

CHANGES IN SERUM INORGANIC PHOSPHORUS DURING INTRAVENOUS GLUCOSE TOLERANCE TESTS: IN PATIENTS WITH PRIMARY (ESSENTIAL) HYPERTENSION, OTHER DISEASE STATES, AND IN NORMAL MAN

Arthur R. Wertheim, ... , Gerald H. Eurman, Helen J. Kalinsky

J Clin Invest. 1954;**33**(4):565-571. <https://doi.org/10.1172/JCI102927>.

Research Article

Find the latest version:

<https://jci.me/102927/pdf>



CHANGES IN SERUM INORGANIC PHOSPHORUS DURING INTRAVENOUS GLUCOSE TOLERANCE TESTS: IN PATIENTS WITH PRIMARY (ESSENTIAL) HYPERTENSION, OTHER DISEASE STATES, AND IN NORMAL MAN¹

By ARTHUR R. WERTHEIM, GERALD H. EURMAN, AND HELEN J. KALINSKY

(From the Columbia University Research Service, Goldwater Memorial Hospital, and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.)

(Submitted for publication July 14, 1953; accepted December 30, 1953)

In normal persons the administration of glucose orally or intravenously is associated with a decrease of serum inorganic phosphorus (1). Forsham and Thorn (2) and Schneeberg (3) have established that in most patients with diabetes mellitus the average fall in serum inorganic phosphorus is much less than the average fall found in patients who do not have this disease.

Intravenous glucose tolerance tests have been performed as part of a study on patients with essential hypertension admitted to the Columbia University Research Service, Goldwater Memorial Hospital, New York. Concomitant changes in serum inorganic phosphorus have been measured. The results of this study are reported. They indicate that some hypertensive patients who are non-diabetic (normal glucose tolerance test and no glycosuria) show serum phosphate curves similar to those previously described as occurring in diabetes mellitus (2, 3).

METHOD

The individuals who served as a control series for this study and the patients with primary (essential) hypertension who comprise the experimental group were placed on a high-carbohydrate diet (minimum of 300 Gm.) for at least three days preceding the experimental period. The intravenous glucose tolerance tests were performed in the morning while the subjects were at rest and in the fasting state. After a fasting venous blood sample had been obtained, 50 cc. of 50 per cent glucose in distilled water was injected intravenously over a period of five minutes, following the technique of Lozner, Winkler, Taylor, and Peters (4). Samples of heparinized blood were drawn 20, 60, 90, 120, and 180 minutes following the glucose injection. The plasma was separated and proteins

precipitated within one hour from the time of withdrawal to minimize *in vitro* shifts in phosphate. No hemolyzed specimens were used. Each of the samples was examined in duplicate for glucose and inorganic phosphorus content. Glucose was determined by a modification of the Folin-Wu procedure described by Shannon, Farber, and Troast (5). This technique affords minimal interference by non-fermentable reducing substances, yielding final results approximating those for true glucose. Inorganic phosphorus values were determined by the method of Fiske and Subbarow (6).

RESULTS

Twenty-two individuals served as a control group. They included physicians, nurses, laboratory personnel, and patients hospitalized because of neurological disease or inactive rheumatoid arthritis. Their ages ranged from 35 to 68 years (average 52.5 years). There were 9 males and 13 females in this group. No individuals who had clinical or laboratory evidence of active infection, liver disease, or diabetes mellitus were included. However, many were chronically ill and had been confined to the hospital for many months. The data on each of these patients, grouped by decades, are presented in Table I.

The data elicited from patients with essential hypertension are presented in Table II. These patients all had on admission diastolic blood pressures of at least 120 mm. Hg at rest. Most of them had one or more of the complications of severe hypertensive disease: eyeground changes, old cerebrovascular accidents, congestive failure, old myocardial infarction, or renal failure of different degrees. The only patients with primary hypertension eliminated from this series were those who: 1) Had recent vascular accidents; 2) were in a detectable phase of congestive failure; or 3) had unequivocal diabetic glucose tolerance curves. The 30 patients with essential hypertension who were

¹ This study was supported in part by grants from the National Institutes of Health, U. S. Public Health Service, the Albert and Mary Lasker Foundation, and the Josiah Macy, Jr. Foundation.

TABLE I
Normotensive patients

Patient Age Sex	Glucose, mg. %						Inorganic phosphate, mg. %						Max. fall PO ₄	
	Minutes after injection						Minutes after injection							
	0'	20'	60'	90'	120'	180'	0'	20'	60'	90'	120'	180'	mg.	%
M. S. 35-F	91	112	55	72	79	88	3.0	2.7	2.8	2.9	3.1	3.0	0.3	10
E. E. 36-F	72	208	145	84	63	63	3.6	3.4	3.2	3.2	3.2	3.2	0.4	11
A. W. 36-M	74	—	59	71	72	83	3.6	—	2.9	3.4	3.3	3.5	0.7	19
A. T. 42-F	76	224	107	96	70	59	3.2	3.2	2.6	2.5	2.7	2.9	0.7	22
C. R. 45-F	68	196	127	78	64	64	3.9	3.2	3.1	3.1	3.2	3.2	0.7	18
L. G. 45-F	58	213	137	80	50	49	3.4	2.7	2.7	2.5	2.7	2.9	0.9	26
R. B. 46-F	66	242	161	91	63	60	3.3	3.0	2.7	2.7	2.9	3.3	0.6	18
M. L. 47-M	53	204	130	96	68	44	3.0	2.9	2.8	2.7	3.0	3.1	0.3	10
F. C. 49-M	60	183	121	81	59	64	3.4	3.2	3.0	3.1	3.2	3.4	0.4	12
J. C. 49-M	80	205	132	115	102	83	2.8	2.5	2.6	2.6	2.7	2.9	0.3	11
H. S. 51-M	78	218	136	107	99	54	3.2	2.9	2.8	2.8	3.1	3.2	0.4	12
M. P. 56-F	59	204	143	99	70	53	3.3	2.8	2.7	2.7	2.9	3.3	0.6	18
S. W. 57-F	60	140	78	64	55	61	3.7	3.5	3.4	3.6	3.5	3.8	0.3	8
Y. S. 59-F	70	250	176	141	77	73	4.0	3.6	3.2	3.1	3.2	3.3	0.9	22
N. S. 60-F	83	218	162	115	80	60	3.6	3.1	2.7	2.8	2.9	3.4	0.9	25
J. C. 60-M	81	150	61	65	86	80	2.2	2.2	2.0	2.5	2.6	2.7	0.2	9
A. K. 61-M	44	152	133	90	56	55	3.0	2.8	2.6	2.6	2.8	2.9	0.4	13
I. P. 62-M	71	147	104	79	66	55	3.9	3.1	3.2	3.4	3.3	3.4	0.8	20
F. L. 63-F	68	198	149	100	71	66	3.7	3.1	2.7	2.7	3.0	3.3	1.0	27
S. S. 63-F	80	184	104	81	68	66	3.1	2.5	2.4	2.8	2.8	2.8	0.7	23
S. D. 64-M	66	186	164	118	88	58	3.5	3.2	3.0	3.1	3.0	3.1	0.5	14
M. K. 68-F	66	226	139	86	55	64	3.6	3.0	2.8	3.0	2.9	3.3	0.8	22
Average	69.3 ±10.7	193.3 ±34.8	123.7 ±34.1	91.3 ±19.0	70.9 ±13.4	63.7 ±11.2	3.36 ±.40	2.98 ±.34	2.81 ±.21	2.90 ±.30	3.0 ±.23	3.2 ±.33	0.58 ±0.24	16.8 ±5.9

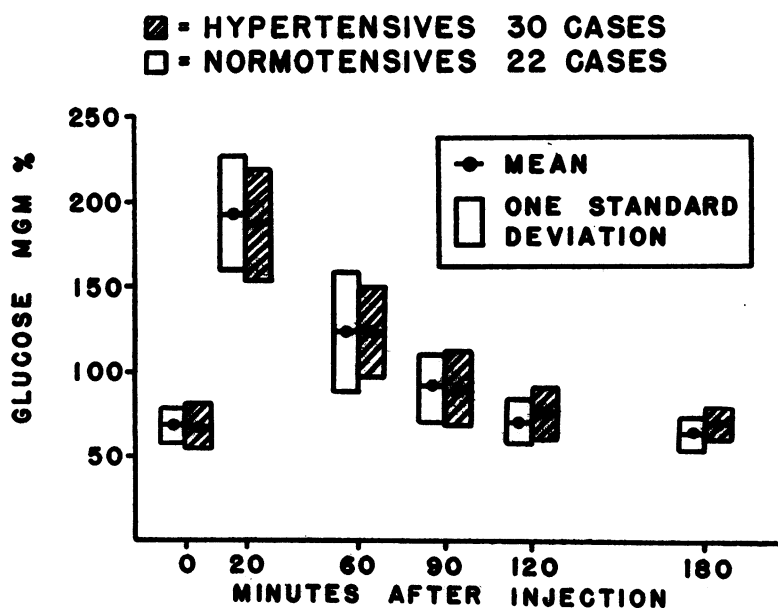


FIG. 1. GLUCOSE TOLERANCE CURVES CHARTED TOGETHER OF 22 NORMOTENSIVE CONTROLS AND 30 PATIENTS WITH PRIMARY HYPERTENSION FOLLOWING THE INTRAVENOUS INJECTION OF 50 CC. OF 50 PER CENT GLUCOSE OVER A FIVE-MINUTE PERIOD

There is no apparent significant difference between the curves obtained in the two groups.

TABLE II
Hypertensive patients

Patient Age Sex	Glucose, mg. %					Inorganic phosphate, mg. %					Renal function			
	Minutes after injection					Minutes after injection					Max. fall PO ₄	%	Pro- teinuria	B.U.N.
	0'	20'	60'	90'	120'	0'	20'	60'	90'	120'				
M.S. 36-M	56	186	120	91	79	4.6	4.5	4.3	4.5	5.1	0.3	7	±	33
S.R. 36-F	51	101	—	54	44	3.3	2.8	2.8	2.9	3.2	0.5	15	0	56
W.S. 38-M	73	180	120	102	94	4.9	4.5	4.3	4.4	4.5	0.6	12	++	12
L.M. 39-M	57	176	120	97	86	4.8	4.8	4.8	4.7	4.9	0.1	2	+	28
L.L. 40-M	82	194	141	118	84	7.2	7.2	7.2	7.2	7.0	0.3	4	++	10
M.F. 42-M	84	250	132	76	57	3.2	3.1	3.1	3.1	3.2	0.1	3	0	5
E.N. 42-M	73	178	75	58	64	3.4	2.8	3.0	3.4	3.5	0.6	18	0	58
F.R. 43-M	54	171	81	62	57	3.0	2.8	2.7	2.9	2.9	0.3	10	++	46
J.N. 44-M	59	161	125	91	87	3.9	3.8	3.5	3.6	3.9	0.4	10	+	41
D.W. 45-F	74	218	173	58	53	4.1	3.7	3.6	3.4	3.6	0.7	17	+	—
B.B. 46-M	57	131	105	65	69	2.7	3.0	3.0	3.4	3.3	0	0	+	59
J.M. 46-M	74	211	117	75	78	3.8	3.6	3.3	3.3	3.5	0.5	13	±	40
G.S. 47-M	57	166	110	73	52	2.5	2.2	2.2	2.0	2.1	0.5	20	±	49
I.R. 48-M	62	125	103	78	73	3.0	2.8	2.6	2.8	3.0	0.4	13	0	—
W.R. 48-M	64	173	102	71	60	3.3	3.0	2.8	3.1	3.3	0.5	15	±	63
H.H. 49-M	95	205	153	125	109	3.6	3.4	3.5	3.6	3.8	0.2	6	+	31
W.W. 49-F	78	210	125	99	80	3.2	2.9	2.8	2.7	2.9	0.2	6	+	52
I.K. 49-M	77	199	139	103	79	3.0	2.8	2.8	3.0	3.3	0.5	16	+	66
G.D. 49-F	100	238	73	66	72	3.9	3.6	3.8	4.2	4.1	0.2	7	+	35
W.M. 49-M	56	178	128	94	80	4.6	4.5	4.4	4.5	4.6	0.3	8	±	43
R.C. 50-M	52	172	136	106	79	3.2	3.3	3.4	3.3	3.4	0	0	++	46
B.V. 54-F	53	232	197	141	107	3.4	3.4	3.4	3.3	3.4	0.1	3	+	73
M.C. 55-F	53	228	173	140	99	2.8	2.6	2.4	2.3	2.4	0.5	18	0	35
R.R. 55-M	65	197	130	97	83	2.8	2.6	2.4	2.4	2.5	0.4	14	0	—
L.S. 56-M	61	218	121	98	73	3.2	3.4	3.4	3.3	3.5	0	0	0	45
P.K. 61-M	65	188	115	96	68	3.4	3.3	3.0	2.8	2.8	0.6	18	0	14
H.C. 63-M	83	183	118	86	82	4.1	3.6	3.3	3.4	3.6	0.8	20	+	42
F.S. 64-M	88	169	133	104	89	2.9	2.6	2.6	2.8	2.8	0.3	10	0	52
C.B. 65-M	68	172	115	76	65	2.7	2.7	2.6	2.5	2.5	0.2	7	±	25
J.R. 68-M	79	199	112	94	71	4.5	3.9	3.5	3.9	4.2	1.0	22	++	50
Average	68.3 ±13.4	186.9 ±32.6	123.8 ±26.6	89.8 ±22.3	75.7 ±15.3	3.63 ±0.90	3.44 ±0.94	3.35 ±0.94	3.42 ±0.97	3.55 ±0.96	0.37 ±0.24	10.4 ±6.5		

included in the series ranged in age from 36 to 68 years (average 49.2 years). There were 24 males and 6 females, a greater proportion of males than in the control group.

A comparison of the glucose tolerance curves obtained from the control and hypertensive groups may be seen in Figure 1. The heavy dot at each time interval indicates the mean glucose level, while one standard deviation is indicated by a block above and below the dot. There is no apparent significant difference between the two groups. This is of importance in reviewing the data concerning the serum inorganic phosphorus changes since the possible inclusion of potential diabetics appears equal in both groups.

Serum phosphate values were determined simultaneously with glucose levels. In the control group, pre-injection levels of serum inorganic phosphate ranged from 2.2 to 4.0 mg. per cent. Each of the patients had a fall in inorganic phosphorus at some time after glucose administration. The average maximum fall for the group was 16.8 per cent of the fasting level.

Among the hypertensive patients, the pre-injection levels of serum inorganic phosphate ranged from 2.5 to 7.2 mg. per cent. While most of these patients had a fall in inorganic phosphate level after glucose administration, three of the thirty

patients had no such change. The average maximal fall for the group was 10.4 per cent of the fasting level. In order to facilitate comparison of the phosphate curves in the control and hypertensive groups, the mean values and one standard deviation have been charted side by side (Figure 2). Since the range of the pre-injection levels in both groups was wide, the changes after glucose administration have been depicted using the fasting level of each curve as the zero point. Inspection of this chart permits determination of the amount of overlap between the two groups. In evaluating the difference between the phosphate curves as depicted here, it should be recalled that the occurrence of the maximum fall in inorganic phosphate may appear from 20 to 90 minutes after glucose administration. As a result there will tend to be a levelling of the curves when a group of observations is placed together.

Knowledge of the accuracy of the method of phosphate determination is necessary in order to evaluate these results. One hundred two serum phosphate levels that had been examined in duplicate were analyzed statistically. The standard deviation between the two runs was 0.045. The standard error of the difference was 0.003. The method is, therefore, highly reproducible.

Since most investigators refer to the maximum

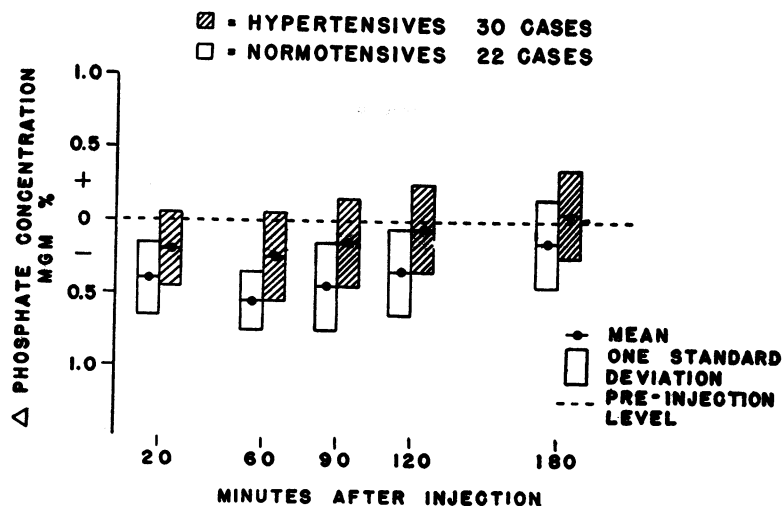


FIG. 2. CHANGES IN SERUM INORGANIC PHOSPHATE LEVELS OF 22 NORMOTENSIVE CONTROLS AND 30 HYPERTENSIVE PATIENTS ARE CHARTED TOGETHER TO FACILITATE COMPARISON OF THE TWO GROUPS

After the intravenous injection of glucose, there is less fall in serum inorganic phosphate levels in patients with primary hypertension than in the normotensive controls.

TABLE III
Hypertension of known etiology

Patient Age Sex	Diagnosis	Glucose, mg %						Inorganic phosphate, mg %						Renal function		
		Minutes after injection						Minutes after injection						Proteinuria	P.S.P.	B.U.N.
		0'	20'	60'	90'	120'	180'	0'	20'	60'	90'	120'	180'			
W. W. 24-M	Chr. G. N.	56	132	95	84	63	56	7.1	7.3	7.1	7.1	7.2	7.1	+	35	74
J. B. 26-M	Chr. G. N.	63	137	73	64	68	73	3.9	3.9	3.9	3.9	4.1	4.0	+	22	18
T. Q. 48-M	Chr. G. N.	77	197	115	82	65	75	3.5	3.4	3.4	3.4	3.5	3.7	+	10	38
M. C. 48-F	Gout; pyelonephritis	65	261	134	75	41	74	3.7	3.6	3.3	3.2	3.3	—	±	15	61
E. V. 41-M	Coarctation aorta	55	169	116	89	73	63	3.4	3.2	3.0	3.3	3.3	3.3	0	70	13

fall in serum inorganic phosphorus as the significant determination, our data were analyzed from this standpoint. The maximum fall in mg. per cent in the normotensives was $0.58 \pm .25$ mg. per cent (standard error of the mean = 0.05); in the hypertensives (excluding the three cases who had no fall in phosphate at any time) the maximum fall was $0.40 \pm .21$ mg. per cent (standard error of the mean = 0.04). The difference between the means was 0.18. The standard error of the difference was .065. As a result the difference between the means exceeds the standard error of the difference by 2.85 times. This permits probability of occurrence by chance of 1 in 231. Therefore, the difference between the two groups is statistically significant.

Results are available from similar studies on five patients with secondary hypertension of known etiology. These are listed in Table III. They indicate that changes in the serum phosphate curves may occur in patients with hypertension of definite cause which resemble those found in the presence of primary hypertension.

DISCUSSION

The intravenous glucose tolerance test, since it eliminates the variable factor of intestinal absorption, has been recommended for the study of the capacity of an individual to handle glucose (2, 4, 7). It was decided to follow the procedure of Lozner, Winkler, Taylor, and Peters (4) using a fixed dose of glucose, since an adequate standard for comparison was available in their published report. The weight difference between the patients in the control and hypertensive groups would not have resulted in a significantly different dosage of glucose had it been administered on a weight basis. Our data on glucose tolerance curves in both the controls and hypertensives closely approximate their results.

Forsham and Thorn (2) reported that, in normals after the intravenous infusion of 0.5 Gm. per Kg. of glucose, "there is a 25 per cent fall of the serum inorganic phosphorus referred to the initial level with a range from 9 to 39 per cent." It should be noted that in their tests the glucose infusion was given over a half-hour period rather than in the five-minute injection method used by us. This may explain why the phosphate fall in our normals

was 16.8 per cent compared with the 25 per cent in their series. After a rapid injection of 25 Gm. of glucose (i.v.), Lazarus, Volk, Jacobi, and Gilady (8) found a mean fall in normals of 14.2 per cent (-10 to -22.5 per cent), a change that is comparable to the series reported here.

Forsham and Thorn commented on the occurrence of poor phosphorus fall in the presence of normal blood sugar curves. They found this to occur in cachexia, disseminated lupus erythematosus, biliary cirrhosis, and Addison's disease. They pointed out that the one feature common to these diseases was depleted liver glycogen. No mention was made of the blood pressures of the subjects. There was no reason to suspect a state of depleted liver glycogen in our non-febrile, well nourished patients. Van Bekkum and Querido (9) have recently reported a decreased phosphate response after intravenous glucose in five patients with progressive muscular dystrophy.

Forsham and Thorn also reported studies in one patient ill with chronic pyelonephritis and azotemia. In spite of phosphate retention, this patient had a 40 per cent fall in the inorganic serum phosphorus level. Although some of the patients in our series had renal damage and some had phosphate retention, we could find no correlation between the fasting level of phosphate (2.5 to 7.2 mg. per cent) and the percentage fall after glucose administration. There was also no apparent correlation between the serum inorganic phosphate changes observed in the patients with essential hypertension and their tests of renal function listed in Table II. Some patients with no proteinuria and normal renal function tests had less fall in phosphate than did others with heavy proteinuria and decreased phenolsulfonphthalein excretion. Three patients with hypertension secondary to chronic glomerulonephritis showed a similar defect. Two other patients with secondary hypertension, one due to coarctation of the aorta and the other due to gout and chronic pyelonephritis, had a normal phosphate response.

As a part of a study of renal function in various disease states, Farber, Earle, and Pellegrino (10) measured glucose Tm in five normal controls, nine individuals with diabetes mellitus, and thirteen with kidney disease. This last group included seven patients with acute glomerulonephritis, two in an exacerbation of chronic glomerulonephritis,

two with chronic nephritis, one with lupus erythematosus, and one with essential hypertension. During the continuous administration of intravenous glucose solution for the determination of maximal tubular resorptive capacity, changes in the serum inorganic phosphate level were also measured. The five controls exhibited a phosphate fall averaging 1.1 mg. per cent. The individuals with diabetes mellitus had an average fall of 0.4 mg. per cent and the patients with renal disease revealed an average fall of 0.3 mg. per cent.

Other investigators (11) studied a group of normal individuals and non-diabetic patients after glucose administration. Two of these patients were diagnosed as having malignant hypertension. They commented that in one of these two patients "under the influence of the infusion there followed a sharp drop in the serum potassium. . . . Remarkably the phosphate did not participate in this decrease."

To date there is no incontrovertible evidence to implicate defective insulin production in producing these abnormal phosphate curves, nor can the other endocrines be clearly involved. Lazarus, Volk, Jacobi, and Gilady (8), studying PO_4 changes and absolute lymphocyte counts in diabetic patients, noted that all the patients who showed an abnormal lymphocyte response to the intravenous injection of glucose showed either no decline in serum phosphate or a non-significant change. They suggested that this correlation between abnormal lymphocyte response and failure of PO_4 fall might indicate pituitary-adrenal dysfunction. Cantarow and Trumper (12) state that unlike the changes seen after epinephrine or thyroxin administration "Pituitrin[®], which produces hyperglycemia . . . causes either no alteration in serum phosphate or, in many instances, a slight increase." While the changes in serum phosphate level after Pituitrin[®] administration mimic in some ways the phosphate pattern demonstrated in some patients with essential hypertension, the posterior pituitary gland has not been shown to function abnormally in this disease. Other investigators (13) have recently concluded that there was no evidence of hypopitressinemia in patients with essential hypertension.

When glucose and phosphate curves are studied repeatedly during the course of prolonged ACTH administration, flat phosphate curves develop (14).

However, this change apparently develops only in the presence of diabetic-type glucose curves. They are, therefore, not similar to the curves described in essential hypertension.

A decreased inorganic phosphate response to intravenous glucose administration may occur under a variety of conditions. It has been demonstrated in patients with diabetes mellitus, in the presence of depleted liver glycogen, in patients with progressive muscular dystrophy and in patients with some forms of renal disease. Patients with primary hypertension may be added to this growing list.

CONCLUSIONS

1. The intravenous glucose tolerance curves and the concomitant changes in the serum inorganic phosphorus level have been studied in 30 patients with essential hypertension, and 22 normotensive patients with a similar age distribution.

2. There is a lesser fall in the serum inorganic phosphorus level in the hypertensive than in the normotensive group. Phosphate curves in some of the hypertensive patients resemble those found in patients with diabetes mellitus. The difference in phosphate fall between normotensive and hypertensive individuals is statistically significant.

REFERENCES

1. Hartman, F. W., and Bolliger, A., Curve of inorganic blood phosphates during the sugar tolerance test. *J. A. M. A.*, 1925, **85**, 653.
2. Forsham, P. H., and Thorn, G. W., Changes in inorganic serum phosphorus during the intravenous glucose tolerance test as an adjunct to the diagnosis of early diabetes mellitus. *Proc. Am. Diabetes A.*, 1949, **9**, 99.
3. Schneeberg, N. G., Serum inorganic phosphorus in the diagnosis of diabetes mellitus. *J. Clin. Endocrinol.*, 1951, **11**, 602.
4. Lozner, E. L., Winkler, A. W., Taylor, F. H. L., and Peters, J. P., The intravenous glucose tolerance test. *J. Clin. Invest.*, 1941, **20**, 507.
5. Shannon, J. A., Farber, S., and Troast, L., The measurement of glucose *T_m* in the normal dog. *Am. J. Physiol.*, 1941, **133**, 752.
6. Fiske, C. H., and Subbarow, Y., The colorimetric determination of phosphorus. *J. Biol. Chem.*, 1925, **66**, 375.
7. Mosenthal, H. O., and Barry, E., Criteria for and interpretation of normal glucose tolerance tests. *Ann. Int. Med.*, 1950, **33**, 1175.
8. Lazarus, S. S., Volk, B. W., Jacobi, M., and Gilady, M. Y., Absolute lymphocyte count and serum inorganic phosphorus after glucose administration in diabetic patients. *Am. J. Clin. Path.*, 1952, **22**, 127.
9. Van Bekkum, D. W., and Querido, A., Inorganic phosphate response to intravenous glucose administration in progressive muscular dystrophy. *J. Clin. Invest.*, 1953, **32**, 1061.
10. Farber, S. J., Earle, D. P., Jr., and Pellegrino, E. D., Unpublished data.
11. Groen, J., Willebrands, A. F., Kamminga, Chr. E., Van Schothorst, H. K., and Godfried, E. G., Effects of glucose administration on the potassium and inorganic phosphate content of the blood serum and the electrocardiogram in normal individuals and in non-diabetic patients. *Acta med. Scandinav.*, 1952, **141**, 352.
12. Cantarow, A., and Trumper, M., *Clinical Biochemistry*, ed. 4, Philadelphia, W. B. Saunders Co., 1950, p. 18.
13. Birchall, R., Tuthill, S. W., Jacobs, W. S., Trautman, W. J., Jr., and Findley, T., Renal excretion of water, sodium and chloride. Comparison of the responses of hypertensive patients with those of normal subjects, patients with specific adrenal or pituitary defects, and a normal subject primed with various hormones. *Circulation*, 1953, **7**, 258.
14. Thorn, G. W., *Proc. of the First Clinical ACTH Conference*. Mote, J. R., ed., Philadelphia, Blakiston, 1950, p. 102.