− 6.5	I	8.3	2.8	47.0		
23	3/ 8 to 13/46	57	272	417	+ 88	524	325	842	− 7	9.01	1.23	11.46	+1.22	−0.75	39.1	3.8	0.18	+ 6.5	− 13	I	7.8	3.0	38.0		None
24	3/14 to 19/46	67	248	417	+102	523	233	842	+ 86	8.99	1.04	11.46	+1.43	+0.51	38.9	4.7	0.24	+ 52	−104	I	8.3	2.4	51.2		
	3/20/46																				7.9	3.2	60.0		

Dietary intake of periods 1 to 12 in amounts per 24 hours: protein (analyzed nitrogen × 6.25) = 61.4 grams, fat (estimated from tables) = 67.1 grams, carbohydrate (estimated from tables) = 125.1 grams, calories (calculated from the values 4 for 1 gram of protein, 9 for 1 gram of fat, and 4 for 1 gram of carbohydrate) = 1,350; periods 13 to 24: protein = 71.2 grams, fat = 69.4 grams, carbohydrate = 173.4 grams, calories = 1,603.

TABLE VI

Data for case 6 (M.H., M.G.H. 278511)

Period number	Date	Calcium				Phosphorus				Nitrogen				Body weight		Urinary 17-ketosteroids	Serum				Treatment	
		Urinary	Fecal	Intake	Balance	Urinary	Fecal	Intake	Balance	Urinary	Intake	Balance	Theoretical balance	Measured	Theoretical		Day of period	Calcium	Phosphorus	Alkaline phosphatase	Estradiol benzoate (i.m.)	Testosterone propionate (i.m.)
		mgm. per 24 hr.				*mgm. per 24 hr.*				*grams per 24 hr.*				*kgm.*		*mgm. per 24 hr.*		*mgm. per 100 ml.*		*B.U.*		
	12/14/40																	10.3	4.4	4.2		
	12/18/40																	10.7	2.5	4.2		
	12/27/40																	10.2	2.9	5.0		
	12/31/40													70.34		7.2						
1	1/ 1 to 5/41	165	338	701	+198	310	219	611	+ 82	6.92	8.4	+0.64	−0.25	70.24	70.02						None	None
2	1/ 6 to 10/41	189	417	701	+ 95	326	190	611	+ 95	6.96	8.4	+0.60	0	70.37	69.84							
3	1/11 to 15/41	150	397	701	+154	310	197	611	+104	6.44	8.4	+1.12	+0.41	70.39	69.62							
4	1/16 to 20/41	164	421	701	+116	244	242	611	+125	6.37	8.4	+1.19	+1.01	70.22	69.49	IV* 7.0						
5	1/21 to 25/41	141	397	701	+163	276	196	611	+139	5.81	8.4	+1.75	+0.87	69.85	69.34							
6	1/26 to 30/41	152	288	701	+261	207	153	611	+251	5.51	8.4	+2.05	+1.80	70.44	69.32							25 mgm. daily
7	1/31 to 2/4/41	137	317	701	+247	132	162	611	+317	4.43	8.4	+3.13	+2.91	70.99	69.47							
8	2/ 5 to 9/41	117	173	701	+411	126	94	611	+391	4.05	8.4	+3.51	+2.79	70.98	69.59							
9	2/10 to 14/41	99	374	701	+228	115	192	611	+304	3.49	8.4	+4.07	+2.85	71.35	69.73							
10	2/15 to 19/41	129	280	701	+292	130	153	611	+328	4.36	8.4	+3.20	+2.73	71.08	69.84							
11	2/20 to 24/41	93	188	701	+420	124	105	611	+382	3.89	8.4	+3.67	+2.58	71.53	69.94	V 11.8	V	9.8	2.0	2.4	1.66mgm. every other day	
12	2/25 to 3/1/41	107	190	701	+404	129	105	611	+377	4.60	8.4	+2.96	+2.63	71.74	70.04							
13	3/ 2 to 6/41	81	161	701	+459	161	84	611	+366	4.20	8.4	+3.36	+2.05	71.72	70.06							
14	3/ 7 to 11/41	96	192	701	+413	134	105	611	+372	4.26	8.4	+3.30	+2.47	71.87	70.14							
15	3/12 to 16/41	84	199	701	+418	170	121	611	+320	4.78	8.4	+2.78	+1.67	71.88	70.10							
16	3/17 to 21/41	105	160	701	+436	159	99	611	+353	4.45	8.4	+3.11	+2.03	71.39	70.12						None	
17	3/22 to 26/41	79	204	701	+418	184	120	611	+307	4.67	8.4	+2.89	+1.47	71.55	70.05							
18	3/27 to 31/41	97	230	701	+374	160	125	611	+326	4.94	8.4	+2.62	+2.09	71.27	70.08							
19	4/ 1 to 5/41	77	269	701	+355	163	161	611	+287	4.63	8.4	+2.93	+1.65	71.44	70.04		IV	10.5	1.8	2.5		
20	4/ 6 to 10/41	118	233	701	+350	186	152	611	+273	5.61	8.4	+1.95	+1.47	71.46	69.97	V 11.2	V	9.5	2.1	2.5		
21	4/11 to 15/41	81	207	701	+413	215	130	611	+266	5.08	8.4	+2.48	+0.90	70.21	69.82							None
22	4/16 to 20/41	95	260	701	+346	385	183	611	+ 43	7.84	8.4	−0.28	−1.95	69.43	69.26							
23	4/21 to 25/41	108	302	701	+291	448	163	611	0	9.13	8.4	−1.57	−2.17	68.51	68.66	II 4.8	II	10.2	3.1	3.1		
24	4/26 to 30/41	126	237	701	+338	367	135	611	+109	9.01	8.4	−1.45	−0.90	68.22	68.25							
25	5/ 1 to 5/41	147	352	701	+202	318	186	611	+107	8.23	8.4	−0.67	+0.09	67.97	67.98							
26	5/ 6 to 10/41	175	284	701	+242	330	180	611	+101	8.13	8.4	−0.57	−0.30	67.35	67.66	IV 7.2	IV	10.2	3.2	4.4		
27	5/11 to 15/41	191	245	701	+265	335	156	611	+120	7.93	8.4	−0.37	−0.18	67.37	67.37							
28	5/16 to 20/41	194	292	701	+215	303	161	611	+147	8.36	8.4	−0.80	+0.60	67.52			IV	10.4	2.8	3.1	3.32 mgm. daily	None
29	5/21 to 25/41	171	209	701	+321	223	136	611	+252	7.29	8.4	+0.27	+1.38	67.62								
30	5/26 to 30/41	161	153	701	+387	257	88	611	+266	7.47	8.4	+0.09	+1.09	67.56								
31	5/31 to 6/4/41	132	282	701	+287	277	166	611	+168	7.42	8.4	+0.14	+0.37	67.27		III 3.8	III	10.2	2.8	3.8		
32	6/ 5 to 8/41	167	347	701	+187	309	216	611	+ 86	8.28	8.4	−0.72	−0.11	66.96								
	No collections for 10 days 6/16/41													69.14		2.4		9.6	2.2	2.5		
33	6/19 to 23/41	128	357	701	+216	369	201	611	+ 41	8.76	8.4	−1.20	−1.01	67.20								
34	6/24 to 27/41	139	199	701	+363	364	110	611	+137	8.09	8.4	−0.53	−0.66	66.75								

* Day of period.

TABLE VI—*Continued*

Period number	Date	Calcium				Phosphorus				Nitrogen				Body weight		Urinary 17-ketosteroids	Serum				Treatment	
		Urinary	Fecal	Intake	Balance	Urinary	Fecal	Intake	Balance	Urinary	Intake	Balance	Theoretical balance	Measured	Theoretical		Day of period	Calcium	Phosphorus	Alkaline phosphatase	Estradiol benzoate (i.m.)	Testosterone propionate (i.m.)
		mgm. per 24 hr.				*mgm. per 24 hr.*				*grams per 24 hr.*				*kgm.*		*mgm. per 24 hr.*		*mgm. per 100 ml.*		*B.U.*		
	No collections for 93 days 9/26/41													69.12		2.8		10.1	2.7	3.0		
35	9/28 to 10/2/41	171	212	701	+318	347	129	611	+135	8.11	8.4	−0.55	−0.36	69.13								
36	10/ 3 to 7/41	169	394	701	+138	360	226	611	+ 25	7.70	8.4	−0.14	−0.66	69.20								None
37	10/ 8 to 12/41	176	329	701	+196	339	184	611	+ 88	7.75	8.4	−0.19	−0.15	68.97								
38	10/13 to 17/41	233	444	701	+ 24	323	249	611	+ 39	7.35	8.4	+0.21	−0.41	68.61								
39	10/18 to 22/41	187	386	701	+128	301	211	611	+ 99	7.59	8.4	−0.03	+0.53	68.87								
40	10/23 to 27/41	142	445	701	+114	234	244	611	+133	6.82	8.4	+0.74	+1.14	69.45								
41	10/28 to 11/1/41	192	420	701	+ 89	180	200	611	+231	5.94	8.4	+1.62	+2.81	70.22								
42	11/ 2 to 6/41	200	312	701	+189	145	153	611	+313	4.95	8.4	+2.61	+3.27	70.49			II	9.9	2.2	2.2		
43	11/ 7 to 11/41	182	331	701	+188	188	174	611	+249	5.14	8.4	+2.42	+2.33	70.23								
44	11/12 to 16/41	216	194	701	+291	197	124	611	+290	5.57	8.4	+1.99	+2.17	70.18								
45	11/17 to 21/41	185	317	701	+199	226	175	611	+210	5.51	8.4	+2.05	+1.67	70.26								
46	11/22 to 26/41	208	268	701	+225	326	157	864	+381	10.06	17.37	+5.57	+4.01	70.60								
47	11/27 to 12/1/41	240	219	701	+242	345	159	864	+360	10.74	17.37	+4.89	+3.59	71.13			V	9.3	1.9	2.7		
48	12/ 2 to 6/41	235	331	701	+135	414	202	864	+248	11.37	17.37	+4.26	+2.71	71.45								25 mgm. daily
49	12/ 7 to 11/41	230	331	701	+140	509	221	864	+134	13.96	17.37	+1.67	+0.96	70.14			III	9.5	2.0	3.0		
50	12/12 to 16/41	166	410	701	+125	558	286	864	+ 20	14.39	17.37	+1.24	−0.65	70.35								
51	12/17 to 21/41	179	491	701	+ 31	655	290	864	− 81	16.08	17.37	−0.45	−1.44	69.92								
	12/22/41 No collections for 91 days 3/21/42													69.86				9.3	2.8	2.6		
52	3/23 to 27/42	166	484	701	+ 51	335	295	611	− 19	8.13	8.4	−0.57	−0.66	69.66		III 5.2	I	10.3	2.3	2.6		
53	3/28 to 4/1/42	148	395	701	+158	332	263	611	+ 16	8.46	8.4	−0.90	−0.95	69.54								
54	4/ 2 to 6/42	83	141	701	+477	389	170	611	+ 52	8.47	8.4	−0.91	−2.80	69.16								
	No collections for 43 days 5/18/42													69.40		7.2		10.6	2.6	3.5		
55	5/20 to 24/42	182	476	701	+ 43	379	221	611	+ 11	7.68	8.4	−0.12	−0.15	68.98		I 7.4	I	10.2	3.1	2.7		
56	5/25 to 29/42	207	341	701	+153	411	194	611	+ 6	7.47	8.4	+0.09	−1.07	69.18			I	10.0	2.8	2.6		
57	5/30 to 6/3/42	240	301	701	+160	359	151	611	+101	7.09	8.4	+0.47	+0.31	68.86			I	10.0	3.0	3.5		
58	6/ 4 to 8/42	253	404	701	+ 44	339	227	611	+ 45	7.16	8.4	+0.40	+0.35	68.44			I	10.3	3.3	3.7		
	6/ 9/42 6/15/42																	10.3 10.0	2.9 2.8	2.7 3.3		

Dietary intake of periods 1 to 45 and 52 to 58 in amounts per 24 hours: protein (analyzed nitrogen × 6.25) = 52.5 grams, fat (estimated from tables) = 63.5 grams, carbohydrate (estimated from tables) = 207.5 grams, calories (calculated from the values 4 for 1 gram of protein, 9 for 1 gram of fat, and 4 for 1 gram of carbohydrate) = 1,611; periods 46 to 51: protein = 108.6 grams, fat = 73.8 grams, carbohydrate = 221.0 gm., calories = 1,983. In addition throughout sugar was given *ad lib*, with an average intake of 30 grams (120 calories).

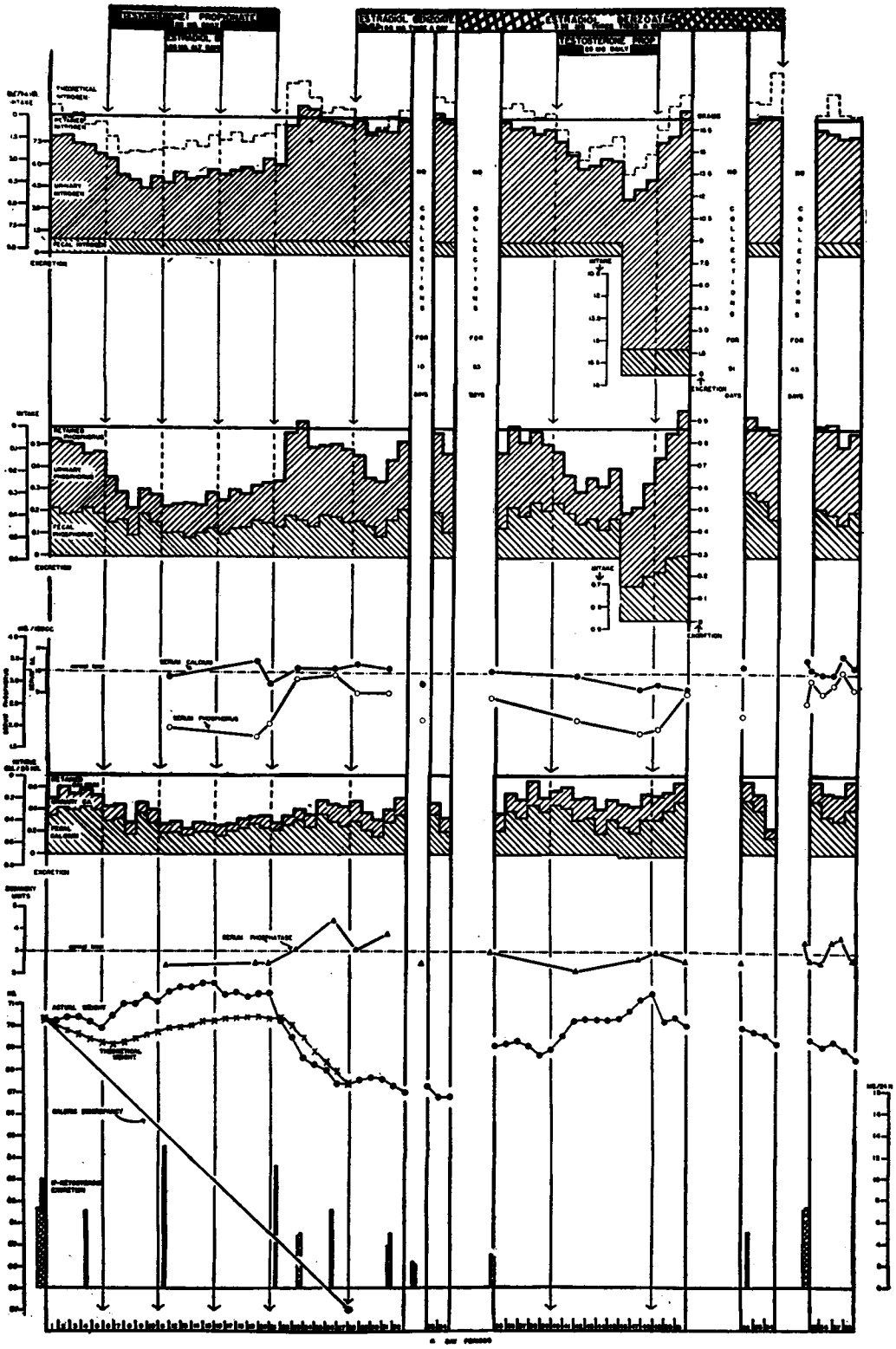

FIG. 6. CASE 6 (M. H., M.G.H. 278511): EFFECT OF TESTOSTERONE PROPIONATE ALONE AND IN COMBINATION WITH ESTRADIOL BENZOATE AND VICE VERSA ON NITROGEN, PHOSPHORUS, AND CALCIUM BALANCES, ON SERUM CALCIUM, PHOSPHORUS, AND ALKALINE PHOSPHATASE LEVELS, ON BODY WEIGHT, AND ON URINARY 17-KETOSTEROID EXCRETION IN A MALE PATIENT WITH SENILE OSTEOPOROSIS

For discussion, see text.

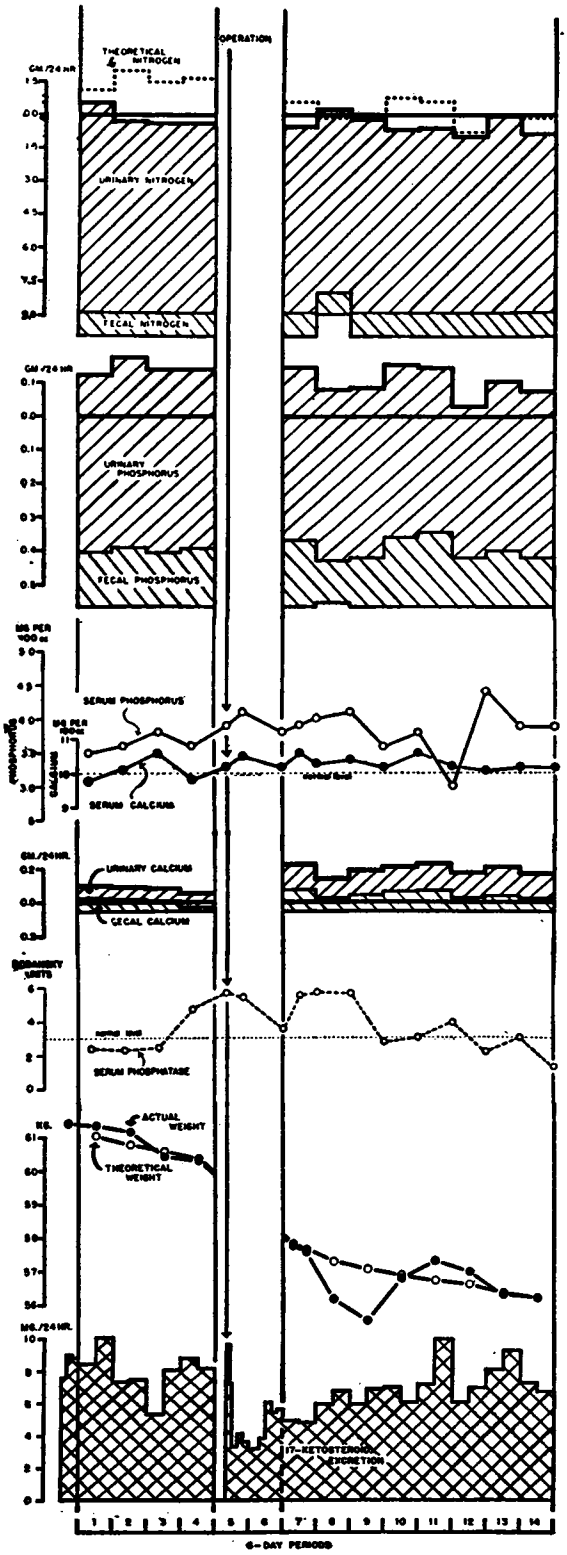

FIG. 7. CASE 7 (E. S., M.G.H. 360207): NITROGEN, PHOSPHORUS, AND CALCIUM BALANCES; SERUM CALCIUM, PHOSPHORUS, AND ALKALINE PHOSPHATASE LEVELS; WEIGHT; AND URINARY 17-KETOSTEROID EXCRETION IN A FEMALE PATIENT WITH OSTEOPOROTIC PROCESS INDUCED BY OPERATION AND IMMOBILIZATION

For discussion, see text.

a week; (*10*) five periods on the same therapy; (*11*) nine periods in which testosterone propionate 25 mgm. intramuscularly daily was added to the estradiol benzoate therapy, during the last 3 of which periods the intakes of nitrogen and phosphorus were markedly increased; (*12*) three periods on the same diet and the same estradiol benzoate therapy but off testosterone propionate therapy; (*13*) ninety-one days at home on the same estradiol benzoate therapy; (*14*) three periods on the original diet without change in the estradiol therapy; (*15*) forty-three days at home off all medication; and finally (*16*) four control periods on the original diet without medication.

Figure 6 is self-explanatory. The observations as a whole confirm those noted in Cases 1 to 4 with postmenopausal osteoporosis.

Again, as in Case 4, the theoretical nitrogen balance as charted is consistently less positive than the actual nitrogen balance which suggests some constant error. This discrepancy is probably to be attributed to errors in the intakes and to estimation of the fecal nitrogen as 10 per cent of the nitrogen intake (see discussion under Case 4). Case 6 received the same diet as Case 4; this diet was analyzed twice with the results given in the discussion under Case 4. Figure 6 was constructed from the analysis of 1941; had it been constructed from the analysis of 1944, as is Table V, the discrepancy would have been almost eliminated. Thus, if one recalculates on the basis of the 1944 analysis, the theoretical nitrogen balance of period 5, and in addition uses the value of 1.283 grams for the fecal nitrogen instead of 10 per cent of the intake, one obtains the values + 0.87 and + 1.30 grams for the theoretical and actual nitrogen balances, respectively, in contrast to the values of + 0.41 and + 2.21 grams. As was pointed out in connection with Case 4, since the above discrepancy is fairly constant, it does not affect the trends induced by treatment.

To be noted especially in Figure 6 are: (*1*) the marked reduction in nitrogen, phosphorus, and calcium excretions with testosterone therapy; (*2*) the lack of rebound in the calcium excretion as opposed to nitrogen and phosphorus following cessation of testosterone therapy; (*3*) the further reduction in the phosphorus and especially in the calcium excretion, but not in the nitrogen excretion, when estradiol benzoate therapy was added to testosterone propionate therapy (periods 16 to 20); (*4*) the improvement in all 3 balances when testosterone propionate was added to estradiol benzoate therapy (periods 40 to 45); (*5*) reduction in the fecal as well as the urinary calcium and phosphorus excretions by both testosterone propionate and estradiol benzoate therapy; (*6*) the effect of both testosterone propionate and estradiol benzoate therapy in lowering the serum phosphorus level; (*7*) the failure of marked increases in the nitrogen and phosphorus bal-

TABLE VII

Data for case 7 (E.S., M.G.H. 360207)

Period number	Date	Calcium				Phosphorus				Nitrogen				Body weight		Urinary 17-ketosteroids	Serum				Treatment
		Urinary	Fecal	Intake	Balance	Urinary	Fecal	Intake	Balance	Urinary	Intake	Balance	Theoretical balance	Measured	Theoretical	Urinary 17-ketosteroids	Day of period	Calcium	Phosphorus	Alkaline phosphatase	
		mgm. per 24 hr.				*mgm. per 24 hr.*				*grams per 24 hr.*				*kgm.*		*mgm. per 24 hr.*		*mgm. per 100 ml.*		*B.U.*	
	6/21 to 22/42															7.6					
	6/22 to 23/42															9.0					
	6/23 to 24/42													61.40		8.8					
1	6/24 to 26/42	71	86	58	− 99	528	161	566	−123	9.43	9.90	−0.52	−1.11	61.32	61.02	8.4	III	9.8	3.5	2.4	
	6/27 to 29/42															10.0					
2	6/30 to 7/2/42	71	80	58	− 93	566	175	566	−175	8.63	9.90	+0.28	−2.02	61.14	60.78	7.3	III	10.1	3.6	2.3	None
	7/ 3 to 5/42															7.4					
3	7/ 6 to 8/42	71	63	58	− 82	547	159	566	−140	8.51	9.90	+0.40	−1.49	60.40	60.56	5.3	III	10.6	3.8	2.4	
	7/ 9 to 11/42															8.0					
4	7/12 to 14/42	80	35	58	− 57	535	171	566	−140	8.51	9.90	+0.40	−1.67	60.28	60.34	8.7	III	9.8	3.6	4.7	
	7/15 to 17/42															8.1					
	7/20/42 1st 12 hours after operation	Operation														9.6		10.2	3.9	5.8	
	7/20/42 2nd 12 hours after operation															7.2					
	7/22 to 23/42															3.3					
	7/23 to 24/42															4.1					
	7/24 to 25/42															3.6		10.5	4.1	5.3	
	7/25 to 26/42	No collections for 12 days														3.1					None
	7/26 to 27/42															3.2					
	7/27 to 28/42															3.8					
	7/28 to 29/42															6.0					
	7/29 to 30/42															5.4					
	7/30 to 31/42													57.73	57.79	5.6					
5	7/31 to 8/2/42	145	134	58	−221	517	197	566	−148	8.37	9.90	+0.54	−0.57	57.55	57.60	4.9	I	10.2	3.8	3.5	
	8/ 3 to 5/42															4.8	I	10.6	3.9	5.5	
6	8/ 6 to 8/42	144	83	56	−167	515	121	555	− 81	8.23	8.91	−0.21	+0.05	56.14	57.28	5.9	I	10.3	4.0	5.7	
	8/ 9 to 11/42															6.7					
7	8/12 to 14/42	142	101	58	−185	507	145	566	− 86	8.72	9.90	+0.19	+0.09	55.50	57.03	5.9	I	10.4	4.1	5.7	
	8/15 to 17/42															6.8					
8	8/18 to 20/42	140	123	58	−205	517	203	566	−154	8.19	9.90	+0.72	−0.78	56.78	56.87	6.9	I	10.2	3.6	2.9	
	8/21 to 23/42															6.0					
9	8/24 to 26/42	144	128	58	−214	493	218	566	−145	8.26	9.90	+0.65	−0.57	57.27	56.70	7.3	I	10.6	3.8	3.0	
	8/27 to 29/42															9.9					None
10	8/30 to 9/1/42	149	85	58	−176	452	144	566	− 30	7.93	9.90	+0.98	+0.79	56.93	56.59	6.0	I	10.2	3.0	3.9	
	9/ 2 to 4/42															6.9					
11	9/ 5 to 7/42	169	95	58	−206	505	164	566	−103	8.82	9.90	+0.09	0	56.30	56.32	8.0	I	10.1	4.4	2.2	
	9/ 8 to 10/42															9.2					
12	9/11 to 13/42	148	81	58	−171	497	145	566	− 76	8.03	9.90	+0.88	+0.13	56.20	56.20	7.2	I	10.2	3.9	3.0	
	9/14 to 15/42															6.7	I	10.2	3.9	1.3	

Dietary intake of periods 1 to 14 in amounts per 24 hours: protein (analyzed nitrogen × 6.25) = 61.9 grams, fat (estimated from tables) = 80.9 grams, carbohydrate (estimated from tables) = 179.4 grams, calories (calculated from the values 4 for 1 gram of protein, 9 for 1 gram of fat, and 4 for 1 gram of carbohydrate) = 1,693.

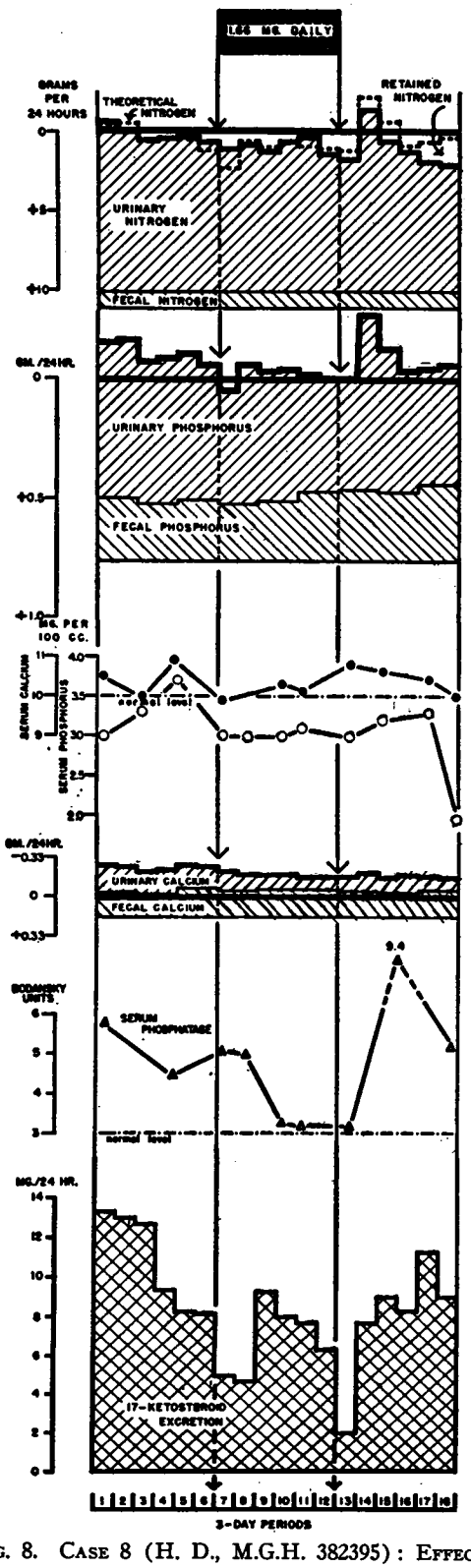

FIG. 8. CASE 8 (H. D., M.G.H. 382395): EFFECT OF ESTRADIOL BENZOATE ON NITROGEN, PHOSPHORUS, AND CALCIUM BALANCES; ON SERUM CALCIUM, PHOSPHORUS, AND ALKALINE PHOSPHATASE LEVELS; AND ON URINARY 17-KETOSTEROID EXCRETION IN A MALE PATIENT WITH OSTEOPOROTIC PROCESS INDUCED BY MULTIPLE FRACTURES, OPERATION, AND IMMOBILIZATION

For discussion, see text.

ances by increased diet to affect the calcium balance (periods 46, 47, 48); (*8*) the absence of any significant change in the serum phosphatase and calcium levels; (*9*) the fall in the urinary 17-ketosteroid level with estradiol benzoate therapy; and (*10*) the tendency to accumulate extracellular fluid during both testosterone propionate and estradiol benzoate therapy as suggested by the theoretical weight curves, with a prompt loss following the cessation of therapy.

C. Osteoporosis resulting from disuse and/or adaptation syndrome

Case 7. "Normal" Female; Effect of Orthopedic Operation; No Specific Therapy.

The metabolic data of Case 7 are shown in Figure 7 and Table VII. Throughout the entire experiment the patient was on a constant, neutral-ash, low calcium diet, except for the immediate post-operative period. She was up and active during the pre-operative period, and immobilized in a cast from the foot to the hip after operation. She underwent an arthrodesis of the right foot on the second day of period 5; there were no analyses for metabolic data during periods 5 and 6, but the 17-ketosteroid excretion was followed.

During the 4 control periods the patient was in negative calcium and phosphorus balance; the former was of the order of magnitude one would expect with patients on this diet (13). As expected, there was a marked increase in the calcium excretion after the operation, which persisted unabated to the end of the investigation (58 days after the operation) (14). The increase in calcium excretion was not entirely in the urine. The 17-ketosteroid excretion was normal pre-operatively, which confirms the contention that she was not debilitated; it rose immediately after operation, and then fell decidedly below the preoperative level for about 20 days. The pattern of response was thus similar to that encountered following any traumatizing event (15). The marked elevation in 17-ketosteroid excretion in period 11 coincided with the patient being allowed up in a wheel chair (16).

Periods 7 through 14 in this untreated case serve as a control for similar studies in Cases 8 and 9, who received estradiol therapy during the post-operative period (Figure 10).

Case 8. Multiple Traumatic Fractures with Operative Reduction of One in a Previously "Normal" Male; Effect of Estradiol Benzoate Therapy.

The metabolic data of Case 8 are shown in Figure 8 and Table VIII. The study, conducted in 3-day periods, consisted of; (*1*) six control periods; (*2*) six periods in which 1.66 mgm. of estradiol benzoate was given

TABLE VIII

Data for case 8 (H.D., M.G.H. 382395)
Fracture 11/15/42

Period number	Date	Calcium				Phosphorus				Nitrogen				Body weight	Urinary citrate	Urinary 17-ketosteroids	Serum				Treatment
		Urinary	Fecal	Intake	Balance	Urinary	Fecal	Intake	Balance	Urinary	Intake	Balance	Theoretical balance	Measured**			Day of perfod	Calcium	Phosphorus	Alkaline phosphatase	Estradiol benzoate (i.m.)
		mgm. per 24 hr.				*mgm. per 24 hr.*				*grams per 24 hr.*				*kgm.*	*mgm. per 24 hr.*			*mgm. per 100 ml.*		*B.U.*	
1	12/29 to 31/42	221	203	175	−249	647	266	760	−153	10.66	11.15	−0.62	−0.43		1151	13.3	I	10.5	3.0	3.4	None
2	1/ 1 to 3/43	225	203	175	−253	655	266	760	−161	9.97	11.15	+0.06	−0.53		1790	13.0					
2	1/ 4 to 6/43	200	196	175	−220	589	245	760	− 74	9.42	11.15	+0.61	+0.54		950	12.7	I	10.0	3.3	5.8	
4	1/ 7 to 9/43	208	196	175	−229	604	245	760	− 89	9.55	11.15	+0.48	+0.73		1162	9.4	III	10.9	3.7		
5	1/10 to 12/43	195	246	175	−266	605	260	760	−105	9.67	11.15	+0.37	+0.42		1190	8.3					
6	1/13 to 15/43 *	192	246	175	−263	550	260	760	− 50	9.41	11.15	+0.63	+1.21		1725	8.2					
7	1/17 to 19/43	163	229	175	−217	474	244	760	+ 42	8.86	11.15	+1.17	+2.27		2004	5.0	I	9.9	3.0	4.5	1.66 mgm. daily
8	1/20 to 22/43	144	229	175	−197	577	244	760	− 61	9.17	11.15	+0.87	+0.57	60.02	1813	4.7	III		3.0	5.1	
9	1/23 to 25/43	137	221	175	−183	546	253	760	− 39	8.73	11.15	+1.31	+0.93		2280	9.3	III	10.3	3.0	5.1	
10	1/26 to 28/43	134	221	175	−180	547	253	760	− 40	9.36	11.15	+0.67	+0.75		2670	8.0					
11	1/29 to 31/43	114	223	175	−162	483	297	760	− 20	9.64	11.15	+0.39	+0.91		2500	7.7	I	10.1	3.1	3.3	
12	2/ 1 to 3/43	108	223	175	−156	471	297	760	− 8	8.59	11.15	+1.44	+1.05		2660	6.3					
13	2/ 4 to 6/43	121	225	175	−171	466	300	760	− 6	8.39	11.15	+1.65	+1.19		2388	2.0	I	10.8	3.0	3.2	None
14	2/ 7 to 9/43	182	225	175	−232	723	300	760	−263	11.36	11.15	−1.32	−2.21		1565	7.7					
15	2/10 to 12/43	129	212	175	−167	593	292	760	−135	9.49	11.15	+0.55	−0.63		1680	9.0	I	10.6	3.2	3.2	
16	2/13 to 15/43	142	212	175	−179	503	292	760	− 35	8.65	11.15	+1.39	+0.83	60.83	1880	8.3					
17	2/16 to 18/43	115	223	175	−163	477	324	760	− 41	8.55	11.15	+1.49	+0.60		1832	11.3	I	10.4	3.3	9.4	
18	2/19 to 21/43	112	223	175	−160	496	324	760	− 60	8.05	11.15	+1.98	+0.30	60.48	1880	9.0	III	10.0	1.9	5.2	

Dietary intake of periods 1 to 18 in amounts per 24 hours: protein (analyzed nitrogen × 6.25) = 69.7 grams, fat (estimated from tables) = 50.1 grams, carbohydrate (estimated from tables) = 228.6 grams, calories (calculated from the values 4 for 1 gram of protein, 9 for 1 gram of fat ,and 4 for 1 gram of carbohydrate) = 1,644.

* Collections on 1/16/43 omitted.

** Initial weight 11/15/42 between 70 and 75 kgm.

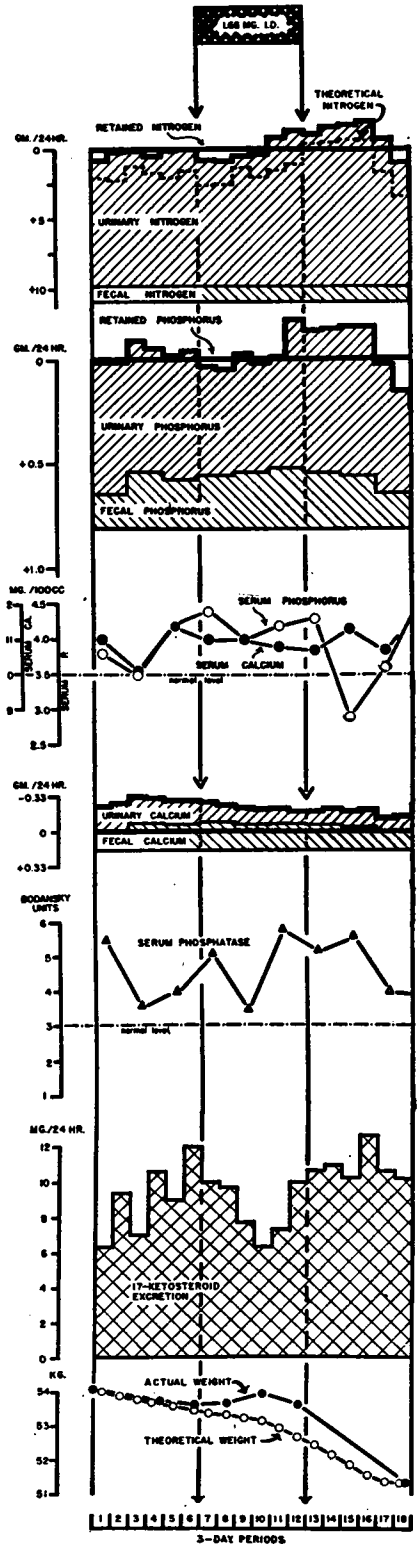

FIG. 9. CASE 9 (C. M., M.G.H. 348774): EFFECT OF ESTRADIOL BENZOATE ON NITROGEN, PHOSPHORUS, AND CALCIUM BALANCES; ON SERUM CALCIUM, PHOSPHORUS, AND ALKALINE PHOSPHATASE LEVELS; ON URINARY 17-KETOSTEROID EXCRETION AND ON WEIGHT IN A MALE PATIENT WITH OSTEOPOROTIC PROCESS INDUCED BY OPERATION AND IMMOBILIZATION

For discussion, see text.

daily by injection; and (*3*) six post-treatment control periods. The stool periods were analyzed 2 at a time.

Figure 8 is self-explanatory. The most important observations concern the calcium metabolism; these are better shown in Figure 10 and will be discussed below. Again, there was a fall in the serum phosphorus, and, if anything, a fall in the serum phosphatase. Of interest is the fall in 17-ketosteroids in period 13, followed by the rise in urinary nitrogen, phosphorus, and calcium in period 14; we believe these to be connected though unexplained phenomena.

Case 9. Bone Grafting Operation in an Ununited Femur of an Otherwise "Normal" Male; Effect of Estradiol Benzoate Therapy.

The metabolic data of Case 9 are shown in Figure 9 and Table IX. The study, conducted in 3-day periods, consisted of: (*1*) six control periods; (*2*) six periods in which 1.66 mgm. of estradiol benzoate was given daily by injection; and (*3*) six post-treatment control periods. The stool periods were analyzed 2 at a time.

Figure 9 is self-explanatory. The theoretical nitrogen balance shows a constant deviation from the measured nitrogen balance which suggests some constant error (*vide supra*). The calcium data, as in Case 8, are better shown in Figure 10, and will be discussed below. It should be noted that the serum phosphorus in this case, as opposed to all of the other cases, did not fall during estradiol therapy. The 17-ketosteroid excretion showed a tendency to fall during the estradiol benzoate therapy, which is also somewhat suggested in Figure 7.

Further analysis of calcium data of Cases 7, 8, and 9

In Figure 10 the calcium data of Cases 8 and 9 with estradiol benzoate therapy are compared with those of Case 7 without such therapy. It is quite clear that estradiol benzoate therapy resulted in a decrease in the urinary calcium excretion, but had little effect on the fecal calcium excretion during the 18 days of administration. However, the tendency for the fecal calcium to decrease in Case 9 after the therapy was stopped may well have been a delayed response to the therapy. The urinary citric acid values carried out and interpreted by Dr. Ephraim Shorr confirm his finding (17) of a rise during estrogen therapy.

D. Osteoporosis of Cushing's syndrome

Case 10. Cushing's Syndrome; Nephrolithiasis; Estradiol Benzoate and Testosterone Propionate Therapy.

The metabolic data of Case 10 are shown in graphic form in Figure 11. For data in tabular form for periods

TABLE IX

Data for case 9 (C.M., M.G.H. 348774)
Operated 11/28/42

Period number	Date	Calcium				Phosphorus				Nitrogen				Body weight		Urinary citrate	Urinary 17-ketosteroids	Serum				Treatment
		Urinary	Fecal	Intake	Balance	Urinary	Fecal	Intake	Balance	Urinary	Intake	Balance	Theoretical balance	Measured*	Theoretical			Day of period	Calcium	Phosphorus	Alkaline phosphatase	Estradiol benzoate (i.m.)
		mgm. per 24 hr.				*mgm. per 24 hr.*				*grams per 24 hr.*				*kgm.*		*mgm. per 24 hr.*			*mgm. per 100 ml.*		*B.U.*	
1	1/ 5 to 7/43	235	192	173	−254	630	166	805	+ 9	8.90	10.87	+0.88	+2.04		54.00	1045	6.3	II	11.0	3.8	5.5	
2	1/ 8 to 10/43	267	192	173	−286	630	166	805	+ 9	9.58	10.87	+0.20	+2.28		53.88	1192	9.4					
3	1/11 to 13/43	247	275	173	−349	623	269	805	− 87	9.67	10.87	+0.11	+1.31		53.75	1120	7.0	II	10.1	3.5	3.6	None
4	1/14 to 16/43	239	275	173	−341	588	269	805	− 52	9.27	10.87	+0.51	+1.77	53.69	53.66	1221	10.6					
5	1/17 to 19/43	229	261	173	−317	588	236	805	− 19	9.63	10.87	+0.15	+2.10		53.54	1120	9.0	II	11.4	4.2	4.0	
6	1/20 to 22/43	227	261	173	−315	613	236	805	− 44	9.74	10.87	+0.04	+1.68	53.59	53.41	1150	12.0					
7	1/23 to 25/43	198	278	173	−303	525	258	805	+ 22	8.95	10.87	+0.83	+2.59		53.35	1141	10.0	II	11.0	4.4	5.1	
8	1/26 to 28/43	171	278	173	−276	515	258	805	+ 32	8.83	10.87	+0.95	+2.55	53.63	53.30	1550	9.7					
9	1/29 to 31/43	158	254	173	−239	562	269	805	− 26	9.29	10.87	+0.49	+1.41		53.21	1800	7.7	II	11.0	4.0	3.5	1.66 mgm. daily
10	2/ 1 to 3/43	152	254	173	−233	519	269	805	+ 17	9.43	10.87	+0.35	+2.01	53.92	53.11	1765	6.3					
11	2/ 4 to 7/43	148	265	173	−240	528	295	805	− 18	10.49	10.87	−0.71	+1.53		52.91	2122	7.3	II	10.8	4.2	5.8	
12	2/ 8 to 10/43	121	265	173	−213	695	295	805	−185	11.07	10.87	−1.29	−1.17	53.60	52.66		10.0					
13	2/11 to 13/43	127	251	173	−205	668	269	805	−132	10.82	10.87	−1.04	−0.45		52.43	1691	10.7	I	10.7	4.3	5.2	
14	2/14 to 16/43	148	251	173	−226	680	269	805	−144	11.36	10.87	−1.58	−0.47		52.16	1555	11.0					
15	2/17 to 19/43	143	230	173	−200	694	257	805	−146	11.51	10.87	−1.73	−0.69		51.87	1275	10.3	I	11.3	2.9	5.6	None
16	2/20 to 22/43	155	230	173	−212	697	257	805	−149	11.66	10.87	−1.88	−0.65		51.57		12.7					
17	2/23 to 25/43	155	177	173	−159	608	169	805	−128	10.44	10.87	−0.66	+1.62		51.38	1151	10.7	I	10.7	3.6	4.0	
18	2/26 to 28/43	157	177	173	−161	489	169	805	+147	8.78	10.87	+1.00	+3.41	51.33	51.33	1272	10.3	III	11.9	4.6	3.9	

Dietary intake of periods 1 to 18 in amounts per 24 hours: protein (analyzed nitrogen × 6.25) = 67.9 grams, fat (estimated from tables) = 57.2 grams, carbohydrate (estimated from tables) = 210.1 grams, calories (calculated from the values 4 for 1 gram of protein, 9 for 1 gram of fat, and 4 for 1 gram of carbohydrate) = 1,627.

* Initial weight 54.06 kgm.

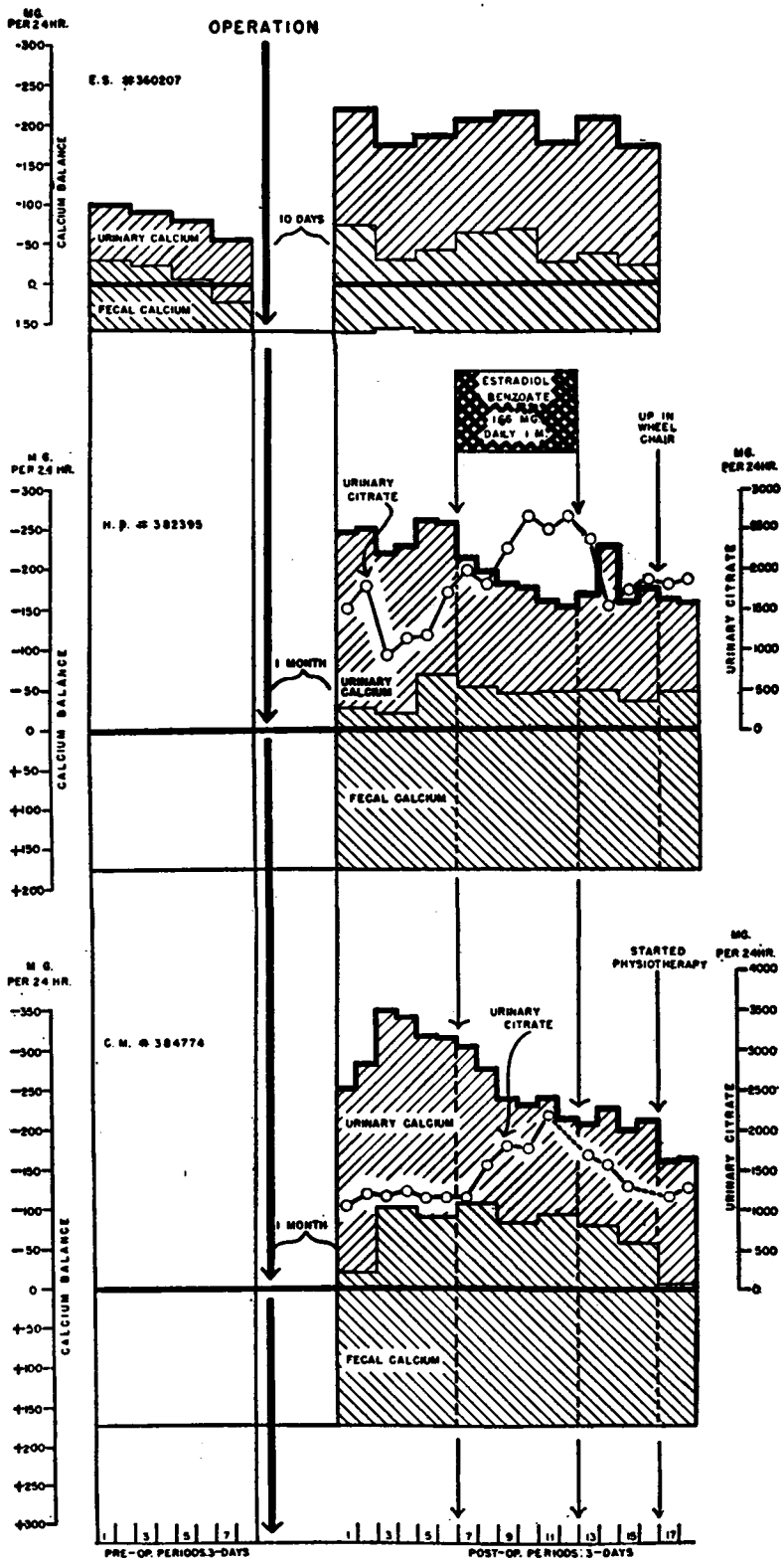

FIG. 10. METABOLIC DATA FOR CALCIUM OF CASES 7, 8, AND 9. EFFECT OF ESTRADIOL BENZOATE AS COMPARED WITH NO THERAPY ON THE CALCIUM BALANCES IN PATIENTS WITH OSTEOPOROTIC PROCESS DUE TO OPERATION AND IMMOBILIZATION

For discussion, see text.

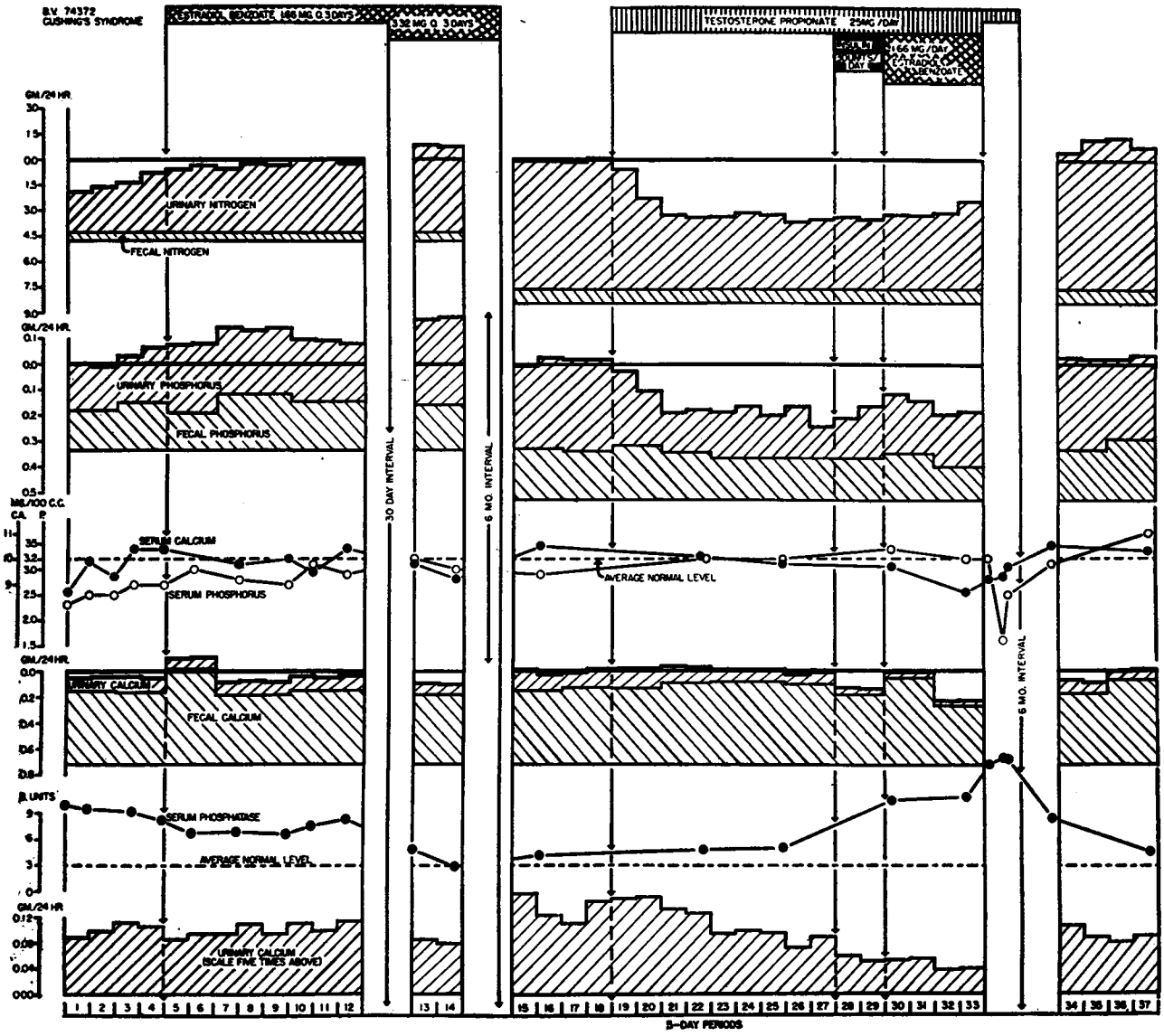

FIG. 11. CASE 10 (B. V., M.G.H. 74372): EFFECT OF ESTRADIOL BENZOATE AND TESTOSTERONE PROPIONATE ON NITROGEN, PHOSPHORUS, AND CALCIUM BALANCES, AND ON SERUM CALCIUM, PHOSPHORUS AND ALKALINE PHOSPHATASE IN A FEMALE PATIENT WITH OSTEOPOROSIS DUE TO CUSHING'S SYNDROME

For discussion, see text.

At the bottom of the chart, the urinary calcium is shown separately on an enlarged scale.

1 through 33, see (2). The study covers 37 five-day periods obtained on 4 hospital admissions. Two diets were used: one for periods 1 through 14, and a second for periods 15 through 37. The nitrogen intake shown in Figure 11 for periods 17 through 33 is an analyzed value, and differs from that previously published which was taken from a table. The data in Figure 11 are self-explanatory. It should first be noted that the phosphorus balance corresponds reasonably well with the sum of the nitrogen and calcium balances during the last 23 periods, but not the first 14. This suggests some constant error in the first 14 periods, probably the value for the nitrogen intake. A more detailed analysis to emphasize the close agreement between the nitrogen, potassium, phosphorus, and sulphur balances of periods 15 through 33 has already been published (9). Although Albright *et al* (2) concluded from these studies that estrogen was without beneficial effect, this was true with respect to the nitrogen balance but not altogether true with respect to the calcium balance. Thus, with the larger dose of estradiol benzoate in periods 13 to 14 there is an increase, probably significant, in the calcium balance. Further-

more, when estradiol benzoate was added to testosterone propionate therapy in periods 30 through 33, there was a further fall in the urinary calcium excretion and an increase in the positive calcium balance. Other observations to be underlined in Figure 11 are: (*1*) the marked decrease in the urinary nitrogen, phosphorus, and calcium excretions with testosterone propionate therapy; (*2*) the marked rise in the serum phosphatase level when the increase in calcium balance became appreciable (see periods 30 through 33). Whereas Figure 11 suggested that insulin had a marked effect on calcium balance (see periods 28 and 29) the authors are inclined to discount this because of the essentially negative result in a second patient with Cushing's syndrome so treated (18).

Case 11. Cushing's Syndrome with Osteoporosis; Estradiol Benzoate, Testosterone Propionate, and Methyl Testosterone Therapy.

The metabolic data on Case 11 are shown in graphic form in Figure 12. For data in tabular form for periods 1 through 36, see (2). The study covers 55 five-day periods obtained on 6 hospital admissions. The data in Figure 12 are self-explanatory. It should first be noted that the phosphorus balance corresponds reasonably well with the sum of the nitrogen and calcium balances throughout. As in Case 10, one cannot conclude, as did Albright, *et al* (2), that estrogen therapy is without beneficial effect. It was started before the metabolic study was initiated; so its initial effect is hard to evaluate (see periods 1 through 7); however, further studies undertaken 35 days after omitting estrogen show that the calcium balance has changed from positive to negative (compare periods 8 and 9 with 6). Other points to be noted in Figure 12 are: (*1*) the lowering of the urinary nitrogen, phosphorus, and calcium excretions with testosterone propionate therapy (periods 10 through 18, and 23 through 36) and with methyl testosterone therapy (periods 50 through 55); (*2*) the fact that the fecal phosphorus and calcium excretions were also lowered with these 2 testosterone compounds; (*3*) the quick rebound in the nitrogen and phosphorus and not the calcium metabolisms on cessation of testosterone propionate therapy (see periods 19 through 22); (*4*) the steady improvement in calcium metabolism with continued administration of testosterone propionate therapy; (*5*) the elevation of the serum phosphatase with improvement in the calcium balance; and (*6*) the rise in the serum phosphorus level following omission of estradiol benzoate therapy in period 6. The marked improvement in calcium balance in periods 29 through 36 is probably to be attributed to continued testosterone propionate therapy, but the initiation of vitamin D therapy in period 29 makes the exact interpretation difficult. Dehydroisoandrosterone acetate in periods 42 to 46 did not prevent the rebound in nitrogen and phosphorus metabolisms from omission of testosterone propionate therapy.

Case 12. Cushing's Syndrome with Osteoporosis; Progesterone and Testosterone Propionate Therapy.

The metabolic data of Case 12 are shown in graphic form in Figure 13. For data in tabular form, see (2). The study, conducted in 5-day periods, consisted of: (*1*) five control periods; (*2*) seven periods on progesterone therapy, 25 mgm. per day; and (*3*) four periods on testosterone propionate therapy, 25 mgm. intramuscularly per day.

The data in Figure 13 are self-explanatory. As pointed out by Albright, *et al* (2), the progesterone therapy, if anything, had a slightly beneficial effect on nitrogen, phosphorus, and calcium. The effect was not nearly so marked as that obtained in periods 13 to 16 with testosterone propionate therapy. Of interest is the rise in the alkaline phosphatase level in period 16, when the calcium balance became appreciable. It should be noted that the 17-ketosteroid excretion was not lowered by progesterone or elevated by testosterone propionate; the latter finding is surprising, and not in agreement with other studies.

CERTAIN THERAPEUTIC ASPECTS CONCERNING POSTMENOPAUSAL OSTEOPOROSIS

A large number of cases, many complicated by fractures, have been treated with estrogens alone and in combination with testosterone compounds during the past 5 years. As a group, these patients have responded very satisfactorily. Within weeks to months, the pain in the spine and other bones usually has been considerably or completely eliminated. There has frequently been an increase in weight, apparently an increase in the thickness of the skin and an improvement in the general well-being Whereas the study is impossible to control, we have the impression that fractures, especially of the hip, in old ladies have responded better than they would have otherwise. However, in spite of these favorable clinical manifestations, it has been difficult to produce undisputed evidence that the bones (excluding fracture-sites) as visualized by x-ray have become more calcified than before the therapy was instituted. Nevertheless, the recent films of several of the longest-treated cases are fairly convincing.

Dosages have ranged as follows: diethylstilbestrol 0.5 to 1 mgm. daily p.o., estrone sulfate [6] 2.50 to 3.75 mgm. daily p.o., estradiol benzoate 1.66 to 3.32 mgm. 3 times a week i.m., and estradiol dipropionate 5 mgm. weekly i.m. A few patients have been treated by implantation of pellets. Excessive estrogenic effect on the endometrium has been controlled whenever a responsive uterus was present, by interrupting the estrogenic therapy periodically (every 4 to 6 weeks

[6] Conjugated equine estrogens (Premarin [Ayerst, McKenna and Harrison]).

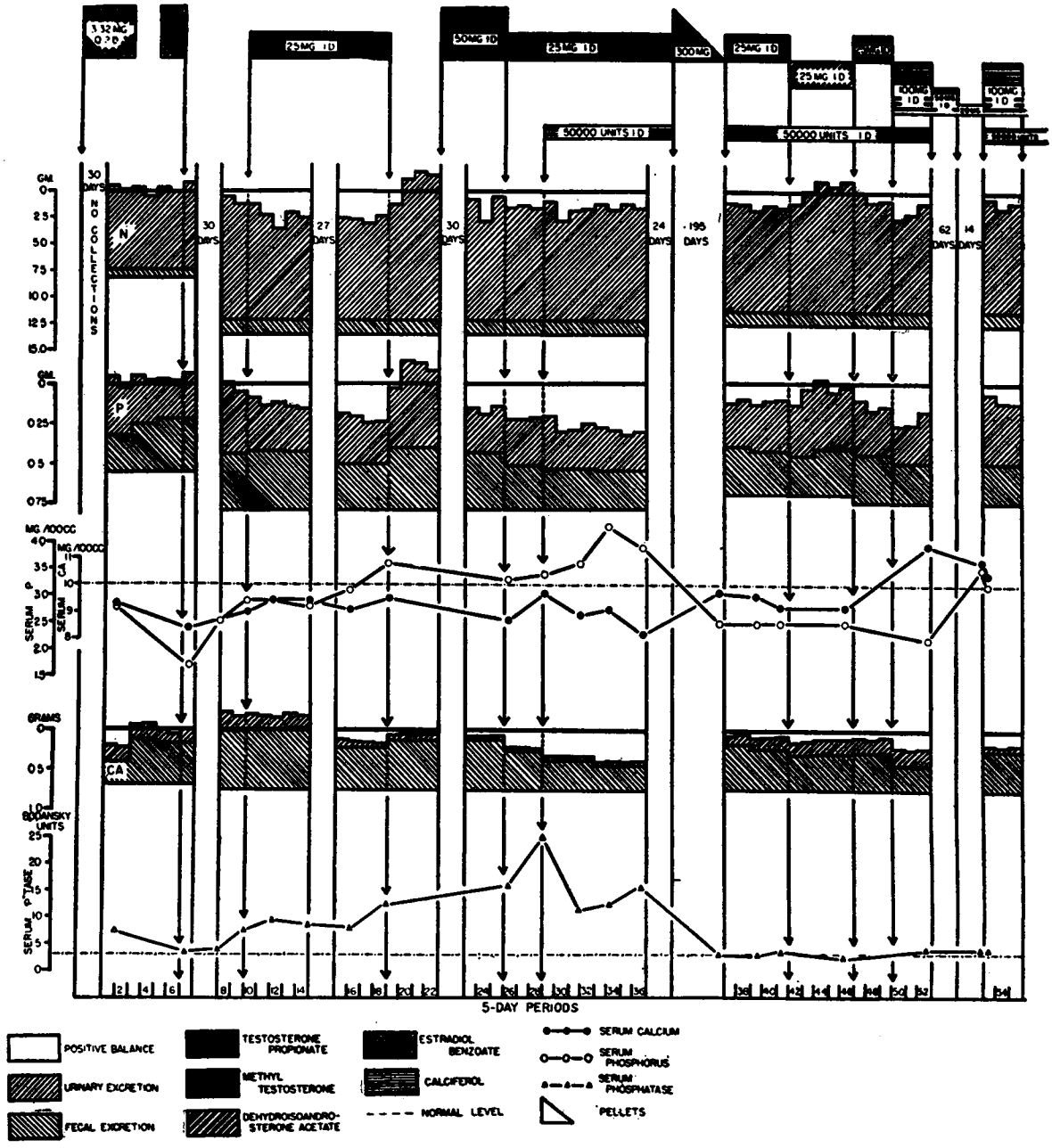

FIG. 12. CASE 11 (R. B., M.G.H. 3397): EFFECT OF ESTRADIOL BENZOATE, TESTOSTERONE PROPIONATE AND METHYL TESTOSTERONE ON NITROGEN, PHOSPHORUS, AND CALCIUM BALANCES; AND ON SERUM CALCIUM, PHOSPHORUS, AND ALKALINE PHOSPHATASE IN A FEMALE PATIENT WITH OSTEOPOROSIS DUE TO CUSHING'S SYNDROME

For discussion, see text.

for 1 to 2 weeks), or by administering at regular intervals (every 4 to 6 weeks) a course of progesterone (5 mgm. daily i.m. for 5 days) or of anhydro-hydroxyprogesterone (40 to 60 mgm. daily p.o. for 5 days). Testosterone compounds cannot be given in most patients with the impunity suggested from Case 4; she was remarkably free from the masculinizing effect of such medication. Most women will not tolerate more than 300 mgm. per month of androgen. We have given methyl

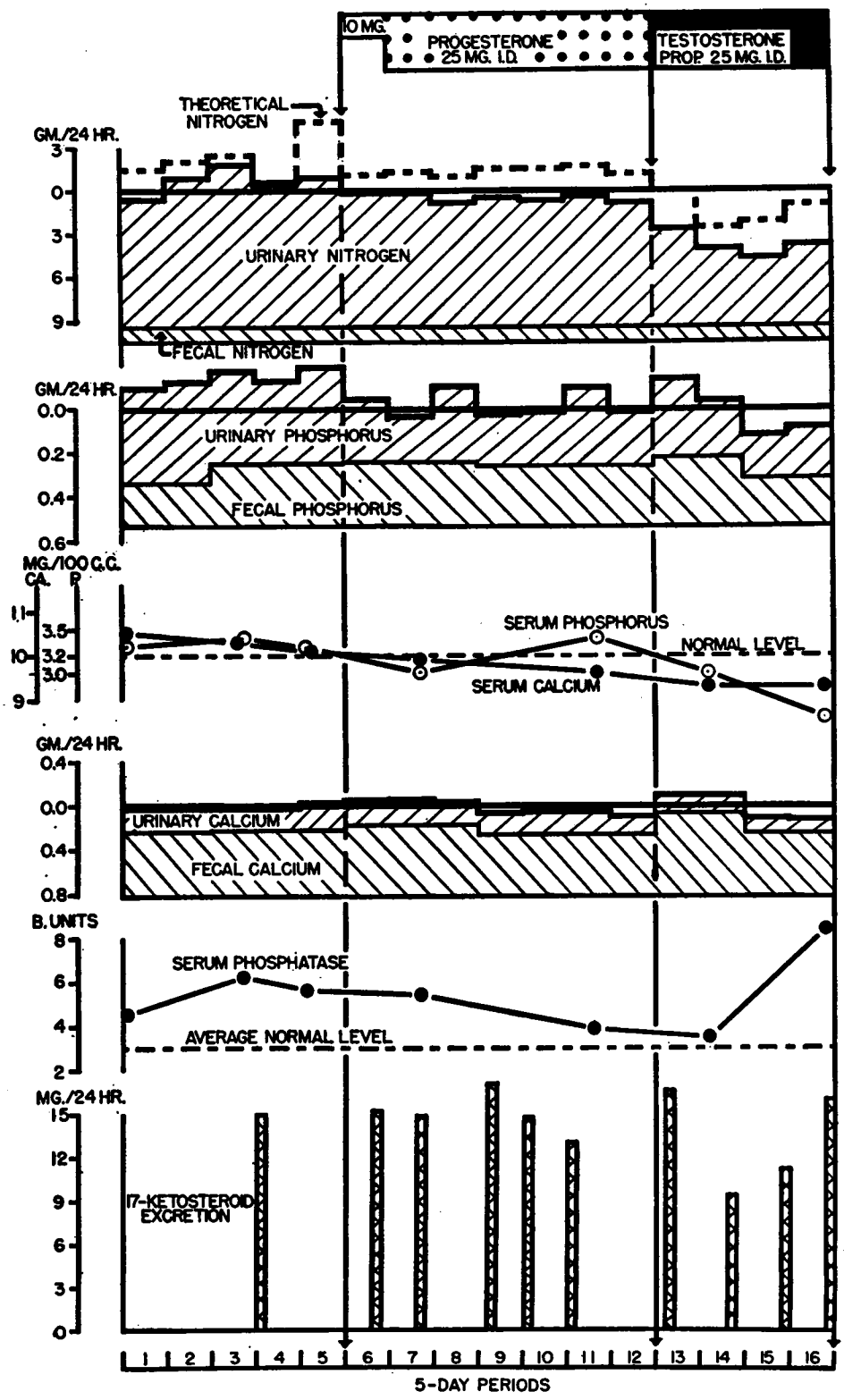

FIG. 13. CASE 12 (B. A., M.G.H. 234190): EFFECT OF PROGESTERONE AND TESTOSTERONE PROPIONATE ON NITROGEN, PHOSPHORUS, AND CALCIUM BALANCES; ON SERUM CALCIUM, PHOSPHORUS, AND ALKALINE PHOSPHATASE; AND ON URINARY 17-KETOSTEROID EXCRETION IN A FEMALE PATIENT WITH OSTEOPOROSIS DUE TO CUSHING'S SYNDROME

For discussion, see text.

testosterone 10 to 20 mgm. daily p.o., and testosterone propionate 10 to 20 or 25 mgm. a week i.m. One of the most successful methods of administering testosterone compounds to these patients is to implant one or two pellets of testosterone (75 mgm. each [Schering]) every 3 to 4 months. We usually give some form of testosterone at least for the first 6 to 12 weeks.

Since many of the steroids cause sodium retention, the above endocrine therapy may cause edema in certain elderly patients, especially if they have low serum protein levels. If this is not controlled by a low sodium chloride diet, and/or ammonium chloride, the steroid therapy may have to be modified.

Because of the possible danger that continued estrogenic medication may lead to cancer, it has been our practice to interrupt the medication for 7 to 14 days every 4 to 6 weeks, even though the uterus is out. An examination of the vaginal smear every 6 months provides a further safeguard (19). If the uterus is in, a record should be kept of the vaginal bleeding; any bleeding not according to plan (that is, not following estrogen or progesterone withdrawal) should promptly be investigated further.

Since osteoporosis is a deficiency in bone matrix protoplasm, a high protein diet is probably indicated; since it is not a disease of calcium and phosphorus metabolism, excessively high intakes of these minerals and of vitamin D are probably not indicated. Prolonged immobilization should, of course, be avoided if possible, because of the danger of superimposed atrophy of disuse.

SUMMARY

1. Osteoporosis is defined as that form of undermineralization of bone in which the primary defect is a hypofunction of the osteoblasts in laying down bone matrix; eight etiological subgroups are listed.

2. The effect of certain steroid hormones (notably estrogens, androgens, and progesterone) has been studied in 11 cases of osteoporosis: 5 cases of the post-menopausal type, 1 case of the senile type, 2 cases of the type seen following orthopedic operations (atrophy of disuse), and 3 cases of the Cushing's syndrome type.

3. Estrogens in the 2 forms used (estradiol benzoate and diethylstilbestrol) decreased the calcium and phosphorus excretions in the 4 types of osteoporosis studied. Additional observations on estrogen therapy follow.

a. The fecal as well as the urinary calcium and phosphorus excretions were decreased in most instances.
b. The effects were usually manifested within 6 days; did not reach a maximum until after 30 days; and persisted for 30 to 50 days after cessation of therapy.
c. The synthetic estrogen, diethylstilbestrol, appeared to be as effective as the naturally-occurring estrogen, estradiol.
d. The ranges of dosages employed were for estradiol benzoate 3.32 mgm. daily to 1.66 mgm. every 3 days intramuscularly, and for diethylstilbestrol 1 to 15 mgm. daily by mouth. There was no convincing evidence that the larger doses of estradiol benzoate were more effective than the smaller; in one instance (Figure 3) 3.32 mgm. seemed less effective than 1.66 mgm. every third day. In the one case studied, 15 mgm. of diethylstilbestrol daily was probably more effective than 1 mgm. daily.
e. The serum phosphorus levels, which tend to be high in the post-menopausal group, fell in almost all instances.
f. The serum alkaline phosphatase levels, contrary to expectations, did not rise.
g. The urinary nitrogen excretion showed a poorly-sustained decrease.
h. The urinary 17-ketosteroid excretion showed a moderate decrease with estradiol.

4. Androgens in the 2 forms used (testosterone propionate and methyl testosterone) likewise decreased the calcium and phosphorus excretions in the 3 types of osteoporosis (post-menopausal, senile, and Cushing's syndrome) studied. Additional observations on androgen therapy follow.

a. As in the case of estrogens, the fecal as well as the urinary calcium and phosphorus excretions were decreased; the effect of the therapy on the calcium metabolism was slow in reaching its maximum, and persisted for a long time after cessation of therapy; the serum phosphorus levels tended to fall; the

serum alkaline phosphatase levels failed to rise except in the three cases of Cushing's syndrome.

b. In contrast to estrogens, the decrease in the urinary nitrogen excretion was marked and prolonged.

c. The ranges of dosages employed were for testosterone propionate 25 to 50 mgm. daily intramuscularly, and for methyl testosterone 40 to 100 mgm. daily by mouth.

d. Methyl testosterone appeared to be as effective as testosterone propionate.

5. Progesterone, in the dosages of 10, 25, and 100 mgm. daily, had no definite effect whether given alone or in combination with estrogen.

6. The effect on the calcum metabolism of estrogen and androgen in combination was greater than that of either alone in the post-menopausal and senile groups.

7. In Cushing's syndrome estrogen probably does have a beneficial effect on the calcium balance, previous statements to the contrary from this clinic notwithstanding! However, testosterone compounds have a much more striking effect in this condition, as opposed to other types of osteoporosis.

8. The data contain observations on the effect of pregnenolone and dehydroisoandrosterone acetate.

9. A short discussion of certain therapeutic aspects of post-menopausal osteoporosis is included.

The authors are grateful to Drs. Max Gilbert and Erwin Schwenk of the Schering Corporation, Bloomfield, New Jersey, for generous supplies of estradiol benzoate (Progynon-B), estradiol dipropionate (Progynon-DP), testosterone propionate (Oreton), methyl testosterone (Oreton-M), progesterone (Proluton), anhydro-hydroxy-progesterone (Pranone), dehydroisoandrosterone acetate, pregnenolone, and other steroids.

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APPENDIX

Case histories

Case 1. F. F. (M.G.H. 156453), a 42-year-old woman, had a bilateral oophorectomy at the age of 41 for endometriosis; following the operation she had "nocturnal seizures," the exact nature of which was not determined. During the following year there was a gradual onset of back pain with increasing dorsal kyphosis and a loss of energy. On admission one year after operation, the patient was in good physical condition except for the deformities of her spine; her blood pressure was 130/80. X-rays revealed typical codfish deformity of many of the dorsal and lumbar vertebrae, a collapse of some vertebrae, and anterior wedging of others. Laboratory studies: serum calcium 10.5 mgm. per cent, serum phosphorus 4.2 mgm. per cent, serum alkaline phosphatase 3.6 Bodansky units, serum total protein 7.3 grams per cent, normal glucose tolerance test, some hypoglycemia unresponsiveness in an insulin tolerance test, basal metabolic rate of minus 6, follicle-stimulating hormone test positive for 25 mouse units per 100 ml., and 17-ketosteroid excretion of 4.3 mgm. per 24 hours. This case was mentioned in previous communications (1 [Case 1], 3 [Case 37], 20 [Case 82], 21).

Case 2. E. P. (M.G.H. 203540), a 60-year-old patient, had a physiological menopause at 53. Thirteen months before admission she fell down 6 steps and fractured her first lumbar vertebra; she was kept in bed 5 months for this injury, and then allowed up with a brace. Eight months before admission the 9th dorsal vertebra collapsed. Except for back and chest pain, the patient had no complaints, and was in good general health upon admission. Her blood pressure was 120/90. X-ray examination revealed the fractures of the first lumbar and the 9th dorsal vertebrae, marked osteoporosis of the spine and pelvis, but not of the skull, and gall stones. Laboratory studies: serum calcium 10.1 mgm. per cent; serum phosphorus 3.5 mgm. per cent; serum alkaline phosphatase 3.7 Bodansky units; serum total protein 7.6 grams per cent; no Bence-Jones protein in the urine. This case was mentioned in previous communications (1 [Case 2], 3 [Case 13], 20 [Case 85], 21).

Case 3. A. M. R. (M.G.H. 29358), a 60-year-old physician, developed menopause at 45 following radium treatment of submucous fibroids. Four years before admission she experienced pain in the back while trying to raise a window, and in the ensuing 4 years developed several fractures of vertebrae and progressive deformity of the spine. Physical examination on admission revealed the deformity of the spine and otherwise no abnormalities. Her blood pressure was 148/90. X-ray examination showed deformities of several thoracic and the first lumbar vertebrae, and osteoporosis of the bones of the spine and pelvis but not of the skull. Laboratory studies: serum calcium 10.1 mgm. per cent; serum phosphorus 3.0 mgm. per cent; serum phosphatase 3.7 Bodansky units; serum total protein 6.3 grams per cent. This case has been mentioned in previous communications (1 [Case 3], 3 [Case 32], 20 [Case 84], 21).

Case 4. R. W. (M.G.H. 319940), a 56-year-old woman, had a cholecystectomy at 26, and thyroidectomy for thyrotoxicosis at 46. At 48, an artificial menopause was induced with radium for metropathia hemorrhagica. Three years before admission the patient strained her back opening a heavy window, and thereafter had several episodes of sharp pain in the back when lifting. Physical examination showed a nervous woman with a tremor of her head, and considerable deformity of her back. Her blood pressure was 115/75. X-ray examination revealed extensive osteoporosis with multiple fractured vertebrae; bones of skull were approximately normal in density. Laboratory studies: no abnormalities of the urine, stools, or blood cells; urine calcium 2 to 4 plus by the Sulkowitch test; serum calcium 10.6 mgm. per cent; serum phosphorus 3.1 mgm. per cent; serum alkaline phosphatase 3.7 Bodansky units; serum chloride 93.2 m.eq. per l.; serum carbon dioxide combining power 28.1 m.eq. per l.; non-protein nitrogen level 26 mgm. per cent; and total protein 7.8 grams per cent with an albumin/globulin ratio of 1.7. Electrocardiographic tracing was normal; follicle-stimulating hormone excretion in the urine was high (consistent with the menopause). This case has been mentioned in a previous communication (21).

Case 5. S. B. (M.G.H. 430664), a 58-year-old woman, had at the age of 28 a bilateral oophorectomy with a hysterectomy for pelvic lacerations following childbirth. For some years she had occasional hot flashes and attacks of palpitation and nervousness. At the age of 50 she began to notice weakness and the gradual onset of skeletal deformities involving the skull, shoulder girdle, lower ribs, pelvis, and bones of the legs. At 54 she had acute tonsillitis, and then a tonsillectomy. At 57 she had pneumonia, and after 3 weeks in bed, increased weakness and pain in her tibiae. About this time she used braces on her legs because of difficulty in walking. Shortly afterward she developed low-back pain on weight-bearing.

On admission, the patient was undernourished and deformed with atrophic skin and muscles, dorsal kyphosis and right cervical-dorsal scoliosis, enlarged parietal bosses, bowing of the femora and tibiae, and collapse of the lumbar spine so that the ribs touched the wings of the iliae. The chest was distorted; veins of the neck were distended; cor pulmonale was present; blood pressure was 156/80.

X-rays of the skull, shoulder girdle, lower ribs, pelvis, femora, tibiae, and entire thoracic and lumbar spine except for the upper three dorsal vertebrae showed Paget's disease; in addition there were marked generalized decreased density of bones and typical codfish deformity of many vertebrae. There were pulmonary fibrosis, cardiac enlargement and displacement, and tortuosity of the aorta. Laboratory studies: serum calcium 10.5 mgm. per cent, serum phosphorus 4.2 mgm. per cent, serum alkaline phosphatase 34.3 Bodansky units, serum total protein 7.3 grams per cent, serum non-protein nitrogen 31 mgm. per cent, serum sodium 140.0 m.eq. per l., serum potassium 4.7 m.eq. per l., serum chloride 101 m.eq. per l., serum carbon dioxide content 34.2 m.eq. per l., follicle-stimulating hormone test positive for 192 mouse units per 24 hours, and 17-ketosteroid excretion of 2.6 mgm. per 24 hours. The venous pressure was 65 mm. of water; the vital capacity was 1,200 ml.

Case 6. M. H. (M.G.H. 278511), a male of 72 years, developed pain in the back after a minor injury 1 year before admission (1–1–41). The symptoms persisted in spite of local therapy, and he was referred to the hospital. The only abnormal findings on physical examination were a thin skin and deformities of the spine; his blood pressure was 140/80. X-ray examination of the spine showed marked decrease in density of the vertebrae with a codfish deformity of some, and wedging or collapse of others. Laboratory studies: serum calcium 10.0 mgm. per cent; serum phosphorus 3.1 mgm. per cent; serum alkaline phosphatase 4.2 Bodansky units; serum total protein 7.0 grams per cent; non-protein nitrogen 18 mgm. per cent; urinary 17-ketosteroid excretion 7.2 and 6.9 mgm. per 24 hours; follicle-stimulating hormone excretion in the urine normal; gastric acidity normal. The normal level of the follicle-stimulating hormone excretion is evidence against the idea of the osteoporosis having been due to the "male menopause." This case has been mentioned in previous communications (6, 9, 21).

Case 7. E. S. (M.G.H. 360207), a female of 35 years, had poliomyelitis at the age of 9 involving the left leg alone, and since the age of 14 had worn a 6-pound brace on the left leg. She had always been very active. For the 10 years prior to study she had had metatarsal pain in the right foot, and for 3 years had turned her right ankle frequently. She was admitted for a triple arthrodesis and muscle transplant to strengthen the right ankle. The menstrual history was normal. From the point of view of the experiment the patient can be considered a normal adult female in every respect, except for the residuals of the poliomyelitis of the left leg; her blood pressure was 120/80. Laboratory studies: serum calcium 9.8 mgm. per cent; serum phosphorus 3.5 mgm. per cent; serum alkaline phosphatase 2.4 Bodansky units; and serum total protein 4.7 grams per cent; urinary 17-ketosteroid excretion 7.6 mgm. per 24 hours. This case has been mentioned briefly elsewhere (22).

Case 8. H. D. (M.G.H. 382395), a male fireman of 50 years, fell 3 stories and suffered fractures of ribs, pelvis, right tibia and right fibula, and multiple contusions and abrasions. The patient was in shock on admission, but responded promptly to a blood transfusion. On physical examination he was found to be a well-preserved man without organic disease; blood pressure was 110/60. A Kirschner wire was inserted through the os calcis and a Zimmer bow applied. During the next 2 weeks the fractures were reduced by traction and by several manipulations under anesthesia. The patient was transferred to the metabolic ward where studies were begun 44 days after the accident. Laboratory studies: serum calcium 10.7 mgm. per cent; serum phosphorus 3.3 mgm. per cent; serum alkaline phosphatase 2.7 Bodansky units; serum total protein 6.7 grams per cent. This case has been mentioned briefly elsewhere (23).

Case 9. C. M. (M.G.H. 348774), a male of 24 years, sustained a fracture of the pelvis and of the right femur in an automobile accident 9 months before study. The fe-

mur failed to unite properly and, although the patient was active and able to walk about with a cane, he had unusual motion and instability in his right femur because of the poor union. He was readmitted for bone grafting. Physical examination revealed a young adult male who was normal in all respects except for the incomplete union of his right femur; his blood pressure was 105/60. Laboratory studies: serum calcium 10.3 mgm. per cent; serum phosphorus 4.5 mgm. per cent; serum alkaline phosphatase 2.9 Bodansky units, and serum total protein 6.0 grams per cent. This case has been mentioned briefly elsewhere (24).

Case 10. B. V. (M.G.H. 74372), a female of 25 years, with Cushing's syndrome of 5 years duration. The case history of this patient has been published elsewhere (2 [Case 1]). This case has been mentioned also in other previous communications (6, 9, 20 [Case 37]).

Case 11. R. B. (M.G.H. 3397), a female of 50 years, with Cushing's syndrome of 5 years duration. The case history of this patient has been published elsewhere (2 [Case 2]). This case has been mentioned also in other previous communications (6, 9, 20 [Case 36], 25 [Case 2]).

Case 12. B .A. (M.G.H. 234190), a female of 43 years, with Cushing's syndrome of 6 years duration. A complete case history with autopsy findings is reported elsewhere (26). This case has also been mentioned in previous communications (2 [Case 3], 20 [Case 38]).

BIBLIOGRAPHY

1. Albright, F., Bloomberg, E., and Smith, P. H., Post-menopausal osteoporosis. Tr. Assoc. Am. Physicians, 1940, **55**, 298.
2. Albright, F., Parson, W., and Bloomberg, E., Cushing's syndrome interpreted as hyperadrenocorticism leading to hypergluconeogenesis; results of treatment with testosterone propionate. J. Clin. Endocrinol., 1941, **1**, 375.
3. Albright, F., Smith, P. H., and Richardson, A. M., Post-menopausal osteoporosis: its clinical features. J. A. M. A., 1941, **116**, 2465.
4. Reifenstein, E. C., Jr., and Albright, F., Paget's disease: its pathologic physiology and the importance of this in the complications arising from fracture and immobilization. New Eng. J. Med., 1944, **231**, 343.
5. Albright, F., Burnett, C. H., Cope, O., and Parson, W., Acute atrophy of bone (osteoporosis) simulating hyperparathyroidism. J. Clin. Endocrinol., 1941, **1**, 711.
6. Albright, F., Cushing's syndrome. Its pathological physiology, its relationship to the adrenogenital syndrome, and its connection with the problem of the reaction of the body to injurious agents ("alarm reaction" of Selye). The Harvey Lecture Series, 1942-1943, **38**, 123.
7. Selye, H., The alarm reaction. Cyclopedia Med. Surg. and Spec., F. A. Davis Company, Philadelphia, 1940, 15. Also, Selye, H., The general adaptation syndrome and the diseases of adaptation. J. Clin. Endocrinol., 1946, **6**, 117.
8. Reifenstein, E. C., Jr., Kinsell, L. W., and Albright, F., Observations on the use of the serum phosphorus level as an index of pituitary growth hormone activity; the effect of estrogen therapy in acromegaly. Endocrinol., 1946, **39**, 71. Also Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing. Trans. of 12th Meeting, February 4–5, 1946, p. 97; distributed by Josiah Macy, Jr. Foundation, New York.
9. Reifenstein, E. C., Jr., Albright, F., and Wells, S. L., The accumulation, interpretation, and presentation of data pertaining to metabolic balances, notably those of calcium, phosphorus, and nitrogen. J. Clin. Endocrinol., 1945, **5**, 367.
10. Talbot, N. B., Saltzman, A. H., Wixom, R. L., and Wolfe, J. K., The colorimetric assay of urinary corticosteroid-like substances. J. Biol. Chem., 1945, **160**, 535.
11. Klinefelter, H. F., Jr., Albright, F., and Griswold, G. C., Experience with a quantitative test for normal or decreased amounts of follicle stimulating hormone in the urine in endocrinological diagnosis. J. Clin. Endocrinol., 1943, **3**, 529.
12. Abels, J. C., and Dobriner, K., Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing, Transactions of Seventh Meeting, June 9–10, 1944, p. 122; distributed by Josiah Macy, Jr. Foundation, New York.
13. Farquharson, R. F., Salter, W. T., Tibbets, D. M., and Aub, J. C., Studies of calcium and phosphorus metabolism. XII. The effect of the ingestion of acid-producing substances. J. Clin. Invest., 1931, **10**, 221.
14. Howard, J. E., Parson, W., and Bigham, R. S., Jr., Studies on fracture convalescence. III. The urinary excretion of calcium and phosphorus. Bull. Johns Hopkins Hosp., 1945, **77**, 291.
15. Forbes, A. P., Donaldson, E. C., Reifenstein, E. C., Jr., and Albright, F., The effect of trauma and disease on the urinary 17-ketosteroid excretion in man. J. Clin. Endocrinol. To be published.
16. Browne, J. S. L., Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing, Transactions of the Fifth Meeting, October 8–9, 1943, p. 91; distributed by Josiah Macy, Jr. Foundation, New York.
17. Shorr, E., Bernheim, A. R., and Taussky, H., The relation of urinary citric acid excretion to the menstrual cycle and the steroidal reproductive hormones. Science, 1942, **95**, 606.
18. Reifenstein, E. C., Jr., and Albright, F., Conferences on Metabolic Aspects of Convalescence Including Bone and Wound Healing, Transactions of the Fifth Meeting, October 8–9, 1943, p. 79; distributed by Josiah Macy, Jr. Foundation, New York.
19. Fremont-Smith, M., Graham, R. M., Janzen, L. T., and Meigs, J. V., The vaginal smear in the diag-

nosis of uterine cancer. J. Clin. Endocrinol., 1945, **5**, 40.

20. Fraser, R. W., Forbes, A. P., Albright, F., Sulkowitch, H., and Reifenstein, E. C., Jr., Colorimetric assay of 17-ketosteroids in urine; a survey of the use of this test in endocrine investigation, diagnosis, and therapy. J. Clin. Endocrinol., 1941, **1**, 234.
21. Reifenstein, E. C., Jr., Albright, F., Parson, W., and Bloomberg, E., The effect of estradiol benzoate, of testosterone propionate, and of combinations of both on post-menopausal osteoporosis and senile osteoporosis. Endocrinol., 1942, **30**, S1024.
22. Reifenstein, E. C., Jr., and Albright, F., Conferences on Metabolic Aspects of Convalescence Including Bone and Wound Healing, Transactions of First Meeting, September 11–12, 1942, p. 37; Transactions of Second Meeting, December 11–12, 1942, p. 69 and 96; and Transactions of Fourth Meeting, June 11–12, 1943, p. 77; distributed by Josiah Macy, Jr. Foundation, New York.
23. Reifenstein, E. C., Jr., and Albright, F., Conferences on Metabolic Aspects of Convalescence Including Bone and Wound Healing, Transactions of Third Meeting, March 12–13, 1943, p. 63; and Transactions of Fourth Meeting, June 11–12, 1943, p. 77; distributed by Josiah Macy, Jr. Foundation, New York.
24. Reifenstein, E. C., Jr., and Albright, F., Conferences on Metabolic Aspects of Convalescence Including Bone and Wound Healing, Transactions of Fourth Meeting, June 11–12, 1943, p. 77; distributed by Josiah Macy, Jr. Foundation, New York.
25. Reifenstein, E. C., Jr., Forbes, A. P., Albright, F., Donaldson, E., and Carroll, E., Effect of methyl testosterone on urinary 17-ketosteroids of adrenal origin. J. Clin. Invest., 1945, **24**, 416.
26. Albright, F., and MacMahon, H. E., Clinical Pathological Conference. Bull. New Eng. Med. Center, 1941, **3**, 35.