

Thomas Addis and the Dietary Treatment of Kidney Disease

Kevin V. Lemley, M.D., Ph.D.¹

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

1. Institut für Anatomie und Zellbiologie, Im Neuenheimer Feld 307,6900 Heidelberg 1, Federal Republic of Germany.

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.⁴ Earlier attempts at a functional assessment of renal structure had foundered 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 nephrectomy⁵ or graded damage to the kidney

in experimental uranium nephritis.⁶ Interestingly, Addis and his colleagues did find that the ratio U-V/B overestimated kidney weight by approximately 17% after compensatory hypertrophy. The discrepancy was rectified in a morphologic study by Jean Oliver⁷ 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.⁸ 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".⁹ 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."¹⁰

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 count¹²) 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 Smadel¹³ 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 Homans¹⁴ 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, $W = RT \log(LVB)$.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' 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 protein malnutrition, 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 Dock¹⁹). 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."

Addis, Forty Years Later

With increasing use of the renal biopsy -and the attendant proliferation of pathologic diagnoses - the use of such general diagnostic categories as Bright's disease decreased during the years after Addis' death. The Addis test (quantitative examination of the urinary sediment) and the urea ratio test also soon fell into disuse. The success of steroids and cytotoxic agents in the treatment of different glomerulopathies, of antibiotics in treatment of pyelonephritis and the availability of dialysis and transplantation (albeit for the few, before 1972) lead to a de-emphasizing of dietary therapy, at least in the United States. Dietary therapy had always been most widely accepted in chronic renal disease because of its effect on

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 proposed²⁰ 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,²¹ 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 are difficult to examine inasmuch as their effects

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".²² 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.²³ 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.

Written References Include

1. Rytand DA: Medicine and the Stanford University School of Medicine, Circa 1932: The Way it Was. May 1984.
2. Festschrift for Thomas Addis, Stanford Medical Bulletin, February 1948, Volume 6, Number 1.
3. Bloomfield AL: Stanford Medical Bulletin, August 1958, Volume 16, Number 3.
4. Rather LJ: Stanford Medical Bulletin, Volume 17, Number 3, 1959.
5. Smith HW: The Kidney - Structure and Function in Health and Disease. Oxford University Press, New York, 1951.
6. Harvey AM: Classics in Clinical Science: The Concept of Clearance. *Am. J. Med.* 68:6-7, 1980.
7. Harvey AM: Science at the Bedside: Clinical Research in American Medicine 1905-1945, Baltimore, Johns Hopkins University Press, 1981, pp. 386-387.
8. Shumacker HB: Leo Eloesser, M.D.: Eulogy for a Free Spirit. Philosophical Library, New York, 1982.
9. Giovannetti S: Dietary Treatment of Chronic Renal Failure: Why Is It Not Used More Frequently? *Nephron* 40:1-12, 1985.
10. Peitzman SJ: Thomas Addis (1881-1949): Mixing patients, rats, and politics. *Kidney International* 37:833-840, 1990.

Notes

1. Kevin V. Lemley, Linus Pauling: Thomas Addis, M.D. Volume 64, Biographical Memoirs of the National Academy of Sciences.
2. See MM Wintrobe: Blood, Pure and Eloquent. McGraw-Hill Book Co., New York, 1980, p. 628.
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.

5. Addis T, Meyers BA, Oliver J: *Arch. Int. Med.* 34:243-257, 1924.
6. Watanabe CK, Oliver J, Addis T: *J. Exp. Med.* 28:359-376, 1918.
7. Oliver J: The regulation of renal activity. X. The morphologic study. *Arch. Int. Med.* 34:258-265, 1924.
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."
9. Moller E., Macintosh JF & Van Slyke DD, 1929. Studies of urea excretion. II. Relationship between urine volume and the rate of urea excretion by normal adults. *J. Clin. Invest.* 6:427-465.
10. Smith Hw: The Kidney: Structure and Function in Health and Disease, Oxford University Press, NY, 1951, p. 66.
11. Barrett E, Addis T: *J. Clin. Invest.* 26:875-878, 1947; Addis T, Barrett E, Menzies JT: *J. Clin. Invest.* 26:879-882, 1947.
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.
13. Farr LE, Smadel JE: The effect of dietary protein intake on the course of nephrotoxic nephritis in rats. *J. Exp. Med.* 70:615-627, 1939.
14. Allen FM: Studies concerning glycosuria and diabetes. Harvard University Press, 1913; Homans J: A study of experimental diabetes in the canine and its relation to human diabetes. *J. Med. Res.* 33:1, 1915.
15. See JD Newburgh: The Changes Which Alter Renal Osmotic Work. *J. Clin. Invest.* 22:439-446, 1943.
16. Lichtwitz L: Die Praxis der Nierenkrankheiten. 2nd edition. Springer, Berlin, 1925, pp 230-234.
17. David A. Rytand, M.D. recalls this aspect as unique to Addis' approach.
18. Persike EC, Addis T: *Arch. Int. Med.* 81:612-622, 1948.
19. Dock W: The rate of oxygen utilization by rat kidneys at different rates of urea excretion. *Am. J. Physiol.* 106:745-749, 1933. 20. Brenner BM, Meyer TW, Hostetter TH: Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive

glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N. Eng. J. Med.* 307:652, 1982.

21. Walser M: Progression of chronic renal failure in man. *Kidney International* 37:1195-1210, 1990.
22. Bankir L, Bouby N: Vasopressin and urinary concentration: additional risk factors in the progression of chronic renal failure. *Am. J. Kidney Dis.* XVII (Suppl. 1):20-26, 1991.
23. Bouby N, Bachman S, Bichet D, Bankir L: Effect of water intake on the progression of chronic renal failure in the 5/6 nephrectomized t&X. *Am. J. Physiol.* 258 (Renal Fluid Electrolyte Physiol. 27):F973-F979, 1990.

Bibliography

1908

Addis T: The coagulation time of the blood in man. *Quart. J. Exper. Physiol.* 1:305-334, 1908.

1909

Addis T: The effect of the administration of calcium salts and of citric acid on the calcium content and coagulation time of the blood. *Quart. J. Med.* 2:149-164, 1908-1909.

Addis T: The ineffectiveness of calcium salts and of citric acid as used to modify the coagulation time of the blood for therapeutic purposes. With a description of a modification of McGowan's method of estimating the coagulation time of the blood. *Brit. Med. J.* 1:997-999, 1909.

Addis T: Coagulation time of the blood. [Correspondence]. *Brit. Med. J.* 1:1151-1152, 1909.

Addis T: Coagulation time of the blood. [Correspondence]. *Brit. Med. J.* 1:1269-1270, 1909.

1910

Addis T: The coagulation time of the blood in disease. *Edinburgh Med. J. Series 3*, 5:38-53, 1910

Addis T: Hereditary haemophilia: deficiency in the coagulability of the blood the only immediate cause of the condition. *Quart. J. Med.* 4:14-32, 1910.

Addis T: The pathogenesis of hereditary haemophilia. [Abstract and discussion]. *Brit. Med. J.* 2:1422, 1910.

1911

Addis T: The pathogenesis of hereditary haemophilia. *J. Path. & Bact.* 15:427-452, 1911.

1912

Addis T: The bactericidal and hemolytic powers of "paraffin" plasma and of serum. *J. Infect. Dis.* 10:200-209, 1912.

Wilbur RL and Addis T: Urobilin: its clinical significance. Preliminary report. *JAMA* 59:929-933, 1912.

1913

Bramwell E and Addis T: Myotonia atrophica. *Edinburgh Med. J.* n.s. 11:21-44, 1913.

Addis T: Clinical methods of estimating the degree of acidosis in diabetes. *Calif. State J. Med.* 11:440-442, 1913.

Wilbur RL and Addis T: Urobilin: its clinical significance. *Trans. Assoc. Am. Physicians* 28:617-682, 1913.

1914

Wilbur RL and Addis T: Urobilin: its clinical significance. *Arch. Int. Med.* 13:235-286, 1914.

1915

Addis T: A working hypothesis of hemoglobin pigment metabolism. *Arch. Int. Med.* 15:413-37, 1915.

Addis T: The preparation of diabetic patients for operation. *JAMA* 64:1130-1134, 1915.

1916

Addis T and Watanabe CK: The rate of urea excretion. First paper. A criticism of Ambard and Weill's laws of urea excretion. *J. Biol. Chem.* 24:203-220, 1916.

Addis T: The effect of intravenous injections of fresh human serum and of phosphated blood on the coagulation time of the blood in hereditary hemophilia. *Proc. Soc. Exp. Biol. & Med.* 14:19-23, 1916.

Addis T and Watanabe CK: The rate of urea excretion. II. The rate of excretion of administered urea in young healthy adults on a constant diet. *J. Biol. Chem.* 27:249-266, 1916.

Addis T and Watanabe CK: The volume of urine in young healthy adults on a constant diet. *J. Biol. Chem.* 27:267-272, 1916.

Addis T and Barnett GD: The effect of pituitrin and adrenalin on the urea-excreting function of the kidney. *Proc. Soc. Exp. Biol. & Med.* 14:49, 1916.

Addis T and Watanabe CK: A method for the measurement of the urea-excreting function of the kidneys. *J. Biol. Chem.* 28:251-259, 1916.

1917

Watanabe CK, Oliver JR and Addis T: The function of the kidneys under strain in uranium nephritis and the relationship between anatomy and function under these conditions. *Proc. Soc. Exp. Biol. & Med.* 14:147, 1917.

Addis T and Shevky AE: Sources of error in the estimation of dextrose by the colorimetric picrate method. *Proc. Soc. Exp. Biol. & Med.* 15:79, 1917-1918.

Addis T and Watanabe CK: The rate of urea excretion. III. The effect of changes in blood urea concentration on the rate of urea excretion. *J. Biol. Chem.* 29:391-398, 1917.

Addis T and Watanabe CK: The rate of urea excretion IV. The effect of changes in the volume of urine on the rate of urea excretion. *J. Biol. Chem.* 29:399-404, 1917.

Addis T and Watanabe CK: The causes of variation in the concentration of urea in the blood of young healthy adults. *Arch. Int. Med.* 19:507-517, 1917.

Barnett GD and Addis T: Urea as a source of blood ammonia. *Biol. Chem.* 30:41-46, 1917.

Addis T and Shevky AE: The return of urea from the kidney to the blood. *Am. J. Physiol.* 43:363-370 1917.

Addis T: The ratio between the urea content of the urine and of the blood after the administration of large quantities of urea. An approximate index of the quantity of actively functioning kidney tissue. *J. Urol.* 1:263-287, 1917.

Addis T: The early diagnosis of diabetes. A simple method involving strain on the capacity of the tissues to utilize glucose. *JAMA* 69:109-111, 1917.

1918

Addis T, Barnett GD and Shevky AE: The regulation of renal activity. I. Regulation of urea excretion by the concentration of urea in the blood and in the urine. *Am. J. Physiol.* 46:1-10, 1918.

Addis T, Shevky AE and Bevier G: The regulation of renal activity. II. Regulation of urea excretion by anatomical factors. *Am. J. Physiol.* 46:11-21, 1918.

Addis T, Barnett GD and Shevky AE: The regulation of renal activity. III. Regulation of urea excretion by unknown factors. *Am. J. Physiol.* 46:22-27, 1918.

Addis T, Barnett GD and Shevky AE: The regulation of renal activity. IV. Regulation of urea excretion by adrenalin. *Am. J. Physiol.* 46: 39-51, 1918.

Addis T, Barnett GD and Shevky AE: The regulation of renal activity. V. Regulation of urea excretion by pituitrin. *Am. J. Physiol.* 46:52-62, 1918.

Addis T, Foster MG and Barnett GD: The regulation of renal activity. VI. The effect of adrenalin and pituitrin on the action of the kidney under strain. *Am. J. Physiol.* 46:84-89, 1918.

Addis T, Shevky AD and Bevier G: The regulation of renal activity. VII. The balance between the regulation by adrenalin and by pituitrin. *Am. J. Physiol.* 46:129-146, 1918.

Addis T and Shevky AE: The rate of color production in alkaline solutions of dextrose and picrate. *J. Biol. Chem.* 35:43-51, 1918.

Addis T and Shevky AE: A modification of the picrate method for blood sugar determinations. *J. Biol. Chem.* 35:53-59, 1918.

Watanabe CK, Oliver J and Addis T: Determination of the quantity of secreting tissue in the living kidney. *J. Exp. Med.* 28:359-376, 1918.

1919

Addis T: A pulse rate standard for recruits. *JAMA* 72:181-185, 1919.

Addis T and Kerr WJ: The relative frequency in recruits with and without thyroid enlargement of certain signs and symptoms which occur in neurocirculatory asthenia. *Arch. Int. Med.* 23:316-333, 1919.

Addis T: The future of the teaching of clinical medicine. *Edinburgh Med. J.* 23:235-243, 1919.

1922

Addis T: Determination of the extent and nature of the renal lesion in Bright's disease. *California State J. Med.* 20:90-93, 1922.

Addis T: Blood pressure and pulse rate levels. First paper. The levels under basal and daytime conditions. *Arch. Int. Med.* 29:539-553, 1922.

Addis T: Blood pressure and pulse rate reactions. Second paper. *Arch. Int. Med.* 30:240-268, 1922.

Addis T: Protein restriction in Bright's disease. *Med. Clin. North Am.* 6:209-212, 1922.

Addis T: Renal function and the amount of functioning tissue. The ratio: Urea in one hour's urine/Urea in 100 c.c. of blood, after giving urea and water. *Arch. Int. Med.* 30:378-385, 1922.

Spalding AB, Shevky MC and Addis T: The extent of the renal lesion in the toxemias of pregnancy. *Am. J. Obst. & Gynec.* 4:350-361, 1922.

Addis T and Foster MG: The specific gravity of the urine. *Arch. Int. Med.* 30:555-558, 1922.

Addis T and Shevky MC: A test of the capacity of the kidney to produce a urine of high specific gravity. *Arch. Int. Med.* 30:559-562, 1922.

1923

Addis T and Drury DR: The rate of urea excretion. V. The effect of changes in blood urea concentration on the rate of urea excretion. *J. Biol. Chem.* 55:105-111, 1923.

Addis T and Drury DR: The rate of urea excretion. VII. The effect of various other factors than blood urea concentration on the rate of urea excretion. *Biol. Chem.* 55:629-638, 1923.

Addis T and Drury DR: The rate of urea excretion. VIII. The effect of changes in urine volume on the rate of urea excretion. *Biol. Chem.* 55:639-651, 1923.

Addis T: The clinical significance of abnormalities in urine volume. *Arch. Int. Med.* 31:783-796, 1923.

Taylor FB, Drury DR and Addis T: The regulation of renal activity. VIII. The relation between the rate of urea excretion and the size of the kidneys. *Am. J. Physiol.* 65:55-61, 1923.

1924

Stafford DD and Addis T: Diastase determinations in urine and blood as a method for the measurement of the functional capacity of the kidney. *Quart. J. Med.* 17:151-161, 1924.

Sharlit H, Lyle WG with comments by Thomas Addis: The specific gravity of the urine. *Arch. Int. Med.* 33:109-117, 1924.

- Addis T, Meyers BA and Oliver J: The regulation of renal activity. IX. The effect of unilateral nephrectomy on the function and structure of the remaining kidney. *Arch. Int. Med.* 34:243-257, 1924.
- Addis T and Foster MG: The concentrating capacity of the kidney. *Arch. Int. Med.* 34:462-480, 1924.
- 1925**
- Addis T: Urea determinations in blood and urine *J. Lab. & Clin. Med.* 10:402-409, 1925.
- Addis T, Meyers BA and Bayer L: The regulation of renal activity. XL The rate of phosphate excretion by the kidney. The effect of variation in the concentration of phosphate in the plasma on the rate of phosphate excretion. *Am. J. Physiol.* 72:125-142, 1925.
- Addis T: Renal failure casts. *JAMA* 84:1013-1015, 1925.
- MacKay LL, MacKay EM and Addis T: Compensatory hypertrophy of the kidney: The effect of pregnancy and of lactation. *Proc. Soc. Exp. Biol. & Med.* 22:536-537, 1925.
- Addis T: A clinical classification of Bright's diseases. *JAMA* 85:163-167, 1925.
- Addis T: A clinical classification of Bright's disease. *Trans. Assoc. Am. Physicians* 40:101-115, 1925.
- MacKay LL, MacKay EM and Addis T: The effect of various factors on the degree of compensatory hypertrophy of the kidney after unilateral nephrectomy. *J. Clin. Invest.* 1:576, 1925.
- 1926**
- Addis T: The number of formed elements in the urinary sediment of normal individuals. *J. Clin. Invest.* 2:409-415, 1926.
- Addis T: The effect of some physiological variables on the number of casts, red blood cells and white blood cells and epithelial cells in the urine of normal individuals. *J. Clin. Invest.* 2:417-421, 1926. MacKay LL, MacKay EM and Addis T: Phosphate and kidney weight. *Proc. Soc. Exp. Biol. & Med.* 24:130, 1926.
- Addis T, MacKay EM and MacKay LL: The effect on the kidney of the long continued administration of diets containing an excess of certain food elements. I. Excess of protein and cystine. *J. Biol. Chem.* 71:139-156, 1926.
- Addis T, MacKay EM and MacKay LL: The effect on the kidney of the long continued administration of diets containing an excess of certain food elements. II. Excess of acid and of alkali. *J. Biol. Chem.* 71:157-166, 1926.
- 1927**
- MacKay LL, MacKay EM and Addis T: Influence of age on degree of renal hypertrophy produced by high protein diets. *Proc. Soc. Exp. Biol. & Med.* 24:335-336, 1927.
- MacKay LL, MacKay EM and Addis T: Do high protein diets increase weight of kidney because they increase nitrogen excretion? *Proc. Soc. Exp. Biol. & Med.* 24:336-337, 1927.
- 1928**
- Addis T: Compensatory hypertrophy of the lung after unilateral pneumonectomy. *J. Exp. Med.* 47:51-56, 1928.
- Addis T: An error in the urease method for the determination of urea. *Proc. Soc. Exp. Biol. & Med.* 25:365-367, 1928. MacKay EM,
- MacKay LL and Addis T: Factors which determine renal weight.V. The protein intake. *Am. J. Physiol.* 86:459-465, 1928.
- MacKay EM, MacKay LL and Addis T: Factors which determine renal weight.VI. Influence of age on the relation of renal weight to the protein intake and the degree of renal hypertrophy produced by high protein diets. *Am. J. Physiol.* 86:466-470, 1928.
- Addis T: The renal lesion in Bright's disease. [Harvey Lecture] *Am. J. Med. Sci.* 76:617- 637, 1928.
- 1929**
- Addis T: The renal lesion in Bright's disease. *Harvey Lecture Series* 23:222-250, 1927- 1928.[appeared 1929]
- 1930**
- Addis T and Raulston BO: A reversible form of experimental uremia. *Trans. Assoc. Am. Physicians* 45:3 18-320, 1930.
- 1931**
- MacKay LL, MacKay E and Addis T: Factors which determine renal weight. XII. The nitrogen intake as varied by the addition of urea to the diet. *J. Nutrition* 4:379-383, 1931.
- Addis T: Haemorrhagic Bright's disease. I. Natural history. *Bull. Johns Hopkins Hosp.* 49:203-224, 1931.
- Addis T: Haemorrhagic Bright's disease. II. Prognosis, etiology and treatment. *Bull. Johns Hopkins Hosp.* 49:271-285, 1931.
- Addis T and Oliver J: The Renal Lesion in Bright's disease. N.Y., Paul B. Hoeber, 1931.
- 1932**
- Addis T: Proteinuria and cylinduria. *Proc. Calif. Acad. Med.* 2:38-52, 1931/32.
- Addis T: Hypertrophy of the gastro-intestinal tract and high residue diets. *Am. J. Physiol.* 99:417-423, 1932.
- MacKay EM, MacKay LL and Addis T: The degree of compensatory renal hypertrophy following unilateral nephrectomy. I. The influence of age. *J. Exp. Med.* 56:255-265, 1932.
- 1933**
- Addis T: Science and practice in Bright's disease. *Ann. Int. Med.* 6:1077-1079, 1933.
- 1935**
- Addis T: Compensatory hypertrophy of paired organs after one has been removed. *International*

- Physiological Congress. 15th Summaries of Communications. P. 4, 1935.
- Addis T: Total body and organ proteins - changes under varying dietary conditions. International Physiological Congress. 15th Summaries of Communications. P. 4, 1935.
- 1936**
- Addis T, Poo LJ, Lew W and Yuen DW: Gravimetric methods for the determination of total body protein and organ protein. *J. Biol. Chem.* 113:497-504, 1936.
- Addis T, Poo LJ and Lew W: The quantities of protein lost by the various organs and tissues of the body during a fast. *J. Biol. Chem.* 115:111-116, 1936.
- Addis T, Poo LJ and Lew W: Protein loss from liver during a two day fast. *J. Biol. Chem.* 115:117-118, 1936.
- Addis T, Poo LJ and Lew W: The rate of protein formation in the organs and tissues of the body. I. After casein refeeding. *J. Biol. Chem.* 116:343-352, 1936.
- 1938**
- MacKay LL, Addis T and MacKay EM: The degree of compensatory renal hypertrophy following unilateral nephrectomy. II. The influence of the protein intake. *J. Exp. Med.* 67:515-519, 1938.
- Addis T, Karnofsky D, Lew W and Poo LJ: The protein content of the organs and tissues of the body after administration of thyroxine and dinitrophenol and after thyroidectomy. *J. Biol. Chem.* 124:33-41, 1938.
- 1939**
- Addis T: The treatment of chronic renal insufficiency. *J. Urol.* 41:126-136, 1939. Addis T: Metabolism of intraperitoneally injected serum protein. *Proc. Soc. Exp. Biol. & Med.* 40:336-338, 1939.
- Walter F and Addis T: Organ work and organ weight. *J. Exp. Med.* 69:467-483, 1939.
- Poo LJ, Lew W and Addis T: Protein anabolism of organs and tissues during pregnancy and lactation. *J. Biol. Chem.* 128:69-77, 1939.
- Addis T and Lew W: Age and the rate of venous enlargement under increased venous pressure. *Proc. Soc. Exp. Biol. & Med.* 42:602-603, 1939.
- Addis T and Lew W: Diet and death in acute uremia. *J. Clin. Invest.* 18:773-775, 1939.
- 1940**
- Addis, T, Lee DD, Lew W and Poo LJ: The protein content of the organs and tissues at different levels of protein consumption. *J. Nutrition* 19:199-205, 1940.
- Addis T, Lee DD, Lew W and Poo LJ: The utilization of parenterally administered horse serum by the rat. *Am. J. Physiol.* 128:544-546, 1940.
- Addis T and Lew W: The restoration of lost organ tissue. The rate and degree of restoration. *J. Exp. Med.* 71:325-333, 1940.
- Addis T and Lew W: Protein consumption and the restoration of lost organ tissue. *J. Exp. Med.* 71:563-568, 1940.
- Addis T: Theory and practice in the dietetic treatment of glomerular nephritis. *J. Am. Dietet. Assoc.* 16:306-312, 1940.
- Poo LJ, Lew W, Lee DD and Addis T: Protein anabolism in the organs and tissues of pregnant rats at different levels of protein consumption. *J. Nutrition* 19:505-515, 1940.
- Yuen DW, Poo LJ, Lew W and Addis T: Protein anabolism in the heart, kidney and liver after consumption of various food proteins. *Am. J. Physiol.* 129:685-690, 1940.
- Addis T: Treatment of nephritis by rest. *J. Missouri State Med. Assoc.* 37:458-460, 1940.
- Addis T: The osmotic work of the kidney and the treatment of glomerular nephritis. *Trans. Assoc. Am. Physicians* 55:223-229, 1940.
- 1942**
- Sugarman J, Friedman M, Barrett E and Addis T: The distribution, flow, protein and urea content of renal lymph. *Am. J. Physiol.* 138:108-112, 1942.
- Addis T: Proteinuria. *Trans. Assoc. Am. Physicians* 57:106-108, 1942.
- 1943**
- Addis T: The effect of variation in food protein consumption on the protein of the organs and tissues of the body. *Pacific Science Congress Proc.* 6:677-679, 1939 [printed 1943]
- 1945**
- Addis T: Renal degenerations due to protein reabsorption by the kidney. *Stanford Med. Bull.* 3:67-69, 1945. 1946
- Addis T, Barrett E, Lew W, Poo LJ and Yuen DW: Danger of intravenous injection of protein solutions after sudden loss of renal tissue. *Arch. Int. Med.* 77:254-259, 1946.
- 1947**
- Addis T, Barrett E, Poo LJ and Yuen DW: The relation between the serum urea concentration and the protein consumption of normal individuals. *J. Clin. Invest.* 26:869-874, 1947.
- Barrett E and Addis T: The serum creatinine concentration of normal individuals. *J. Clin. Invest* 26:875-878, 1947.
- Addis T, Barrett E and Menzies JT: A clinical method for the approximate determination of serum creatinine concentration. *J. Clin. Invest.* 26:879-882, 1947.
- 1948**
- Addis T, Gray H and Barrett E: Food protein effect on plasma specific gravity, plasma protein, and hematocrit value. *J. Exp. Med.* 87:353-368, 1948.
- Gray H and Addis T: Rat colony testing by Zucker's weight-age relation. *Am. J. Physiol.* 153:35-

40, 1948. Persike EC and Addis T: Food protein consumption in glomerulonephritis. Effect on proteinuria and concentration of serum protein. *Arch. Int. Med.* 81:612-622, 1948.

Addis T: Glomerular nephritis. Diagnosis and Treatment. MacMillan, New York, 1948.

1949

Addis T, Barrett E, Boyd RI and Ureen HJ: Renin proteinuria in the rat. I. The relation between the proteinuria and the pressor effect of renin. *J. Exp. Med.* 89:131-140, 1949.

Addis T and Boyd RI: Adrenalectomy and rennin proteinuria in the rat. *Federation Proc.* 8:1, 1949.

Reichert FL, Richards V, Holman E, Bloomfield AL, Addis T, Rytand DA and Lewis JK: The medical and surgical treatment of hypertension. *Ann. Surg.* 129:349-357, 1949.

Addis T: The mechanism of proteinuria. *Proc. NatAcad.Sci.* 35:194-198, 1949.

Persike EC and Addis T: Increased rate of urea formation following removal of renal tissue. *Am. J. Physiol.* 158:149-156, 1949.

1950

Addis T and Gray H: Body size and organ Weight *Growth* 14:49-80, 1950.

Addis T and Gray H: Body size and suprarenal weight. *Growth* 14:81-92, 1950.

Addis T and Gray H: Body size and gonad weight *Growth* 14:93-106, 1950. Persike EC, Lippman RW,

Addis T, Reichert FL and Richards V: Surgical treatment for

hypertensive complications of advanced renal disease. *Arch. Int. Med.* 83:348-354, 1950.

Addis T, Marmorston J, Goodman HC, Sellers AL and Smith M: Effect of adrenalectomy on spontaneous and induced proteinuria in the rat. *Proc. Soc. Exp. Biol. & Med.* 74:43-46, 1950. Rather LJ and

Addis T: Renin proteinuria in the rat. II. Evidence that renin does not interfere with the tubular resorption of purified human hemoglobin or bovine albumin. *J. Exp. Med.* 91:567-572, 1950.

1951

Addis T, Barrett E, Poo LJ, Ureen HJ and Lippman RW: The relation between protein consumption and diurnal variations of the endogenous creatinine clearance in normal individuals. *J. Clin. Invest.* 30:206-209, 1951.

Addis T, Lippman RW, Lew W, Poo LJ and Wong W: Effect of dietary protein consumption upon body growth and organ size in the rat. *Am. J. Physiol.* 165:491-496, 1951.

Addis T, Barrett E, Poo LG and Ureen H: Prerenal proteinuria. I. Particle size. *Arch. Int. Med.* 88:337-345, 1951.

Jameson E and

Addis T: Prerenal proteinuria. III. Electrophoretic studies. *Arch. Int. Med.* 88:350-355, 1951.

1952

Addis T, Lippman RW, Lew W, Poo LJ and Wong W: Effect of diet upon body growth and organ size in the rat after partial nephrectomy. *Am. J. Physiol.* 168:114-120, 1952.