Thomas Addis and the Dietary Treatment of Kidney Disease
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Thomas Addis was a physician-scientist with a distinctively quantitative and rigorous approach to clinical problems. His name is associated with the study of kidney function and structure-function correlation, and to the diagnosis and dietary treatment of the class of kidney disorders once collectively known as Bright's disease. During his life he developed a national and international reputation as a result of his research and his success in treating patients. His approach to diagnosis and treatment, however, never came into widespread clinical use and fell into almost total disuse in the United States soon after his death. In the last decade, the application of dietary therapy in renal disease has enjoyed a renaissance and Addis' work is being rediscovered and appreciated once more. A biographical memoir on Dr. Addis, from which parts of this article are drawn, is currently in press.¹

Addis published over 130 scientific and clinical papers, as well as two important books (The Renal Lesion in Bright's Disease, with J. R. Oliver, and Glomerular Nephritis: Diagnosis and Treatment). A complete bibliography appears at the end of this article. Almost his entire career was spent on the faculty of the Department of Medicine of the Stanford University School of Medicine. He received the following prizes and lectureships: a Carnegie Research Fellowship, the Gibbs Prize, and in 1942 the Cullen Prize (awarded by the Royal College of Physicians of Edinburgh); he delivered the Harvey Lecture (1928), the Thayer Lectures (1931), and was Visiting Fellow at the Rockefeller Institute in 1928. Addis was a member of the Association of American Physicians, the American Physiological Society, the Society for Experimental Biology and Medicine, the American Society for Clinical Investigation (President of that society in 1930) and the National Academy of Sciences from 1944. He was as well a Fellow of the Royal College of Physicians (Edinburgh) and the American College of Physicians.

Addis' Early Laboratory Work (1909-1919)
Addis' earliest work was conducted as a research fellow in Heidelberg and Berlin, and concerned coagulation of the blood. He showed that - contrary to earlier claims - oral administration of either citric acid or calcium lactate had no effect on blood coagulation in patients with a variety of diseases, both hemorrhagic and thrombotic. These studies used Addis' modification of McGowan's coagulation assay, a modification which he validated by daily triplicate determinations of his own coagulation time over fifty days. Addis also investigated the pathogenesis of hereditary hemophilia, suggesting that the disease is due to a defect in the conversion of prothrombin to thrombin, rather than in the activity of the thrombin itself or a cellular defect.²

After moving to Stanford, Addis conducted spectroscopic studies of hemoglobin breakdown products (bile pigments) in hemolytic disease states such as pernicious anemia. He also published several studies on diabetes mellitus, just before the advent of insulin therapy. He developed an approach to the early diagnosis of diabetes mellitus in patients incidentally found to have glycosuria (sugar in the urine). His method was based on a graded increase in the "strain" imposed on the glucose-utilizing tissues by increasing daily glucose loads, an early form of glucose tolerance test in which glycosuria rather than blood sugar was measured. This approach is in fact quite similar to that which he later employed in studying kidney function.³

Urea Excretion and the Amount of Functioning Renal Tissue (1916-1925)
From the time of Richard Bright's first clinical and pathologic descriptions (in 1827) of the constellation of kidney ailments which so long bore his name, it had been known that the blood urea concentration rises in diseases

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of the kidney. Because the kidneys are the sole excretory organs for urea (formed during protein catabolism), blood urea concentrations rise whenever renal excretory function is compromised. As early as 1856 Picard recommended the measurement of blood urea as a diagnostic tool. Little more was done with these observations, though, until the turn of the century and the development of analytical procedures (principally by Folin, Wu, Van Slyke and Marshall) to determine the urea concentrations in small samples of blood and urine. This ushered in an era of dynamic tests of kidney function based on the rate of urea excretion and the blood urea concentration.

From 1916 to 1925 Addis and his colleagues produced about thirty publications on the quantitative assessment of renal function in man and in the rabbit, through measurement of urea excretion. In the human experiments, Addis, his students and his coworkers were the subjects - supplying specimens for hundreds of blood and urine urea determinations. In all these studies, the goal was a functional assessment of the anatomic state of the normal and diseased kidney. Addis was thereby continuing an intellectual tradition dating back to Richard Bright and Rene Laennec, two 19th century pioneers in clinical-pathologic correlation. Bright in particular had sought to understand kidney disease "by reference to Morbid Anatomy" (as he stated it in his famous Reports on Medical Cases). Given the very poor level of understanding of kidney physiology at the time, it is not surprising that Addis and many of his contemporaries sought a bedrock of reliable knowledge in the better understood pathology of the kidney.

In 1917 Addis published a long paper in which he described his own test to assess "the work of the kidney". In it he outlines the characteristics of an ideal substance for testing the secretory (i.e. excretory) function of the kidney: it must be "a true end-product... incapable of chemical alteration within the body... whose only path of excretion [is] through the kidneys"; its blood concentration should also be susceptible to alteration by systemic administration. Earlier attempts at a functional assessment of renal structure had founded on the great variability of renal excretory function even under normal conditions, variability arising largely from the changing excretory needs of the body. Addis and his colleagues were convinced that such variability was found only in short-term studies of renal function and was due to a changing balance in the factors which normally regulate renal activity. Over 24 hour periods, the forces tended to cancel one another, leading to a greater stability in measured renal function. The fundamental index of function which Addis and his colleagues settled upon was the ratio U-V/B, the Addis urea ratio - where U is the urine urea concentration, V the urine volumetric flow rate, and B the blood urea concentration. Thus, the product UV is the urinary excretion rate of urea. The urea ratio was found to be approximately constant in a given individual, at least for urine flows over about 2 cc/minute, the augmentation limit of Van Slyke.

Subsequent papers described the factors which contribute to the short-term variability in renal excretory function, factors which could be controlled during clinical examination. Among the factors subject to external control was the blood urea concentration B. It was established that the variation in the ratio U-V/B decreases with increasing blood urea concentrations. Addis' interpretation of this finding was that the "strain" of excreting large amounts of urea would push the kidney to the maximum work of which it was capable. Thus patients were studied after receiving an acute oral urea load. Tests of renal function were in addition conducted in a fasting state and during a water diuresis (which Van Slyke had also shown to decrease variability). Through such efforts to suppress or stabilize regulatory influences, the coefficient of variation for urea ratios in a single individual in Addis' lab was reduced to 5.1%.

Addis conceived of the excretory capability of the kidney as the resultant of two factors: the total functioning mass of secretory tissue (the relatively constant factor) and the level of renal activity (the variable factor). The influence of renal mass on excretory function was suggested by the observation that the body weights and hence the kidney weights of rabbits and men fall in approximately the same proportion as their respective urea ratios (35:1 and 33:1, respectively). This was also suggested by studies of the urea ratio in animals with reduced functional mass as a result of nephrectomy or graded damage to the kidney.
in experimental uranium nephritis. Interestingly, Addis and his colleagues did find that the ratio \( \frac{U}{V} \) overestimated kidney weight by approximately 17% after compensatory hypertrophy. The discrepancy was rectified in a morphologic study by Jean Oliver in which he showed a disproportionately large amount of renal hypertrophy following uninephrectomy was due to hypertrophy in the proximal convoluted tubules. At this time renal excretory function was thought to be primarily a secretory process (the importance of glomerular filtration was not yet fully appreciated) and the most "effective" portion of the nephron for urea secretion was considered to be the convoluted tubule.

The further evolution of studies of kidney function was advanced considerably by the development of the concept of renal clearance. That the urea ratio actually expresses the virtual volume of blood freed of urea by the action of the kidney in a unit time was first proposed by Addis in his Harvey Lecture. He acknowledged that this interpretation was pointed out to him by his Stanford colleague G. D. Barnett. On the other hand, Van Slyke and his colleagues at the Rockefeller Medical Institute, who had been doing similar detailed studies on urea excretion for years, were the first to use the word "clearance". Homer Smith later speculated that it "is difficult to judge the importance of words as the vehicles of ideas, but... had Barnett or Addis used Van Slyke's happy expression 'cleared' instead of 'freed', renal physiology might have been significantly catalyzed in 1917 or thereabouts."

The urea excretion ratio was measured by Addis in patients with Bright's disease from about 1920. More widespread use of the urea clearance as a measure of kidney function was cut short by the introduction of the creatinine clearance and eventually the insulin clearance as clinical and research markers of glomerular filtration from the late 1920's to the 1930's. Although he continued to use the urea ratio as an index of the osmotic work of the kidney, Addis did adopt the creatinine clearance as a reliable functional test. He later contributed to the development of practical clinical methods for the determination of the serum creatinine concentration.

**Clinical Classification of Bright's Disease (1922-1933)**

Richard Bright first described the complex of albuminuria, edema (dropsy) and postmortem gross pathological findings of granular kidneys and an enlarged heart in his *Cases* in 1827. Bright's concept was subsequently expanded by many investigators. In 1853 Wilks suggested that there were cardiovascular causes of renal disease, and Muller introduced the term *nephrosis* in 1905 to describe chronic renal disease without signs of inflammation. In 1914 Volhard and Fahr divided Bright's disease into nephrosis, nephritis (inflammatory renal disease) and arteriosclerosis - a classification which provided the basic framework for pathological diagnosis until the proliferation of histopathologic entities which followed the widespread introduction of renal biopsy in the 1950's.

Since the introduction of functional dynamic tests early in the 1900's, Addis felt that the understanding of Bright's disease had "been following a path which leads away from morphology". Addis was concerned with determining the nature and extent of Bright's disease during life (i.e. making a clinical rather than a pathological diagnosis) while retaining the traditional anatomical basis for classifying the disease. His approach to the clinical classification of Bright's disease was therefore two-fold: quantitative examination of the urinary sediment (the Addis count) indicated the nature of the lesion and the urinary urea clearance (the urea ratio) indicated the extent of the lesion. From this dual approach, Addis and his colleagues built up a tripartite clinical classification of Bright's disease analogous to that of Volhard and Fahr: hemorrhagic (nephritis), degenerative (nephrosis) and arteriosclerotic Bright's disease.

Although not entirely satisfactory, this classification was intended to serve as a "local scaffolding" until a better understanding of the etiology of the disease could be attained. Addis hoped to accomplish this through follow-up of patients with Bright's disease over years or even decades, including the final clinicopathologic correlation in the form of post-mortem examination. Much of this early work in the classification of Bright's disease was summarized in a book written jointly with the pathologist Jean R. Oliver, *The Renal Lesion in Bright's Disease* (1931).
Studies of the effects of renal ablation and uranium toxicity on renal structure suggested that the clinical outcome in Bright's disease depended on the balance of processes of tissue destruction and tissue restoration, the latter largely through hypertrophy. The clinician should therefore attempt to impede the former and enhance the latter, where possible. This was not a simple task. High levels of protein ingestion clearly increased the maximum degree of renal hypertrophy which followed loss of renal mass, but Fahr and Smadel\(^{13}\) demonstrated that high-protein diets also increased the rate of renal destruction in rats with experimental nephritis.

An attempt was therefore made to define some form of effective therapy, although Addis conceded that the almost total ignorance regarding therapy at this time might have been a "good and sufficient excuse for abstention from all forms of treatment". Experimental and theoretical considerations, however, suggested "a plan of action". Since the provisional cause of progression in Bright's disease was "the product of a combination of a disease process and the demand on the damaged organ to do its usual amount of work", a theory of therapeutic "rest" from renal work was advanced. This was certainly a common therapeutic "principle" at the time. Addis was undoubtedly familiar with the contemporary practice of thoracoplasty - collapsing and resting the tuberculous lung - as practiced by his friend and colleague, the surgeon Leo Eloesser, and, given his earlier work on diabetes, he was probably also aware of the studies of Allen and of Homans\(^{14}\) on the destructive effect of "overuse" in the experimentally damaged pancreas. To apply these insights, however, it was first necessary to define what constitutes renal work.

The theory which Addis developed proposed that renal work consists of the thermodynamic work of concentrating the urinary solutes, particularly the major urinary solute, urea. This hypothesis had the advantage of quantitative simplicity - the "reversible" work involved in production of a unit volume of urine is proportional to the logarithm of the urine-to-blood concentration ratio of the substance being excreted, \(W = RT\log(\text{L/V B})\).\(^{15}\) Specifics of the theory changed with increasing understanding of the physiology of the kidney, especially the demonstrations by Rehberg (1926) and Smith and colleagues (1938) of the extremely large volume of glomerular filtrate produced by the kidneys (180 liters per day). Thus the early conception of renal work as urea secretion by the proximal convoluted tubules eventually evolved into the idea of work as water extraction from an increasingly concentrated tubular fluid. The physician could help the kidney rest by decreasing the amount of urea which had to be excreted by prescribing a low-protein diet, decreasing the U/B concentration gradient by prescribing a liberal water intake (if the circulatory system allowed) to dilute the urea in the urine, as well as enough salt in the diet (after the edema-forming phase of the disease was past) to raise the urine salt concentration to approximately that of the blood. In the latter case, the work of salt concentration would approach zero. Otherwise, diluting the urine to decrease urea work would actually increase the salt (diluting) work.

The role of dietetic therapy in Bright's disease had been considered by clinicians repeatedly from the 19th century on. Approaches varied from an appreciation of the ability of a low-protein diet to reduce uremic symptoms to the widespread use of the "milk diet", with its relatively high protein content.\(^{16}\) Addis used dietary therapy in treating Bright's disease from the early 1920's, as did others such as Ambard and Volhard. Addis' approach took into account not only the principle of minimization of renal work, but also the need to replace urinary protein losses,\(^{17}\) the likelihood that with decreased appetite in renal disease less than the prescribed amount of protein would actually be ingested, vitamin supplementation in light of a restricted food intake and the special requirements for growth in children (for whom he prescribed up to 2 grams of protein per kilogram of body weight per day, almost four times the amount for adults). In addition, he showed that proteinuria in patients with Bright's disease increases with increasing levels of dietary protein intake, without changes in the serum protein concentration (unless dietary protein has been manifestly inadequate).\(^{18}\) Addis's considerable success in treating patients with chronic Bright's disease may have resulted in part from his realization of the need to individualize dietary therapy in his patients, in order to gain the benefits of a low-protein diet without incurring an excessive risk of proteinmalnutrition, as well as
from the utility of his team approach (doctor-dietician-laboratory staff) in establishing that balance.

**Organ Growth and Hypertrophy (1924-1949)**

With the development of the concept of therapeutic rest, a reliable index of renal work was needed. Although the thermodynamic definition of renal work played a major theoretical role, it also had limitations. In particular, the repeated measurement of urine and blood concentrations of urea and sodium and quantitative urine collection were time-consuming and cumbersome. The idea of organ weight as an indirect measure of organ work was therefore exploited. The use of organ weight to reflect work was supported by an analogy with the increase in muscle mass which results from sustained increases in muscle work. Thus, the anatomical results of organ work were measured rather than the thermodynamic work itself.

In order to utilize this approach, organ weights had to be normalized for age, sex and diet, and the relationship between organ weight and body weight established. Weights of different organs under specific "stresses" were examined: hypertrophy of the gastrointestinal tract under conditions of increased dietary bulk (increasing the work of moving material through the tract), changes in the weight of paired organs after removal of one of them, changes in organ weights following alterations in overall metabolism (e.g., by thyroidectomy, thyroid hormone administration, pregnancy). In the kidney, the effects on growth of age at the time of nephrectomy, protein intake, dietary urea administration and other factors were studied.

After about 1940 Addis became very critical of the phrase "compensatory hypertrophy", since its use usually belied a profound ignorance regarding the nature of the organ function being compensated. "In this endeavor nothing is more likely to still curiosity and initiative than a nomenclature that implies knowledge where only ignorance exists." Addis preferred the phrase "restoration of lost tissue". Even so, growth of the remaining nephrons following partial nephrectomy seemed to him to lower the urea work load per gram of remnant nephron, and thus was apparently an adaptive response to increased renal work load per nephron.

**Mechanisms of Proteinuria (1932-1949)**

Another major topic which Addis investigated was the relationship between proteinuria and kidney disease. He suggested that pathologic proteinuria might be due simply to an intensification of those normal (physiological) processes and factors which cause the appearance of the minimal amounts of protein found in normal urine. He considered mediation of proteinuria through local kidney hemodynamics probable.

Much of his research on this topic was conducted in laboratory rats: including studies of protein-overload proteinuria, renin-induced proteinuria and the effects of adrenalectomy, and sex differences in the levels of proteinuria in rats. A number of interesting phenomena were described, but conclusions ready to find expression in clinical practice were in the main not achieved. The specific goal of these investigations was to understand the role of proteinuria in the progression from latent to degenerative phases of glomerular nephritis (see below) and, in particular, the relevance of proteinuria to tubular degeneration, which he considered "the central mystery of the disease".

**The Book Glomerular Nephritis: Diagnosis and Treatment**

*Glomerular nephritis: Diagnosis and treatment* (1948) is a synthesis of over thirty years of work by Addis and his coworkers in the Clinic for Renal Diseases. To those who had been close to Addis' work over the years, little in the book would have seemed particularly new. Many of its conclusions were based on papers published years before. However, Addis clearly felt that he had finally accumulated enough data and clinical experience to present a case for the broader clinical adoption of the diagnostic and therapeutic methods he had perfected over decades.

*Glomerular nephritis* is largely dedicated to an explication and defense of the principle of rest from osmotic work in the treatment of glomerular nephritis (hemorrhagic Bright's disease). In focusing on glomerular nephritis, Addis had picked one of the most perspicuous causes of Bright's disease. Unlike pyelonephritis (an infection) or vascular diseases, the initial insult (-hemolytic streptococcal infection) was almost invariably of limited duration, and what Addis
followed in his patients was the evolution of a pathologic process intrinsic to the kidney, the oscillating and tenuous balance of forces of tissue restoration and destruction during the long latent stage of glomerular nephritis. The forces which he studied were the kidney's own: "The laws that govern the maintenance and growth of structure and the operation of the functions of the body are still in effect. The disease has only changed the conditions under which they act." His rest therapy was without doubt Addis' most original contribution to the treatment of kidney disease. As he put it, "in dealing with a damaged or diseased organ, we must strive first of all to rest that organ from its work". Addis contrasted rest with "inactivity" - the former includes the very active processes of repair and regeneration. His identification of renal work with urea excretion, though, is now generally considered to have been misguided and probably contributed to the disaffection of many investigators with his ideas. Why did Addis consider urea excretion to be the decisive form of renal work? In rats, a high-protein diet and unilateral nephrectomy both lead to hypertrophy of the (remaining) renal mass - in fact, the renal growth curves in these two situations are almost identical. The effect of these two factors on renal growth is also approximately additive. It was natural to consider that the basic stimulus to renal growth might therefore be the same in both these cases. The remaining kidney after contralateral nephrectomy faces an increased excretory work load per unit tissue mass. Since one obvious consequence of a high protein diet is also excretion of larger amounts of urea (the final breakdown product of protein in the body and the major urinary solute), Addis could quite logically propose that the osmotic excretory work of the kidney was the common factor causing renal hypertrophy in both cases and thus was the pathogenetically most important form of renal work.

Addis was quite aware of inconsistencies in his rest theory (in particular with the importance it assigned to the osmotic work of the kidney). The sophistication of his reasoning in holding to the osmotic theory in spite of these objections has often been overlooked in light of the resounding rejection the theory itself received at the hands of improved physiological understanding. Addis was in particular aware of the large discrepancy between the calculated thermodynamic work of the kidney in concentrating urea and values of renal metabolism determined from measured organ oxygen consumption (the fundamental work was performed by his Stanford colleague William Dock). Even allowing for a major component of thermodynamic inefficiency, solute concentration could account for only about 4% of total renal metabolic expenditure. Yet Addis felt that no data spoke either "for or against the objection that the energy requirements for osmotic work are so small that they cannot be regarded as effective with respect to any major events within the kidney. The objection itself is based on analogy and arises because of a difficulty conceiving that a small change in energy relations may sometimes lead to large material results". Thus, although he used renal hypertrophy as a convenient marker for renal work, Addis rejected a simple direct proportionality between work and growth.

As always, the acid test for Addis was the implications of theory for clinical practice. The rat experiments were for him just "secondary, even if necessary, supports. It is true that if they had not vindicated the rest hypothesis we should have concluded that we had been misled in the interpretation of our clinical experience. Clinical history is full of such mistakes. But if our clinical experience of many years had not seemed to confirm the theory we should not have ventured to advance it as a basis for the action of others."
uremic symptoms, and not because it prolonged renal survival. So protein intake could be liberalized once dialysis was available. The same fate befell the Kempner (Duke) rice diet - a very effective intervention in many cases of hypertension - which was replaced by the new diuretics in the 1950s.

In the 1970s a new "unification" began to emerge in the understanding of progressive renal insufficiency. Observations of a steady, predictable decline in kidney function once about three-quarters of the functional mass is lost were made by Mitch, Walser and others. There was also a renewed appreciation for the acute effects of dietary protein loads on kidney filtration rate. In 1982 a mechanism was proposed which tied dietary protein intake and compensatory hyperfunction itself to progression of a large number of renal diseases, as well as to the slow loss of renal function with age. These developments catalyzed interest in the dietary treatment of chronic renal failure in the United States. Interestingly, dietary therapy had been extensively explored in Europe (largely by Carmelo Giordano and Sergio Giovannetti in Italy) from the early 1960s. These studies included the further refinement of supplementing very low protein diets with essential amino acids and/or -ketoacid analogs (introduced by Giordano, Giovannetti, Schloerb and others in the 1960s).

Evidence for the effectiveness of low-protein diets in slowing progression has so far been stronger in experimental animal models of renal disease than in humans. This may in part result from difficulties in quantitating renal functional changes by standard clinical methods, problems with dietary compliance and the conflicting requirements of controlled research and patient care. Nevertheless, as prospective studies using accurate methods for assessing glomerular filtration rate have begun to be completed, evidence is accumulating that a low-protein diet (supplemented with essential amino acids and/or -ketoacid analogs) does slow disease progression in many patients with chronic renal insufficiency. Investigations continue on the effects of other dietary constituents, such as phosphorus and lipids, which have also been suggested to influence renal disease progression. These factors appear to be synergistic with those of low-protein diets (e.g. low-protein, low-salt and low-phosphorous diets all retard renal and glomerular hypertrophy) or multifactorial (dietary fatty acids influence immune function, blood pressure and plasma membrane properties).

Recently Bouby, Bankir and their colleagues have described a common effect of both dietary protein intake and urine concentration on renal structure and function, an effect quite reminiscent of Addis' s ideas on urea "work". While acute protein loads seem to increase kidney filtration rate via a hormonally mediated mechanism, chronic elevation of urine concentrating work secondary to a high protein intake leads to hypertrophy of that part of the tubule (the thick ascending limb of Henle's loop) which forms the "engine" for the active transport processes driving urine concentration. Urea-enhanced activity in this tubule segment decreases a feedback signal to the glomerulus (distal sodium chloride concentration) and thereby increases filtration rate with all its deleterious consequences. Bouby and colleagues demonstrated that a diet high in water content is able to reduce proteinuria, systemic blood pressure, renal hypertrophy (especially of the thick ascending limb) and the extent of glomerular sclerosis in rats following subtotal nephrectomy. In this context it is interesting to remember that Addis encouraged a liberal water intake in his patients in order to reduce concentrating work.

In light of these studies, it is likely that dietary therapy of chronic renal disease will find increasing application in the future, at least in less severe forms and earlier stages of disease. If Addis seems to have pushed dietary therapy to its absolute limits, it must be remembered that forty years ago dietary therapy was virtually the only effective method available. Even so, its effectiveness in severe cases consisted only in postponing decline and death. We therefore close with words from the final pages of *Glomerular Nephritis* which illustrate the pathos of a physician all too often faced with the limitations of contemporary therapy: "It is our job to do our best to keep them [our patients] on the firing line to the very last gasp. Since our best endeavor amounts to almost nothing, we need not take ourselves too seriously. The situation is now
more clearly than ever not in our hands and can no longer be influenced appreciably by us. More and more we cease to play even a minor role in the drama. We retreat to the wings to watch the last act of the tragedy."

Sources
Sources consulted for this memoir include several former colleagues of Tom Addis: L. J. Rather, D. A. Rytand, R. Cohn, M. Krupp, L. Bayer, B. Scribner.

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Notes
3. Addis, T. JAMA 69:109-111, 1917: "It is a generally applicable principle that a defect in function becomes more and more apparent, the greater the strain to which [the organ] is subjected."
4. These criteria closely parallel the characteristics of an ideal marker of glomerular filtration, as enunciated later by Homer Smith. The emphasis on filtration - rather than simply excretion - arose as advances in renal physiology clarified the relative roles of the three factors involved in urinary excretion: glomerular filtration, tubular secretion and tubular reabsorption. The principal drawback in fact to using urea excretion to assess renal function is that it is the product of all three processes - filtration, secretion and reabsorption - and as a composite index has compounded problems of variability.
8. Addis, T: The Renal Lesion in Bright's Disease. Harvey Lecture Series 23:222-250, 1927-1928. Here he described blood flow through the kidney "as consisting of 2 portions, a portion which passes through unchanged and another portion from which the urea is completely removed."
12. The quantitative determination from a timed urine collection of the rates of excretion of formed elements (such as red blood cells, white blood cells and casts) and protein.
17. David A. Rytand, M.D. recalls this aspect as unique to Addis' approach.


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