Ethacrynic Acid

Effectiveness and Mode of Diuretic Action in Man

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Ethacrynic acid is an unsaturated ketone derivative of phenoxyacetic acid, chemically different from other known diuretic agents. Compounds of this general class have a significant ability to bind sulfhydryl groups in vitro. Ethacrynic acid was shown by Baer and associates to be highly effective as a diuretic in the dog, but not in the rat. A preliminary report from this laboratory indicated that the compound was a highly potent natriuretic and diuretic agent in man. This study also suggested that ethacrynic acid had a unique mode of action in the nephron.

In the present communication results of a 2-year experience with ethacrynic acid are reported. During this period ethacrynic acid was found to produce effective natriuresis and diuresis in a study of 82 patients, many of whom had edema which was refractory to treatment with other diuretic agents. The results of a series of investigations designed to explore some of the mechanisms by which the compound alters electrolyte excretion and acid-base balance are also reported.

Methods

Fifteen normal volunteers and 67 patients selected from the medical wards of the Presbyterian Hospital participated in the study. The diagnoses of the patients appear in table 1. Eighteen individuals were studied on the medical wards of...
Comparison of ethacrynic acid to mercuhydrin and to chlorothiazide. The natriuretic response to ethacrynic acid exceeded that to the other agents and was additive when administered in combination with either.

Figure 3
Potentiation of a carbonic anhydrase inhibitor by ethacrynic acid. In two subjects with congestive heart failure the natriuretic response to the administration of ethacrynic acid and acetazolamide together exceeded the sum of the responses to the two drugs when administered individually.

Results
Effectiveness and Spectrum of Response
Figure 1 presents the urinary excretion rates of sodium, potassium, and chloride during a
48-hour period of drug administration to eight patients with heart failure and to seven patients with cirrhosis and ascites. Many of these patients had edema which was unresponsive to conventional diuretic therapy, and all had control urinary Na⁺ excretion rates less than 10 mEq./day. Two of the eight cardiac patients excreted more than 1,000 mEq. of sodium during the 2-day treatment period, illustrating the great potency of the drug. Also, ethacrynic acid permitted mobilization of edema fluid in 17 patients who had been refractory to all other measures.

The diuretic response pattern to a given dose (200 mg.) of ethacrynic acid varied greatly from patient to patient (fig. 1), but the effectiveness of the compound remained relatively constant in a given patient. In general patients refractory to this drug were also refractory to all other agents. Chloride and sodium ions comprised the major increment in urinary electrolyte excretion along with variable amounts of potassium.

Comparison with Other Diuretic Agents and Effect of Combined Therapy

In figure 2, the diuretic effect of ethacrynic acid is compared to that of mercuhydrin and to that of thiazide diuretics in several patients. Ethacrynic acid induced a greater natriuresis and diuresis than the other diuretics. Furthermore, its diuretic effects were found to be additive to those produced by

![Graph of urinary electrolyte excretion and weight changes over time](image)

**Figure 4**

Effect of prolonged administration of ethacrynic acid to a patient with congestive heart failure and massive edema. Natriuresis declined with continuous administration but was restored by intermittent therapy. The study also illustrates that a natriuretic-diuretic response could be obtained in a hyponatremic patient with serum sodium concentration rising as diuresis was effected. Prolonged administration induced hypokalemia, hypochloremia, and alkalosis.

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patients indicated that the diuretic response to ethacrynic acid diminished with continuous therapy, but was effectively restored by intermittent therapy, a phenomenon characteristic of other diuretics. This is illustrated by the study graphed in figure 4, which also demonstrates that edema fluid could be mobilized in patients with significant hyponatremia and hypochloremia.

Effect on Blood Pressure

Ethacrynic acid had no hypotensive effect in two patients with hypertension secondary to chronic pyelonephritis. In six patients with essential hypertension the administration of 100 to 200 mg. of ethacrynic acid daily for 6 to 10 days produced a moderate lowering of blood pressure, which in no instance exceeded 20 per cent of control levels.

Effect in Renal Clearance Studies

Figure 5 summarizes the results of six renal clearance studies in which ethacrynic acid was administered during maximal water diuresis. The diuretic produced little change in glomerular filtration rate (inulin clearance) or in renal plasma flow (PAH clearance), while causing large increases in the excretion rates of sodium and chloride along with smaller increments in potassium output. The resulting sharp rise of the ratio of sodium clearance to inulin clearance indicated that the drug acted to inhibit the renal tubular reabsorption of sodium.

The large rise in urine volume and total solute output that occurred after intravenous ethacrynic acid was associated with a mean increase in osmolar clearance of 15.1 ml. per minute. The calculated clearance of osmotically free water \( C_{H_2O}^F \) fell by a mean of 3.9 ml. per minute. In five other studies in which ethacrynic acid was administered intravenously during maximal antidiuresis, comparable increases in urine volume and osmolar clearance were observed concomitant with a fall in the \( T'_H_2O \) to levels approaching 0.

Ethacrynic acid increased chloride excretion more than sodium excretion (fig. 5). This might suggest that the diuretic acts primarily
to block chloride reabsorption. However, calculations from a representative study summarized in table 2 suggest an alternative hypothesis to explain the excessive chloride loss, namely, that ethacrynic acid may block the renal tubular transport system for Na⁺ (with Cl⁻) proximally, and that subsequently some of this rejected Na⁺ is reabsorbed in exchange for K⁺ or H⁺ or both in more distal portions of the nephron. Total sodium reabsorption by the renal tubules fell after ethacrynic acid (table 2); nevertheless the amount of sodium reabsorbed without chloride (i.e., the Na⁺ reabsorbed by ion exchange) actually increased after the diuretic. The increase in the reabsorption of “Na⁺ without Cl⁻” exceeded the excess of chloride over sodium excreted in the urine. This therefore suggests that the diuretic acts predominantly to block NaCl reabsorption, but because it does not interfere with ion exchange mechanisms less sodium than chloride reaches the final urine.

Effect on Uric Acid

Intravenous ethacrynic acid had a variable effect upon urate excretion (fig. 6), but in most subjects uric acid clearance increased. However, more prolonged oral administration of ethacrynic acid produced hyperuricemia and diminished uric acid excretion in some patients. This dual influence is similar to that observed after chlorothiazide suggesting that with ethacrynic acid, too, the lower blood levels of oral administration may inhibit the net tubular secretion of uric acid whereas the higher blood levels of intravenous administration may suppress uric acid reabsorption and mask the concurrent effect on secretion.

Effect on Aldosterone Secretion

Typical effects of ethacrynic acid upon the adrenal secretion rate of aldosterone appear in table 3. In three normal subjects and in one patient with essential hypertension the administration of this diuretic for several days induced a significant rise in aldosterone secretion. In two of these patients aldosterone secretion after ethacrynic acid rose even above the high control levels that had been
produced by administration of a low-sodium diet. However, the response of two patients with congestive heart failure differed; in one, diuresis induced little change in aldosterone and in the other aldosterone secretion actually fell after diuresis, as cardiac compensation was improved by loss of edema.

**Endogenous Aldosterone as a Major Determinant of Potassium Excretion after Ethacrynic Acid**

The kaliuresis induced by ethacrynic acid may be secondary to (1) inhibition of potassium reabsorption in the proximal tubules or (2) increased potassium secretion (via ion exchange for sodium) in distal portions of the nephron.

Data from two studies indicated that the kaliuresis observed after ethacrynic acid probably occurs by increased distal $K^+$ secretion in exchange for sodium under the influence of aldosterone (fig. 7). Thus ethacrynic acid failed to cause a rise in potassium excretion during natriuresis and diuresis of an adrenalectomized subject and in another subject maintained on an aldosterone antagonist. But significant increments in urinary

![Figure 6](http://circ.ahajournals.org/)

**Figure 6**

Effect of intravenous ethacrynic acid upon the renal clearance of uric acid. Each point represents the average of three consecutive 10-minute control or experimental periods.

![Figure 7](http://circ.ahajournals.org/)

**Figure 7**

Influence of adrenal mineralocorticoid upon the kaliuretic effect of ethacrynic acid.

**Table 3**

<table>
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<th>Diagnosis</th>
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<th>Diet</th>
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<th>Aldosterone (μg./24 hr.) After</th>
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potassium after ethacrynic acid were observed in these same two subjects when large amounts of adrenal mineralocorticoid were given to the former and when spironolactone was discontinued in the latter.

Figure 8 shows that the ratio of potassium to sodium excretion after ethacrynic acid correlated directly with the patients' aldosterone secretion rate; this occurred despite the fact that the patients had a variety of diseases, received dissimilar amounts of dietary sodium and responded with differing degrees of natriuresis. Taken together with the other two types of study (fig. 7), these data indicate that the urinary K⁺ output via Na⁺-K⁺ exchange after ethacrynic acid is determined to a major degree by the concurrent endogenous aldosterone activity.

**Extracellular Alkalosis and Compensatory Hypoventilation after Prolonged Treatment**

Prolonged administration of ethacrynic acid led to the development of alkalosis of the extracellular fluid in both normal subjects and in patients with edema. In figure 9 data are presented from studies of six normal volunteers who received the drug for from 3 to 7 days consecutively while on constant 250 mg. (four subjects) or 5 Gm. (two subjects)
daily salt intakes. In all subjects diuresis with ethacrynic acid increased arterial blood pH, bicarbonate concentrations and pCO₂ levels.

Alveolar ventilation declined.* This pattern indicates that the metabolic alkalosis produced by the drug was accompanied by a compensatory alveolar hypoventilation.

**Figure 10**

Relationship of K⁺ depletion to systemic alkalosis during diuretic therapy. During treatment with chlorothiazide there was a direct relationship between cumulative urinary K⁺ losses and the rise in plasma [CO₂]. However, marked elevations of plasma [CO₂] were observed after ethacrynic acid before significant potassium depletion was apparent.

**Three Mechanisms for Induction of Alkalosis by Ethacrynic Acid**

Three mechanisms have been identified by which ethacrynic acid may induce alkalosis. These are (1) by producing K⁺ depletion, (2) by promoting increased renal excretion of hydrogen ions, and (3) by inducing extracellular fluid space contraction.

**Potassium Depletion as a Cause of Alkalosis**

In potassium depletion shift of hydrogen ions (and to a lesser extent sodium ions) into cells in exchange for lost intracellular potassium has been proposed as a mechanism for the extracellular alkalosis.⁹,¹⁰ That this mechanism may obtain also for diuretic-induced hypokalemia was suggested by balance studies in normal subjects in which the administration of chlorothiazide induced K⁺ loss and extracellular alkalosis with unchanged or decreased net hydrogen ion excretion by the

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*Measurements of ventilation before and at the end of a course of ethacrynic acid were performed by Dr. Roberta Goldring in the laboratory of Dr. A. P. Fishman.
In several such studies a direct relationship between potassium depletion and the resulting alkalosis could be demonstrated after thiazide administration (fig. 10). The fact that in similar studies with ethacrynic acid (fig. 10) systemic alkalosis did not bear such a direct relationship to potassium depletion suggested that mechanisms other than K⁺ loss were involved in the production of the acid-base disturbance.

**Hydrogen Loss as a Cause for Alkalosis**

The effect of ethacrynic acid upon renal acid excretion is illustrated by a study of a normal subject (fig. 11). The daily excretion of NH₄⁺, TA, and HCO₃⁻ are depicted along with the cumulative daily losses of H⁺, K⁺, and weight. In this patient, who is representative of eight others similarly studied, the drug produced a lower urinary pH, no change or a fall in HCO₃⁻ output, and a rise in the excretion rates of ammonium and titratable acid. Thus, total urinary hydrogen ion excretion increased and systemic alkalosis resulted.

**Extracellular Fluid Space Contraction as a Cause for Alkalosis**

The third mechanism by which ethacrynic acid may induce alkalosis has been observed only in patients with edema who responded with a copious diuresis. Balance studies indicated that ethacrynic acid in edematous patients may cause very large urinary losses of sodium chloride and water which are not accompanied by urinary losses of bicarbonate. It can be demonstrated that this loss of non-bicarbonate-containing extracellular fluid results in a contraction of the extracellular fluid space around the amount of extracellular bicarbonate initially present. This raises the plasma bicarbonate concentration, but not the concentration of CO₂ dissolved in extracellular fluid because carbon dioxide escapes via the lungs. Hence, the buffer ratio of bicarbonate to dissolved CO₂ increases and an
alkalosis, related to contraction of the volume of the extracellular fluid, results.

**Persistence of Alkalosis after Ethacrynic Acid: Importance of Chloride to Recovery**

Alkalosis and high blood bicarbonate levels have persisted for several days after discontinuation of ethacrynic acid in both normal subjects and in patients with edema. This persistence of high bicarbonate levels requires an explanation. It does not appear to be due to potassium depletion. In one subject on a low-salt diet (fig. 12) alkalosis persisted for 6 days after therapy was discontinued despite oral K⁺ supplements.

All of the patients who maintained a systemic alkalosis for more than 3 days were retaining salt avidly due to a low-salt diet or heart failure or cirrhosis. All had sustained significant losses of chloride due to therapy. That chloride depletion and hypochloremia may be partly responsible for persistent alkalosis is suggested by a study of patient G.A. (fig. 12). This normal subject remained alkalotic after diuresis with ethacrynic acid as he was maintained on a low-salt diet. However, his arterial blood CO₂ fell rapidly to normal when chloride was supplied in the diet. Similarly, in another study, (fig. 11) when dietary chloride was increased “excess” bicarbonate was rapidly excreted into the urine. This indicates that the repletion of chloride markedly reduced renal excretion of H⁺, which before repletion had persisted at high levels despite a systemic alkalosis.

**Side Effects**

Side effects of ethacrynic acid were anorexia (8), transient azotemia in patients with renal disease (5), and asymptomatic hyperuricemia (8). Excessively rapid diuresis in one cardiac patient produced orthostatic hypotension, and massive diuresis in two cirrhotic subjects induced hepatic pre-coma and coma, which required electrolyte replacement.

**Discussion**

This study of 82 patients confirms and extends earlier reports³, ⁵, ¹³–¹⁷ that ethacrynic acid is a highly potent natriuretic and diuretic agent in man. The great magnitude of the natriuretic responses to the compound plus the fact that its effects are additive to those of all other diuretics suggest that it will prove most useful in the treatment of patients with refractory edema. The rapidity of onset of its diuretic action and the fact that it can be administered either by mouth or intravenously have established the drug as a useful adjunct in the treatment of pulmonary edema. In addition, it effectively produced diuresis in patients who had a variety of electrolyte disturbances including hypochloremia, hyponatremia, hypokalemia, respiratory acidosis, and metabolic alkalosis. It was also effective in patients with significant degrees of renal insufficiency; this latter feature has recently been studied extensively by Maher et al.¹⁷ The compound also exhibited mild antihypertensive properties in studies of relatively short duration. In more prolonged studies Dollery et al.¹⁵ found ethacrynic acid to have an antihypertensive potency similar to thiazide diuretics.

Whereas the maximally effective single oral dose of ethacrynic acid in man is 4 to 6 mg./Kg.¹⁷ with a duration of action lasting for 6 to 8 hours, the peak dosage chosen for this study was 200 mg. per day usually administered in four divided doses of 50 mg. Since the same diuretic dose may produce from a slight to a massive natriuretic response in different patients, we believe that the sensitivity of each edematous patient who receives this compound should be cautiously determined by a schedule of increasing doses beginning with a single dose of 50 mg. on the first day. Daily dosage can be increased stepwise up to 50 mg. or 100 mg. two to four times daily. Plasma electrolytes should be monitored and the drug should not be given for more than 2 days consecutively until confidence about individual patient responsiveness is gained. With these precautions the consequences of excessively rapid diuresis such as orthostatic hypotension, “contraction” alkalosis, and hepatic pre-coma and coma can be avoided. Like other diuretics the effectiveness of ethacrynic acid tends to diminish with
continuous administration. Therefore edema fluid may be most efficiently mobilized by employing an intermittent dosage schedule in which the drug is given for from 1 to 3 consecutive days. Furthermore, such a schedule may minimize problems of electrolyte imbalance by allowing more time for repletion to occur. However, it must be noted that in certain patients whose response pattern has been established daily therapy with suboptimal doses may also be effective.

The demonstration that the kaliuresis induced by ethacrynic acid probably results from an increased ion exchange of sodium for potassium in the distal nephron under the direct influence of aldosterone has several practical consequences. First, since diuresis generally tends to elevate aldosterone secretion (some cardiac patients being the major exception), it is apparent that prolonged continuous diuretic therapy will favor the production of hypokalemia. Second, a consideration of those situations in which aldosterone secretion is known to be excessive (e.g., low-sodium diet, after prolonged diuretic therapy, cirrhosis with ascites, etc.) will suggest that these are situations in which supplemental K\(^+\) or adjunctive therapy with aldosterone antagonists would be beneficial. Third, since the kaliuresis is in a major degree determined by aldosterone, it can be inhibited by pharmacologic agents, such as spironolactone, which block the action of aldosterone in the kidney.

Since three different mechanisms (urinary K\(^+\) loss, urinary H\(^+\) loss, and extracellular space contraction) may contribute to the production of extracellular alkalosis during diuresis with ethacrynic acid, it is apparent that K\(^+\) supplements alone will not prevent elevation of blood pH if therapy with the agent is continuous. Intermittent drug administration reduces the alkalinizing effect of massive diuresis and also permits homeostatic adjustments for increased H\(^+\) excretion.

Our finding that chloride depletion may be important in the perpetuation of systemic alkalosis because it leads to persistent inappropriate increased renal H\(^+\) excretion perhaps supports the experimental findings of Schwartz et al.\(^{16}\) and Atkins and Schwartz\(^{18}\) in dogs. These workers have presented data which imply that significant renal loss of H\(^+\) (with concomitant increase in HCO\(_3^-\) reabsorption) may continue despite alkalosis and high levels of plasma bicarbonate if the kidneys are both stimulated to retain sodium and then presented with a glomerular filtrate relatively poor in chloride and rich in poorly reabsorbable anion (HCO\(_3^-\)). Such paradoxical renal retention of HCO\(_3^-\) ceased in two studies (figs. 11 and 12) when chloride was supplied in the diet and the concentration of reabsorbable anion (chloride) returned to normal.

The results point to the importance of chloride therapy in correction of alkalosis induced by ethacrynic acid. They imply that (1) hypochloremic alkalosis can be most effectively corrected by administration of chloride (as NaCl or NH\(_4\)Cl by mouth, or saline or arginine monochloride intravenously) and (2) that hypokalemic alkalosis after ethacrynic acid can be most rapidly corrected by giving potassium supplements as the chloride salt rather than as potassium citrate, gluconate, or bicarbonate.

The definition of the role of extracellular fluid space contraction in the production of alkalosis after massive diuresis with ethacrynic acid (through its action to elevate serum bicarbonate to a greater extent than dissolved CO\(_2\) in extracellular fluid) may be of general physiologic interest, since this particular acid base disturbance does not fit traditional definitions of a "metabolic" or a "respiratory" alkalosis. From a practical standpoint elucidation of the role of volume depletion in the production of this alkalosis implies that infusion of saline to expand the volume of extracellular fluid might be an important feature of the therapy to correct alkalosis in patients who may inadvertently have an excessive diuretic response to the drug.

Compensatory alveolar hypoventilation accompanied systemic alkalosis induced by therapy with ethacrynic acid. Due to this respiratory compensation marked elevations of
serum bicarbonate concentration do not necessarily reflect extensive elevations of blood pH. In addition, the compensatory alveolar hypoventilation may, in part, explain the persistence of high blood bicarbonate levels after diuretic therapy was stopped, since an increased pCO₂ is known to raise the renal threshold for bicarbonate excretion.²⁰, ²¹

The effects of ethacrynic acid to decrease both C⁴H₂O and T⁴H₂O in renal clearance studies were interpreted to indicate an action to block sodium reabsorption in the loop of Henle and the distal portions of the nephron. This postulate is consistent with the observations of Goldberg et al.²² who noted reductions of C⁴H₂O and T⁴H₂O after oral administration of ethacrynic acid in man. The prodigious increases in sodium excretion (which exceeded 15 per cent of the filtered sodium in three studies) and the increases in solute clearance that greatly exceeded the amount which could be accounted for by the reduction in free water clearance provided evidence that ethacrynic acid also inhibits sodium reabsorption at sites in the nephron where reabsorption is isosmotic, most likely the proximal tubules. The latter interpretation is in harmony with the findings of Earley and Friedler²³ in dogs. A large action proximally at the site of isosmotic sodium reabsorption is also consistent with the fact that hyponatremia is rarely produced in patients after diuresis with this agent. A direct action on chloride reabsorption has not been completely excluded, but the data presented favor the hypothesis that the drug blocks sodium reabsorption proximally with subsequent exchange of some of the rejected sodium for hydrogen and potassium distally.

Since ethacrynic acid interacts with sulfhydryl groups in vitro and since Kormorn and Cafruny²⁴ have demonstrated that ethacrynic acid reduces the number of histochemically stainable sulfhydryl groups in the proximal and distal tubules of the dog kidney, it is tempting to speculate that the drug acts by interference with a sulfhydryl enzyme system that is involved in the reabsorption of sodium with chloride in the nephron but does not interfere at all or even accelerates the ion exchange systems by which sodium is reabsorbed in exchange for potassium or hydrogen.

Summary

Ethacrynic acid, a chemically different diuretic, has been evaluated in 82 patients. The drug was remarkably potent when administered intravenously (0.5 to 1 mg./Kg.) or by mouth (doses to 50 mg. four times per day). It proved particularly effective in patients with refractory edema, and in edematous states accompanied by azotemia or electrolyte disturbances. Its natriuretic effects added to those of other diuretics and potentiation actually appeared to occur when it was combined with a carbonic-anhydrase inhibitor.

Renal clearance data indicated that ethacrynic acid has a unique mode of action. There was little effect on glomerular filtration or renal plasma flow and its major action was to block sodium and chloride reabsorption probably in both proximal and distal portions of the renal tubules.

Ion exchange mechanisms seemed little affected by the drug because it characteristically increased both hydrogen and potassium ion excretion. In general the degree of induced potassium loss correlated well with the rate of endogenous aldosterone secretion. Furthermore, ethacrynic acid did not cause potassium loss in one adrenalectomized subject nor in another subject pretreated with an aldosterone antagonist.

Diuresis induced by ethacrynic acid was often accompanied by the development of systemic metabolic alkalosis. Factors in the development of this alkalosis were (1) urinary K⁺ loss with hypokalemia, (2) urinary H⁺ loss, and (3) in edematous patients the rapid large loss of relatively HCO₃⁻–free fluid from the extracellular fluid space. The systemic alkalosis was found to be accompanied by compensatory alveolar hypoventilation. These studies of the mechanisms of the alkalosis point to the occasional importance of

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the administration of chloride, of potassium, or of saline as corrective measures.

Diuresis with ethacrynic acid, like other diuretic agents, produced marked increases in the rate of aldosterone secretion of normal subjects. More variable effects were observed in patients with heart disease, possibly because improvement in their circulatory status operated to lower hormone secretion activity.

Ethacrynic acid had effects on urate excretion that resembled thiazide diuretics. Higher blood levels of intravenous administration were uricosuric. Lower blood levels of oral therapy caused renal urate retention and hyperuricemia.

Most of the problems associated with the use of ethacrynic acid appeared to be related more to its pharmacologic potency than to any truly toxic effect. Because of this it is suggested that the sensitivity and response pattern of each patient be determined in stepwise fashion. In most patients with edema an intermittent dosage schedule provides a more efficient diuretic response and allows time intervals for correction of any electrolyte imbalance. If used with a thorough understanding of its pharmacologic effects ethacrynic acid promises to be a most useful agent in the therapy of patients with difficult or refractory edema.

References


"Medicine—A Learned and a Learning Profession"

The medical profession, with its commitment to change, is a learning as well as a learned profession. For centuries, medicine, like the law, relied on the careful observation of actual "cases," and the cautious trial of new methods to see whether they might "work." Advance was agonizingly slow with this "trial and error" learning method; but more recently, medicine, along with other useful arts, has based its learning on a changed scientific approach to its problems. Because of this new approach, and in order to understand contemporary medicine more clearly, it is necessary for us to pause for a moment and glance at Science—the moving force in the modern world which, in the present century, has reached a stature justifying its identification as the fourth learned profession.—Introduction, Edward D. Churchill, M.D. Listen to Leaders in Medicine. Edited by Albert Love and James Saxon Childers. Atlanta, Tupper and Love, Inc., 1963, p. 5.
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