Limitations of diuretic therapy in the management of severe toxemia

The significance of hypoalbuminemia

THOMAS H. BREWER, M.D.
Miami, Florida

THE present treatment of severe toxemia of pregnancy is symptomatic and inadequate. It is based on four principles: sedation, reduction of blood pressure, sodium restriction, and promotion of diuresis. The advent of potent, easily administered diuretics has somewhat obscured a fundamental observation that women with severe pre-eclampsia and eclampsia have a significant reduction in blood and plasma volumes.[1, 2, 3] This is associated clinically with hemoconcentration evidenced by a high hematocrit. The hemoconcentration may be *masked* because so many of these women have a nutritional anemia of pregnancy; a hematocrit of 38 or 40 then will represent significant reduction in plasma volume for these women. Dieckmann[4] clearly interpreted a rising hematocrit as a bad prognostic sign in severe toxemia and used hypertonic glucose in an attempt to correct the hemoconcentration and to expand plasma volume.

When edema accompanies severe toxemia, the clinician often institutes symptomatic therapy aimed somewhat blindly at the "edema." Many medical students have asked me what harm the edema fluid does. I find this an intriguing question and usually answer that the presence of edema only reflects a disturbed metabolism, a potentially dangerous state. When marked generalized edema and a contracted plasma volume occur together, we are presented with a most perplexing picture, for these women are actually dehydrated into their own interstitial spaces. Any therapy which results in a further reduction of the plasma volume by renal excretion of water, sodium, and potassium without the concomitant mobilization of interstitial water and electrolytes will be hazardous to these patients. Such therapy can lead to hypovolemic shock, marked reduction in renal function associated with a decrease in renal blood flow, and potential damage to all vital organs.

This paper presents 3 cases of severe toxemia in which chlorothiazide and mercurial diuretics were used with poor responses. We have observed at least 6 such patients in the past year.

From the Department of Obstetrics-Gynecology, University of Miami School of Medicine, Jackson Memorial Hospital.

Case reports

Case 1. V. R., a 25-year-old gravida iii, para 0, of 34 weeks' gestation, was admitted to Jackson Memorial Hospital, April 15, 1960, from a county clinic because of massive edema associated with a 12 pounds weight gain in 11 days. The blood pressure was 184/104 with 4-plus proteinuria. She had had ankle edema for 3 weeks and headaches throughout pregnancy. On 3 previous prenatal clinic visits, the blood pressure had been borderline, 118/90 on March 11, 118/84 on March 25, and 122/88 on April 1, but there was no proteinuria. On March 25, she had been advised to go on a 1,000 calorie diet. For 2 weeks prior to admission, she had eaten

practically nothing because of a reactive depression caused by her mother's death. On April 1, she was started on 250 mg. chlorothiazide, orally, per day.

This patient was 4 feet, 10 inches tall and weighed 182 pounds. She had massive generalized edema. The blood pressure was 170/110, temperature normal, pulse, 80; respirations, 20. The heart and lungs were normal. The estimated fetal weight was 2,200 grams and fetal heart tones were normal.

Laboratory data on admission. Hemoglobin level was 13.4; hematocrit, 43; urinalysis, 960 mg. per cent protein, 5 to 15 white blood cells per high-power field (centrifuged specimen) and many hyaline casts; blood urea nitrogen level, 11.9 mg. per cent; serum uric acid, 8.1 mg. per cent; alkaline phosphate, 6.1 Bodansky units; serum sodium 139; potassium 4.5; and carbon dioxide combining power, 15.5 mEq. per liter. On the fourth hospital day total serum protein was 4.42 Gm. per cent; with albumin, 1.38 Gm. per cent; and globulins, 3.04 Gm. per cent, by serum protein electrophoresis.

The patient was treated initially with intravenous chlorothiazide, pentobarbital, diphenylhydantoin, and intramuscular magnesium sulfate. The diuretics she received each 24 hours from April 15 through April 20, were chlorothiazide 250 mg., 500 mg., 500 mg., 250 mg., 750 mg., and 500 mg. plus meralluride, respectively. Her blood pressure remained 140 to 150/90 to 100. Because diuretics were ineffective in mobilizing the edema fluid, they were discontinued on the fifth hospital day and 1,000 c.c. 5 per cent mannitol was administered. This osmotic diuretic brought about a moderate increase in urinary output but the patient remained massively edematous. Serum sodium dropped from 138 mEq. per liter on admission to 128 the next day, to 132 on the third day, and to 131 on the fifth day.

Several attempts were made to induce labor with oxytocin drip but all were unsuccessful. On the tenth hospital day, during an oxytocin induction, the fetal heart tones dropped to 90 and a cesarean section was done immediately with delivery of a healthy 2,350 gram premature infant who survived. Marked diuresis began within 2 hours following delivery.

The postoperative course was complicated by fluctuating diastolic hypertension for a week post partum and a urinary tract infection which responded to chloramphenicol. The patient was discharged asymptomatic on the ninth postoperative day with normal blood pressure. On a follow-up visit to the clinic on the twenty-first day, her blood pressure was 130/76.

Case 2. C. H., a 19-year-old primigravida, was transferred to Jackson Memorial Hospital on July 21, 1960, at 38 weeks' gestation, with a history of generalized edema for 4 weeks and severe headaches and epigastric pain for several days. She had been admitted to a smaller county hospital 2 days previously because of a convulsion on July 19. On 2 prenatal visits, in February and April, 1960, the blood pressure had been normal and the urine negative for protein. She failed to return for regular prenatal care. The total weight gain was 59 pounds.

On July 19, the blood pressure was 200/150, the weight 288 pounds, and there was marked generalized edema. She had another convulsion after admission to the county hospital that day. The urine showed 4-plus protein and the blood urea nitrogen level was 15.0 mg. per cent. She was treated with intramuscular hydralazine, oral chlorothiazide, and phenobarbital, and a 400 mg. low-sodium diet. On July 20, the urinary output was only 600 ml. with an intake of 4,613 ml. (Table I). The patient was transferred to our hospital on July 21 with a blood pressure of 178/124. She was grossly obese and edematous; temperature, normal; pulse, 110; respirations, 28. The heart and lungs were clear. The estimated fetal weight was 2,400 grams and fetal heart tones were normal.

Laboratory data on admission. Hemoglobin level was 12.8; hematocrit, 38.5; urinalysis, 10 to 12 white blood cells per high-power field (centrifuged) and 350 mg. per cent protein; blood urea nitrogen level, 28.8 mg. per cent; serum uric acid, 14.4 mg. per cent; creatinine, 2.0 mg. per cent; SGOT, 36 units, total serum proteins, 4.46 Gm. per cent with 1.98 Gm. per cent albumin and 2.48 Gm. per cent globulins by electrophoresis.

The patient was treated with intravenous chlorothiazide, morphine, hydralazine-cryptenamine drip, and intramuscular magnesium sulfate. The blood pressure came down to 150 to 160/90 to 100 and the urinary output on the first day was considered adequate. Table I presents the data of the fluid flow sheet and pertinent follow-up laboratory studies.

Oxytocin induction was attempted unsuccessfully on July 22, the second hospital day, and again on July 23 after artificial rupture of the

Table I. Diuretic therapy and laboratory data (Case 2)*

Diuretic (24 hr. dose)	*Urinary output (ml.)*	*Intake (ml.)*	*Date*	*BUN (mg. %)*	*Na-K-Cl (mEq./L.)*	*Others*
Chlorothiazide, 1.0 Gm., orally	1,350	2,600	7/19/60	15		
Chlorothiazide, 1.0 Gm., orally	600	4,613	7/20			
Chlorothiazide, 0.5 Gm., orally 0.5 Gm., intravenously	2,005	3,440	7/21			Hct. 41
Chlorothiazide, 1.0 Gm., intravenously	1,655	2,175	7/22	28.8	140-4.0-101	Creatinine 2.0 mg. %
Chlorothiazide, 1.0 Gm., intravenously Hydrochlorothiazide, 50 mg., orally	855	4,325	7/23	46.3	134-4.35-98	
Chlorothiazide, 0.5 Gm., intravenously Meralluride 2.0 c.c., intravenously	2,675	2,325	7/24	53.5	125-4.0-95	Hct. 41
Chlorothiazide, 0.25 Gm., intravenously	285	1,700	7/25		126-4.96-95.8	Hct. 40

*Patient died at 7:28 P.M. with massive generalized edema persisting.

membranes at 10:50 A.M. Fetal heart tones became irregular at 2:25 P.M. and no longer audible after 5:45 P.M., July 23.

On July 24, the blood pressure ranged from 230/110 to 190/80 and the patient was digitalized because of tachycardia. Oxytocin drip was again unsuccessful and the patient developed a low-grade temperature elevation of 101.6° F. (rectal) at 10:00 P.M. She was started on intramuscular tetracycline. She was given morphine and magnesium sulfate throughout the hospital course.

On July 25, the fifth hospital day, oxytocin drip was given from 8:25 A.M. until noon at which time the blood pressure suddenly dropped from 190/110 to 90/60 and she became comatose. A phenylephrine drip was begun and at 3:00 P.M., a levarterenol bitartrate drip was set up. The blood pressure then was 140/90 with marked reduction in urinary output. A diagnosis of ruptured uterus was made and, at 6:30 P.M., a cesarean section without anesthesia was done on a moribund patient. A stillborn infant was delivered. The uterus was intact but would not contract and appeared grossly infected, so a subtotal hysterectomy was performed. The patient died in profound shock at 7:28 P.M., immediately postoperatively.

Autopsy revealed a grossly obese woman with massive edema. There were 200 ml. of serous fluid in each pleural space. The lungs showed pulmonary edema. The liver was enlarged (3,050 grams) and pale with a yellow-tan discoloration; there were small petechial hemorrhages scattered over the subdiaphragmatic surfaces. The kidneys were enlarged (250 grams and 270 grams) and appeared edematous. The adrenals were normal. The brain showed a small area of subarachnoid hemorrhage over the parietal region of the left cerebral hemisphere.

Histologic study of the kidneys revealed the glomeruli to be somewhat enlarged with a thickening of the capillary tufts characteristic of "membranous glomerulonephritis" often associated with eclampsia. The liver showed patchy areas of subcapsular hemorrhage with disruption of normal architecture and necrosis of scattered individual cells in the areas of hemorrhage which were not confined to the periportal regions. Most of the liver appeared normal except for generalized edema. The adrenals were normal. Sections of the umbilical cord of the fetus showed no perivascular cellular infiltrations. A blood culture drawn from the heart at autopsy produced a micrococcus, coagulase negative. There was no gross or microscopic evidence of significant infection.

Case 3. G. G., 36-year-old gravida iii, para 0,

of 30 weeks' gestation, was admitted to our emergency room on Sept. 5, 1960, because of convulsions and possible head injury on that day. She had made 4 prenatal visits to a county clinic where the blood pressure had been normal and no proteinuria found on the first 3 visits. On the last visit, August 8, 4 weeks prior to admission, the blood pressure was 100/76; voided urine showed a trace of protein, and the hemoglobin level was 10.2 Gm.

On admission to the emergency room, the right eye and face were contused; she was disoriented and lethargic, the tongue swollen and edematous. The blood pressure was 196/136; temperature, 99° F. (rectal); pulse, 140; and respirations, 20. There was pitting edema of both lower extremities to the knees. Deep tendon reflexes were hyperactive with ankle clonus. While skull films were being made, the patient had a generalized grand mal seizure which was controlled with intravenous sodium amobarbital. Skull films and neurological examination revealed no evidence of central nervous system injury (a radiologist observed in his report that skull films were incomplete). The lungs were clear, and the heart normal except for tachycardia. The fetal heart tones were normal and the estimated fetal weight was 1,200 grams.

Laboratory data on admission. Hemoglobin level was 13.2 Gm.; hematocrit, 43; urinalysis, 500 mg. per cent protein, 10 to 15 white blood cells per high-power field (centrifuged), 3 to 12 red blood cells, a few hyaline and granular casts; serum sodium, 133, potassium, 3.5 (8 hours after admission), carbon dioxide combining power, 11.2, chlorides, 99 mEq. per liter; nonprotein nitrogen, 19 mg. per cent; blood urea nitrogen level, 7.6 mg. per cent; total serum proteins, 5.0 Gm. per cent with 1.94 Gm. per cent albumin and 3.04 Gm. per cent globulins by electrophoresis.

A chest x-ray was normal and an electrocardiogram was borderline with slight S-T depression "probably secondary to rate."

On the labor unit, the patient was treated with intravenous chlorothiazide, sodium amobarbital, diphenylhydantoin, intramuscular magnesium sulfate, and nasal oxygen. Table II indicates the diuretic therapy and charges in serum electrolytes. The blood pressure came down to 125 to 130/100 to 110 with a very narrow pulse pressure and a persistent tachycardia of 130 to 140. The urinary output for the first 16 hours was 1,510 with an intake of 1,495; a venous cutdown was done.

At 2:00 P.M., September 6, 16 hours after admission, the patient went into shock with a weak thready pulse and systolic pressure barely palpable at 80 mm. Hg; she was cold and clammy and in deep coma with no urinary output for over 45 minutes (Fig. 1). At 3:00 P.M., she was given 15 Gm. of salt-poor human serum albumin by push intravenously over a 20 minute period and 10 Gm. more was dripped in thereafter. Within 8 minutes after the beginning of this injection, the blood pressure had risen to 118/96 and urine was seen dripping freely from the catheter. Within 45 minutes, the output was 175 ml. urine, in the next hour it was 330 ml., and the next hour 330 ml. In the 16 hour period following the onset of shock, she received 50 Gm. of salt-poor human serum albumin, had an intake of 2,170 ml. of intravenous 5 per cent glucose and excreted 2,858 ml. of urine; this urine contained only a "trace" of protein. The edema visibly decreased during this time. At the end of the 16 hour period, the hemoglobin had dropped from 13.4 to 8.4 Gm. and hematocrit

Table II. Diuretic therapy and serum electrolytes (Case 3)

Date	*Time*	*Diuretic*	*Na (mEq./L.)*	*K (mEq./L.)*	*Cl (mEq./L.)*	*CO_2 combining power (mEq./L.)*
9/5/60	10:50 P.M.	Chlorothiazide, 500 mg., intravenously			99.2	11.2
9/6	5:00 A.M.	Chlorothiazide, 500 mg., intravenously	133	3.5		19.7
9/7			134	3.0	99.2	
9/8			137	4.0		
9/9			129	5.0	97.5	20.6
9/10	Delivery					
9/11			138	5.0	106	18.4

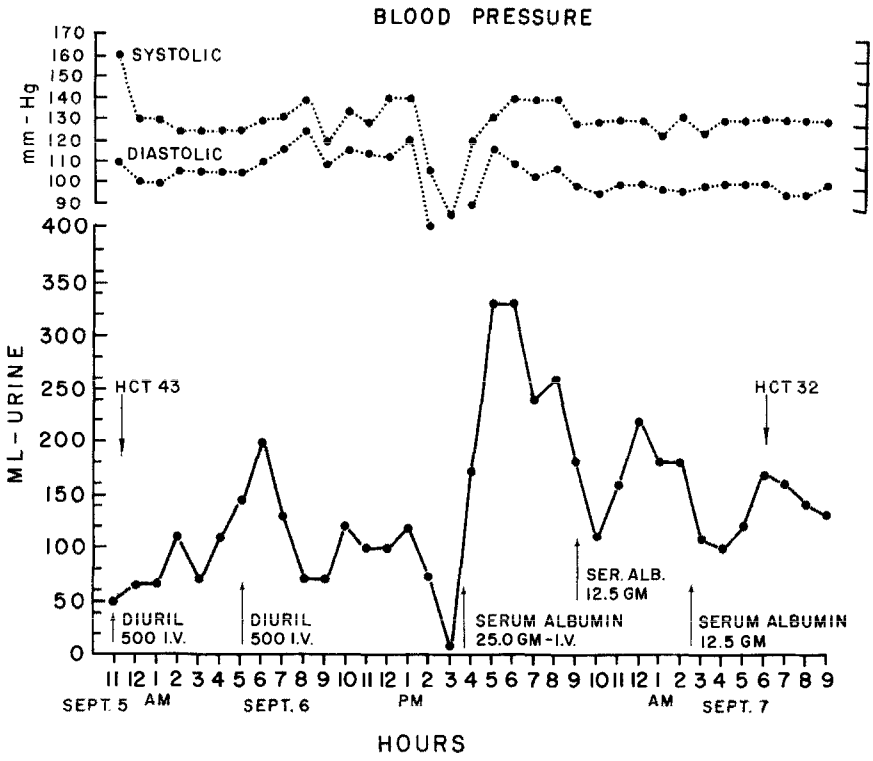

Fig. 1. Case 3. Urinary output by hours, response to intravenous chlorothiazide and human serum albumin in eclampsia.

from 43 to 32. The pulse slowed to 108 to 112 and blood pressure was stabilized at 130/100 for 38 hours and the output was good. A 24 hour urine specimen, collected from 7:00 A.M., September 6, to 7:00 A.M., September 7, contained 191 mEq. sodium, 20 mEq. potassium, and 174 mEq. chloride.

On September 8, the third hospital day, the blood pressure had risen to 150/110 at 8:00 A.M. and she was started on a hydralazine cryptenamine drip. The pulse increased to 120 and urinary output dropped to 50 ml. from 9:00 to 10:00 A.M. She was given, by slow drip, 12.5 Gm. serum albumin at 10:00 A.M. and output increased to 120, 175, and 150 ml. in the next 3 hours. About 1:30 P.M., the patient had an episode of acute bronchospasm and pulmonary edema but responded quickly to treatment with oxygen, rotating tourniquets, intravenous morphine, and aminophylline. She was given digitalis intramuscularly.

On September 9, the fifth hospital day, at 2:00 P.M., she had another episode of bronchospasm without pulmonary edema; this was preceded by a blood pressure elevation to 160/115 for which she received the intravenous hydralazine cryptenamine drip with a subsequent drop to 90/70 and oliguria which lasted for 14 hours. A blood culture done at this time was later reported to be growing *Escherichia coli;* the diagnosis of septicemia was deemed unlikely. At 9:30 P.M., she was started on intravenous chloramphenicol because of pyuria and evidence that cut-down sites were becoming infected. From 7:00 P.M. until 4:00 A.M., the next day, the total urinary output was 70 ml.; at this time she went spontaneously into labor. The fetal heart tones could no longer be heard. At 6:35 A.M., on September 10, she was delivered of a 1,600 grams stillborn infant; the urinary output immeditely rose to 100 to 200 ml. hour. In the 24 hours following delivery, the urinary output was 4,410 ml. with intake of 2,450 ml.

Post partum, the patient had a difficult course complicated by a *Staphylococcus aureus* enterocolitis for which she received neomycin orally. The hemoglobin level dropped to 7.8 Gm. and she was given 500 ml. of whole blood. The cut-down sites healed slowly and she developed phlebitis of the entire greater saphenous vein in

the left leg. The blood pressure remained 150 to 160/90 to 100 for 3 days and then came down to 140/90. She slowly improved and was discharged on the seventeenth postpartum day asymptomatic. On a clinic visit 2 weeks later, she was doing well and the blood pressure was 110/80.

Comment

A significant finding in these patients, and many others with toxemia we have recently observed, is a marked lowering of serum albumin concentrations determined by serum protein electrophoresis. Mack[5] published an informative monograph on the plasma proteins in normal and toxemic pregnancy. He found that a significant reduction in albumin concentrations is commonly encountered in severe toxemia. Many investigators have published similar observations.[6, 7] The significance of these low albumin levels is further emphasized by the fact that these women have a contracted plasma volume; these are hemoconcentrated values and indicate that the total circulating albumin in these women is markedly reduced.

Strauss[8, 9] discussed the role of lowered serum protein osmotic pressure in the edema of toxemia of pregnancy. Obstetricians have generally neglected his work. Dieckmann[10] concluded: "There are no intrinsic changes in the serum proteins which might account for the edema." The recent more accurate determinations of serum protein components by electrophoresis have revealed that albumin concentrations are significantly lower than indicated by the older salt fractionation methods. It is time to reopen the question of the role that low serum proteins, especially low serum albumin, plays in the pathogenesis of the edema and hypovolemia of severe toxemia.

Table III presents the serum protein colloid osmotic pressures in these 3 women calculated by the formula of Wies and Peters, in Dieckmann.[10] These values are low; it is generally agreed that a colloid osmotic pressure below 20 cm. of water is nearly always associated with edema.[11] We now have a clear concept of why diuretics acting only on the kidneys are of limited value in mobilizing the interstitial edema fluid in these severely protein-depleted women. We can also infer that any diuresis obtained by the use of these agents will threaten the integrity of the plasma volume by causing excretion of water and electrolytes which cannot be adequately replaced from the interstitial space and hence cause further reduction in plasma volume. The observed reductions in serum sodium in these patients is further evidence that sodium remains in the interstitial space. This hazard is further enhanced by restricting the patient's intake to glucose and water.

It appears reasonable that the administration of human serum albumin is indicated to restore the colloid osmotic pressure of the serum toward normal and to correct hypovolemia in women with severe toxemia of pregnancy. Since serum albumin has several other important physiologic roles, such as transporting amino acids to the peripheral tissues, helping to maintan the blood pH, binding anions, hormones, and organic compounds, its theoretic value is enhanced. Case 3 showed a dramatic response to intravenous human serum albumin with diuresis and hemodilution following immediate recovery from shock and its associated anuria.

The improvement of renal function which occurs immediately after delivery is worthy of note. It suggests that a mechanical factor

Table III. Calculated serum protein colloid osmotic pressure

Case No.	*Total serum proteins (Gm. %)*	*Albumin (Gm. %)*	*Globulin (Gm. %)*	*Colloid osmotic pressure (cm. water)*
1	4.42	1.38	3.04	12.0
2	4.46	1.98	2.48	14.0
3	5.00	1.94	3.04	14.6

may be in operation for, when the placenta is removed, a considerable amount of each cardiac stroke, which had previously been shunted through the placental site, becomes available for systemic and renal flow. Delivery would be analagous to a blood transfusion and would immediately expand the effective blood volume. de Alvarez[12] has shown renal plasma flow to be reduced as much as 50 per cent and glomerular filtration rate 25 to 30 per cent in severe toxemia. Crosley and associates[13] have pointed out that chlorothiazide administered intravenously in doses as low as 0.7 mg. per kilogram produces a significant reduction in renal plasma flow and glomerular filtration rate related to a fall in cardiac output secondary to decreased venous return. Such effects are not desirable in the severely toxemic patient. The blood urea nitrogen is normal or low in nearly every patient on admission to the hospital; it is only after therapy that they develop evidence of urea retention which is undoubtedly related to reduction in renal blood flow. Schulman[14] recently reported a fatal case of severe toxemia in a patient with a hydatid mole and raised the question of the role that diuretic therapy may have played in the development of the prerenal azotemia.

Winshel,[15] at the recent Hahnemann symposium on salt and water retention, concluded his paper with the following statements which require considerable modification in light of our experience: "It would appear that once a patient is placed on diuretic therapy with chlorothiazide or hydrochlorothiazide, she might well require treatment for the remainder of her pregnancy. The absence of significant toxicity or electrolyte disturbance makes this practical."

Fallis and Ford[16] have recently discussed the limitations of chlorothiazide therapy in liver disease and pointed out that some patients' conditions have been made worse by it. In the management of severe pre-eclampsia and eclampsia, there is a possibility that the liver function may be significantly impaired. It is of fundamental importance to evaluate each individual toxemic patient as thoroughly as possible and constantly to re-evaluate her condition as each day passes. The role of serum albumin in maintaining plasma volume must be remembered.

Summary

1. Three cases of severe toxemia are presented because the patients failed to respond favorably to therapy with the diuretics, chlorothiazides and mercurials.

2. A significant reduction in serum albumin occurred in these patients and the calculated serum protein colloid osmotic pressures were markedly reduced.

3. All 3 patients failed to mobilize a significant amount of the interstitial edema fluid; 2 developed shock and one died.

4. One patient in shock had a dramatic response to intravenous human serum albumin.

Conclusions

In severe pre-eclampsia and eclampsia, associated with a contracted plasma volume, hemoconcentration, depleted serum albumin, and generalized edema, diuretics must be used with extreme caution. The administration of human serum albumin, to restore serum protein, colloid osmotic pressure, and expand plasma volume, has shown great promise in one case and is being further investigated.

REFERENCES

1. Dieckmann, W. J.: Am. J. Obst. & Gynec. **32:** 927, 1936.
2. Freis, E. D., and Kenny, J. F.: J. Clin. Invest. **27:** 283, 1948.
3. Berlin, N. I.: Surg. Gynec. & Obst. **94:** 21, 1952.
4. Dieckmann, W. J.: The Toxemias of Pregnancy, St. Louis, 1952, The C. V. Mosby Company, p. 85.
5. Mack, H. C.: The Plasma Proteins in Pregnancy, Springfield, Ill., 1955, Charles C Thomas, Publisher.
6. MacGillivray, I., and Tovey, J. J.: J. Obst. & Gynaec. Brit. Emp. **64:** 361, 1957.

7. Patton, J. B., et al.: M. J. Australia **1:** 108, 1954.
8. Strauss, M. B.: Am. J. M. Sc. **190:** 811, 1935.
9. Strauss, M. B.: AM. J. OBST. & GYNEC. **38:** 199, 1939.
10. Dieckmann, W. J.: The Toxemias of Pregnancy, St. Louis, 1952, The C. V. Mosby Company, p. 106.
11. Fishberg, A.: Hypertension and Nephritis, Philadelphia, 1954, Lea & Febiger, pp. 152-159.
12. de Alvarez, R. R.: In Mayer, J. H., and Fuchs, M.: Edema Mechanisms and Management, Philadelphia and London, 1960, W. B. Saunders Company, pp. 423-432.
13. Crosley, A. P., et al.: J. Lab. & Clin. Med. **55:** 182, 1960.
14. Schulman, H.: AM. J. OBST. & GYNEC. **80:** 180, 1960.
15. Winshel, A. W.: In Mayer, J. H., and Fuchs, M.: Edema Mechanisms and Management, Philadelphia and London, 1960, W. B. Saunders Company, pp. 458-466.
16. Fallis, N. E., and Ford R. V.: New England J. Med. **263:** 296, 1960.