the "spasm reactor" in your practice
The Machine Age man still possesses a Stone Age stomach; sometimes the job of merely coping with today’s environmental stress may prove too much. For some (the “spasm reactors” in your practice), tension, anxiety and worry may find expression through the voice of gastrointestinal or other smooth muscle spasm. To treat these patients with antispasmodics alone is often to miss the point of origin of their disturbance; to rely solely on tranquilizers often proves discouragingly slow or ineffective in relieving spasm and pain.

To quiet and quell Donnatal can promptly and effectively quell the spasm and quiet the tensions that trigger it. Prescribed by more physicians than any other antispasmodic-sedative, Donnatal continues to provide the classic answer.

The “Donnatal Effect” The characteristic, over-all effect of Donnatal has been observed in many thousands of children and adults, clearly establishing its value as a versatile sedative-antispasmodic. Outstanding in effectiveness, safety, economy, uniformity of composition and dosage convenience, Donnatal continues to be desired and prescribed by a majority of physicians.

In a multiplicity of indications Particularly useful when anxiety and tension accompany, aggravate or account for smooth muscle spasm, Donnatal is indicated for the symptomatic relief of recurring, persistent or chronic visceral spasm. More than two dozen distinct and separate indications for Donnatal are listed on page 974 in the current PDR.

Brief summary Blurring of vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur on higher dosage levels, rarely on usual dosage. Administer with caution to patients with incipient glaucoma or urinary bladder neck obstruction. Contraindicated in acute glaucoma, advanced renal or hepatic disease or a hypersensitivity to any of the ingredients.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>hyoscyamine sulfate</td>
<td>0.1037 mg.</td>
</tr>
<tr>
<td>atropine sulfate</td>
<td>0.0194 mg.</td>
</tr>
<tr>
<td>hyoscine hydrobromide</td>
<td>0.0005 mg.</td>
</tr>
<tr>
<td>phenobarbital (% gr.)</td>
<td>16.2 mg.</td>
</tr>
<tr>
<td>(warning: may be habit forming)</td>
<td></td>
</tr>
</tbody>
</table>

 Quiets the Stress / Quells the Spasm
The MEDICAL COLLEGE OF VIRGINIA QUARTERLY is designed primarily for the postgraduate education of physicians. The QUARTERLY will publish results of original research in basic and clinical sciences, and report on seminars and symposia held at the College. Contributions from outside the MCV faculty are invited.

Manuscripts, submitted in duplicate, should be prepared according to recommendations in the Style Manual for Biological Journals, 2nd Ed., published in 1964 by the American Institute of Biological Sciences, 2000 P Street, N.W., Washington, D.C. 20036.

Subscription rates in the USA and Canada: 1 year, $4; 2 years, $7; 3 years, $9. All other countries: 1 year, $5; 2 years, $8; 3 years, $10. Interns, residents, and students: 1 year, $2.

Correspondence: MEDICAL COLLEGE OF VIRGINIA QUARTERLY, Medical College of Virginia, Richmond, Virginia 23219. Phone: 703/770-4027.

Contents

From the Twenty-First Annual Stoneburner Lecture Series:
Diseases of the Kidney

New Developments in Hemodialysis for Chronic Renal Failure
LEE W. HENDERSON, Philadelphia, Pennsylvania

Conservative Management of Chronic Renal Failure
ROSCOE R. ROBINSON, Durham, North Carolina

Clinical Aspects of Renal Tubular Disorders
WILLIAM F. FALLS, JR., Richmond, Virginia

Focal Glomerulonephritis
ROBERT H. HEPTINSTALL, Baltimore, Maryland

Some Issues in Human Development
VICTOR C. VAUGHAN, Philadelphia, Pennsylvania

Present-Day Psychiatry
HENRY D. LEDERER, Richmond, Virginia

Recent Advances in Pediatric Allergy
F. STANFORD MASSIE, Richmond, Virginia

Student Honors Day: Abstracts of Scientific Presentations
MEDICAL COLLEGE OF VIRGINIA, May, 1968

Contributors to this Issue

Index to Volume Four

Table of Contents for Volume Four


© 1969 by Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University
New Developments in Hemodialysis for Chronic Renal Failure*

LEE W. HENDERSON

Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia 19104

Introduction

I am going to speak mainly about extracorporeal hemodialysis, that is, dialysis conducted with an artificial kidney as opposed to peritoneal dialysis. I am going to direct the majority of my comments toward the extraordinary technique of the maintenance of life in patients with chronic renal failure. I would like to break my discussion into three general areas: 1) a review of the historical development of the dialyzer, including some remarks on what happens at the membrane level; 2) a look at the results we are getting with this kind of hardware; and 3) a comment on some of the newer experimental dialyzers.

Historical Development

Figure 1 shows a dialyzer credited to Abel in 1913. This is a rather ingenious device for all its simplicity. It is a collection of collodion tubes, marked (C), contained in a cylinder of glass. Blood flowed through the collodion tubes and dialysis fluid through the cylinder surrounding them. This was the first successful extracorporeal hemodialyzer on record.

Figure 2 illustrates a device that is probably the most famous of the artificial kidneys. This was designed by Dr. Willem Kolff in Holland in 1943, 30 years after Abel's

* Presented at the Twenty-First Annual Stoneburner Lecture Series, February 22-23, 1968, Medical College of Virginia, Richmond.
first attempt. It consisted of a drum on which blood-filled tubes of cellophane were wrapped. This tubular cellophane was of the garden variety, food-wrapping sort. The loops were strung over a drum of stainless steel. Dr. Kolff’s original, I understand, was made from wooden bed slats and a variety of other makeshift gear that he assembled. This was translated by Dr. Merrill and himself at the Peter Bent Brigham Hospital into the gleaming stainless steel and plexiglass item you see in the figure. The blood leaves the radial artery of the patient. It is taken to the beginning of this helically wound spiral of cellophane. Movement of blood through the spiral is accomplished by the Archimedes screw principle. Eventually the blood is returned, after passing through a bubble trap, into a vein in the patient’s arm. The dialysis fluid is in the trough underneath the drum. The drum rotates with its lower third submerged in the dialysate and wets the membrane.

What happens at the membrane level? Figure 3 is a diagrammatic sketch of a cellophane membrane. The white circles represent large molecular-weight solutes, such as protein and the cellular elements, which are retained because they are too large to traverse the membrane. The smaller dark particles, of course, move easily through the pores of the membrane and are trapped in the dialysis fluid. The driving force is diffusion. Dialysis is, in essence, diffusion across a membrane, and is a simple matter of discharging gradients. The toxic solutes, e.g., urea, that are present in the blood in high concentration, are absent in the dialysis fluid and, therefore, move so as to discharge this concentration difference. The solutes that are small in molecular weight, and are desirable to retain in the blood, such as, possibly, sodium, can be placed in the dialysis fluid in physiologic concentrations. As a result of diffusion, abnormalities of serum sodium would asymptotically approach the normal value of the sodium in the dialysis fluid. Dialysis is a great normalizer.

Figure 4 is a photomicrograph of cellophane. You can see that the pores are less orderly. It looks like a haystack run over by a steam roller. The success of cellophane as a dialysis membrane was an empirical triumph. The selection of the membrane was an arbitrary one. Dr. Kolff used this, and it has been used ever since. There have been strong efforts to find better ones, but cellulosic membranes are still the most widely used item for dialysis.

Just to give you a comparison with our divine prototype, in Figure 5 you see on the left the artificial kidney membrane. Cuprophan is one of the best of the cellulosic dialysis membranes. On the right is the glomerular basement membrane. An axiom in dialysis is that the shorter the diffusion path, the more efficiently you can move solutes. If you had your option, you would take the thinnest dialysis membrane available that could tol-
erate the pressure gradient without rupturing. As you can see, we are still far from the natural membrane.

To move back to the historical side, the next development came when a young surgeon in Philadelphia named William Inouye decided that the large, rotating drum dialyzer which is, to put it in perspective, like a small sarcophagus, could be reduced in size, and that this would be an advantage. He wrapped the cellophane tubing up so that it was now a tightly wound spiral separated by a supporting screen. This membrane package fit neatly into an old pressure cooker. Dialysis fluid was then percolated up through the screen. This was later to develop into the twin-coil kidney. Dr. Inouye reported this modification in 1953. Dr. Kolff improved the design and in 1955 came out with his first twin-coil kidney. The circuitry for the twin-coil is presented in Figure 6 and is relatively straightforward. Blood leaves the artery, moves through a blood pump, and goes to the cellophane coil in the inner bucket. Dialysis fluid is pumped over the cellophane membrane, where diffusion occurs. The blood then returns to bubble traps and is returned to the vein.

There are a variety of artificial kidneys that have been developed since the original rotating drum and the development of the twin-coil kidney. The parallel flow plate dialyzers, such as the Skeggs-Leonards and the Kiil, came along after the development of the rotating drum. The next significant development had to do with the deliberate attention paid by Dr. B. H. Scribner in 1960 to the problem of what could be done with the patient in chronic renal failure. Up until then, such devices had been successfully applied to patients with acute renal failure, but that was all. In 1964, W. Quinton reported a device for ready access to the blood vessels of the patient. Clearly, the limiting feature of repeated

Fig. 4—Electron micrograph of cellophane.

Fig. 5—A comparison of Cuprophan and glomerular basement membrane.
dialysis had to do with access to blood vessels. These vessels had to be cut down on surgically and tied off after the procedure. This could be carried out relatively few times. Mr. Quinton addressed himself to the design of a shunt, and Dr. Scribner applied this to the care of patients with chronic renal failure. In Figure 7 we see such a shunt implanted in the forearm. The radial artery is used, and blood returns to the vein running out of the "snuffbox" on the forearm. The loop on the left can be removed, and this, then, provides access to artery and vein. The kidney leads are attached to the shunt. This has worked exceptionally well. Shunts have been left indwelling on single placement without change for as long as a year. The problem that can arise is infection, usually staphylococcal. Such an infection may result in septicemia. More frequently the shunt clots, so you lose your shunt site and have to reimplant higher in the same vessel or in a different area.

In 1964, a variety of workers began to experiment with simplifying dialysis technique to the point where it could be carried out in the home. Drs. Merrill in Boston, Shal-don in England, and Scribner on the West Coast all became interested in home dialysis. They saw in this a technique that was more economical in that the costs incurred for bed charges in a hospital, nursing personnel, etc., could be eliminated. Home dialysis, then, and placement of the shunt in the leg rather than the arm, so that the patient could put himself on the kidney, was the next major development.

In 1966 Dr. M. J. Brescia, going a step beyond Scribner (1965), created an arteriovenous fistula of the vessels that are usually used for the placement of the shunt and, in that way, created a hypertrophied venous tree that could be negotiated with a percutaneous stick using large gauge needles. There are cosmetic benefits as well as the likelihood that the incidence of infection would be reduced and, hence, the incidence of clotting. This has proved to be the case in the trials that have been carried out so far. We have had several patients
with this particular form of fistula. We have had one patient in particular, a lawyer, who has used both of these techniques. He started with the traditional Quinton arteriovenous shunt and moved on to the Brescia fistula. He thinks that, even though it means the pain of a percutaneous stick every time, the latter is by far the method he prefers.

Results

So much for the technique and equipment. I'd like to focus for a moment on what may be more controversial, namely, the results of all of this. I think that there are a number of parameters that have to be looked at fairly closely before assessing whether this technique is a success or a failure. One guide that is of quite evident importance is the survival rate. Survival figures seem to be quite good, according to the September, 1967 "Report of the Committee on Chronic Kidney Disease" submitted to the Bureau of the Budget.* Of 302 patients followed for up to seven years, survival is 87% at one year, 67% at three years, and 58% at seven years. The number of patients clearly is small, and these figures may change as more patients are added. The cases that are reported at the seven-year mark with 58% survival represent three of the original cases studied by Scribner in 1960. This figure may change radically as we see larger numbers of patients moving through this technique. As far as mortality goes, if we can guarantee seven more years of life for 60% of the people who invest their time, I think this is a handsome success.

Clearly there are other parameters that have to be looked at, not the least of which is the quality of life maintained. Is this the simple preservation of a hopelessly sick person who is not back in the community, or is there real rehabilitiation? In trying to make this assessment, which is an exceptionally difficult one, it is important to ask first, "What does the patient have to invest?" and second, "Is the investment worthwhile?"

To any of you who have had close association with chronic dialysis, it is clearly recognized that this is not a simple technique for the patient to undergo. He has to be prepared to put up with a great deal to survive. This is a technique for people who are intelligent and capable, and if they are not both, as well as conscientious about caring for themselves, they quickly die. Two to three times a week they have to invest six to twelve hours on an artificial kidney. If this is done in a kidney center during traditional working hours, this cuts into their day as productive citizens, unless, of course, they are employed in some unusual occupation that permits work at night. Many centers have solved this by providing nighttime dialysis. In home dialysis, hopefully the patient puts himself on the machine at 8:00 in the evening, sleeps quietly through the night, and awakens in the morning to take himself off the kidney. But, nonetheless, this is a significant investment of time. In addition, you are asking your patient to rigorously restrict his fluid intake. In the face of ongoing thirst, this can be exceptionally difficult. Every drop of fluid taken in excess of, say, a 300-400 cc insensible loss per day (most of these patients do not make a significant quantity of urine), has to be taken out with the artificial kidney. You ask your patients to hold down their intake to 500-800 cc of fluid per day, even though they are thirsty. Protein is restricted; potassium is restricted; sodium is restricted; so that attention to diet is probably the most onerous requirement you are asking these patients to fulfill. Your patient investment here is substantial.

It is quite clear from what I say that it is imperative to select the patient from the standpoint of reliability and emotional stability. A staunch psyche is almost prerequisite. In addition, it is important to have strong family support for patient and procedure. So the pa-

* Prepared by a committee of which Dr. C. W. Gottschalk was Chairman.

Fig. 7—Quinton-Scribner arteriovenous shunt. Stainless steel stabilizers.
tient and family investment is substantial.

What do they get for their investment? Can these people be rehabilitated? Are they back on the firing line? Could they go out and dig a ditch for a living? In general, they cannot. This is a near-normal but not a normal state. The fatigue level of a patient on chronic dialysis is still substantially below normal.

There are ongoing complications that can occur in spite of good dialysis, one of which is neuropathy. Progressive neuropathy of the peripheral sort can provide crippling incapability of the lower extremities. This can rapidly progress even in the face of “adequate” dialysis. The details of why this occurs have yet to be worked out.

Pruritus can be very persistent in some chronic dialysis patients. I was amused when Dr. Setter took me over to view the dialysis unit here at the Medical College of Virginia to see one of the small Chinese carved hand backscratchers lying on the overbed table of one of the chronic dialysis patients. This reminded me of the motto that the medical residents rotating through our service have pasted with adhesive tape over our dialyzer—“Semper pruritus.” Excoriation of the skin with subsequent infection in a patient who does not fight infection well can provide a serious problem.

Anemia is another problem. It is evident that when kidneys are seriously diseased, erythropoietin is present at unmeasurably low levels in the blood; there may be a hemolytic component as well. In addition, the bone marrow does not make red cells normally so that even with good substantial dialysis, these patients do carry a low hemoglobin, usually around 8 gm/100 cc. This may contribute to the fatigue syndrome of the chronic uremic.

Patient rehabilitation is hard to assess. Reports vary enormously depending on whom you read. Most report a reasonable rehabilitation rate (Brown et al., 1962; Gonzalez et al., 1963; Kretchmar et al., 1963; Maher, Freeman and Schreiner, 1965; Rubini, Wolfram and Sokal, 1966; Comty et al., 1966). There are few ditch diggers reported that have done well. You can read the experiences of others, such as Retan, in Detroit, where rehabilitation has been very bad. A lot of the success or failure has to do with the vigor that the investigator or the physician applies to motivate his patients. There is almost a religious atmosphere to the attitudes of the patients trained in the Seattle centers. Dialysis is treated as an end in itself. This becomes a difficult religion to instigate in a patient if there are other programs at the institution which may have a higher priority. This has been difficult for us in our unit with transplantation and chronic dialysis both ongoing. Rehabilitation, then, is a complex function of patient, institution, and professional staff.

Let us move on to another parameter of success. How are we doing numerically? Are we getting ahead? There are a variety of figures given. The most solid come from the “Report of the Committee on Chronic Kidney Disease.” Thirty-five thousand patients per year die of chronic renal failure. Of that group, there are some 7,000 per year who would be good candidates for either dialysis or transplantation. In the last three years there has been an enormous input of effort and money for the setting up of chronic dialysis programs throughout the United States. The USPHS has given grants to establish dialysis units on a trial basis, the Veterans Administration Hospitals have set up a string of hemodialysis units associated with their hospitals, and most university hospitals now have such facilities. All in all, there has been a burgeoning of the hemodialysis effort. How many patients of these 7,000 per year are now on the machines? At this moment, approximately 800. The rather ridiculous logistics of the present situation are apparent. If we are receiving 7,000 patients for care each year, and at the present state of the art are saving only 800, something clearly needs changing.

Moving on to another rather sticky wicket, how about the monetary end? According to the “Report of the Committee on Chronic Kidney Disease,” in-patient chronic dialysis costs, on the average, $14,000 per year per patient. The most economical way to arrange chronic dialysis is at home, but this still costs $5,000 per year, after an initial outlay of about $10,000 for equipment and supplies. This cost of home dialysis in most situations is borne by the patient. Quite clearly, this introduces a selection process into the patient population for chronic dialysis that I am not sure would meet with the best standards of a democratic society. When you realize that an in-patient chronic dialysis slot lasts for at least seven years, if you are doing your job properly, with the annual cost being as high as it is, it is no wonder that most insurance underwriters and hospital administrators blanch when chronic dialysis is proposed. The lives saved-per dollar spent ratio with chronic dialysis leaves a good deal to be desired.

Clearly I feel that this is a dramatic lifesaving technique that the medical profession should be proud to have. It should be broadly available, but in order to make it so there have to be some improvements. One of the improvements is that of cost. Along this line, there was an interesting parenthetical comment injected by a member of the Tokyo Society for Artificial Internal Organs at the 1967 meeting of the American Society for Artificial Internal Organs. This gentleman stood up and said, “Be aware of the Japanese invasion. We are importing cellophane and fiberglass screens and making coils that we will send to the United
States,” at a cost, as I recollect, of about $20. This, taken in perspective of the $70 fee that the coil he was describing was then selling for on the American market, shows one important area of improvement that will come along.

New Designs

There are a number of things on the drawing board for the future that I think bear close attention. Moving to one approach in the new design category, Figure 8, with all apologies to Chester Gould and Dick Tracy, was drawn by my colleague, Dr. L. W. Bluemle, and depicts an imaginary miniature dialyzer. It exemplifies one approach to design. This would be to develop a small, wearable, continuously dialyzing system. I think you can project this dream to say that the patient straps a tank of dialysis fluid around his waist in belt fashion and is good for the day. Miniaturization is one approach that the innovators in artificial kidney design have taken. There are two examples of this approach that I would like to show you. One (Fig. 9) is a so-called accordion, push-pull, or tidal flow dialyzer. It is nothing more than an accordion folding of sheet cellophane into a package that would fit neatly in the palm of your hand. This particular configuration permits enormous membrane area to be put in a small package, and, by an appropriate valving mechanism, this rather small membrane package can be used for dialyzing. This was the brainchild of Dr. Bluemle. There are now at least two groups working with this concept.

Another particularly ingenious approach to the problem is the spinning of cellophane capillary fibers. These are hairlike tubes that are made of cellophane. Again, tremendous membrane area can be packed into a very small place. Another approach to the design problem is to come up with a high efficiency dialyzer in order to cut dialysis time to an absolute minimum. Under improved efficiency can come such developments as better membranes and better membrane supports.

A particular approach to a higher efficiency unit has been worked on in our laboratory by Dr. Bluemle and me. Figure 10 at first glance looks rather complicated. It is a device that employs ultrafiltration, not diffusion, as its means for cleansing blood. Diffusion is inherently a slow process. It would be nice to be able to apply some extrinsic force to move toxic solutes out of the body, and we are attempting to use ultrafiltration pressure as just such a force. The figure shows a cross section of such a diafilter, and the inset illustrates the central blood path. In addition, there are two other paths, one on either side of the blood path. The first is under positive pressure (10 PSI), forcing fluid through an ultrafiltration...
Blood membrane into the blood; the second, on the other side of the blood path is under negative pressure, drawing the fluid right across the flowing blood stream, carrying with it all solutes that have traversed the ultrafiltration membrane. The success of such a device depends on these two membranes and their properties. The glomerular basement membrane, after all, does this sort of thing very nicely. The glomerulus is not a dialysis membrane; it is an ultrafiltration membrane and, as such, has a very high efficiency. The present design is an attempt to match this efficiency by using simultaneous ultrafiltration and reconstitution of blood. We have suitable ultrafiltration membranes available to us now, and I am sure we are going to see developments of this sort as another important step in increasing efficiency.

References


Conservative Management of Chronic Renal Failure*

ROSCOE R. ROBINSON

Division of Nephrology, Duke University Medical Center, Durham, North Carolina 27706

The successful application of chronic dialysis and/or renal transplantation to patients with chronic uremia has sometimes obscured the fact that significant progress has also been made in our understanding of other therapeutic approaches to chronic renal failure. These less dramatic advances are commonly labeled “conservative” in nature, yet they have contributed decisively to the welfare of many uremic patients by improving their sense of well-being and delaying their need for such types of therapy as regularly repetitive dialysis. I shall comment first on certain general principles of management and then review some of the scientific therapeutic maneuvers and concepts that comprise the main foundation for the so-called conservative management of chronic uremia. Although my remarks are directed primarily toward patients with progressive primary renal disease, they are of equal pertinence to patients with renal failure of several types or etiologies.

General Principles of Management

The progressive destruction of renal tissue effects an ever changing clinical pattern in which new and different signs and symptoms appear at differing rates in individual patients. All would agree that conservative therapy should be initiated prior to the appearance of terminal renal failure, but general agreement has not yet been reached on the exact time at which certain dietary programs should be started during the earlier phases of disease. Nevertheless, once therapy has been initiated, additional conservative measures must be added until the entire conservative armamentarium, including an occasional dialysis, becomes insufficient to sustain useful life. Chronic dialysis and/or renal transplantation must then be considered. It is important to realize that conservative therapy, dialysis, and transplantation must be combined carefully for best results. One of these therapeutic approaches cannot be used to the exclusion of the others. Certainly the institution of chronic dialysis does not eliminate the need for conservative therapy. Optimal treatment reflects a continuum of effort utilizing several therapeutic concepts and modalities.

If I can assume today that we are dealing with an azotemic patient whose underlying renal disease is irreversible, our first management responsibility should be the exclusion of factors that may have reversibly intensified the degree of azotemia. In order to appreciate the unique importance of reversible factors in the treatment of chronic uremia, we must also understand the well-established relationship between changes of the blood-urea-nitrogen (BUN) concentration and the creatinine clearance or any other index of filtration rate. From an analysis of Figure 1 it is evident that the BUN concentration varies inversely with associated changes of filtration rate. Although the BUN concentration rises with the earliest reduction of filtration rate, it ordinarily does not exceed the upper limits of normal until the filtration rate has been reduced to between 25% and 50% of normal. Furthermore, from any point of departure, a 50% reduction of the filtration rate can be expected to effect a corresponding twofold increase of the BUN concentration. Obviously the patient whose filtration rate is only 10 ml/min, or approximately 10% of a hypothetically normal value, cannot afford to sustain a further 50% reduction of filtration rate, even transiently. All other factors being constant, a transient reduction of filtration rate from 10 to 5 ml per minute might be accompanied by an increase of the BUN concentration from, perhaps, 75 to 150 mg per 100 ml.

The relationship between functioning renal mass and the signs and symptoms of renal failure can be described similarly (Fig. 1). When the limits of renal reserve have been exceeded, uremic symp-
culture should be mandatory in every patient with chronic renal disease. The presence of a systemic infection with fever and tissue injury can markedly accelerate the development of azotemia by increasing protein catabolism and the subsequent presentation of nitrogenous products to the organ for excretion. Correctable causes of urinary tract obstruction must also be sought. Intravenous urography is the safest technique for such a diagnostic search, but special roentgenographic techniques utilizing large doses of contrast media may be required in patients with severe renal failure.

Lastly, the presence of salt and/or water depletion, when viewed collectively, represents an extremely common event leading to a reversible intensification of renal failure. Gastrointestinal losses from nausea and vomiting or even overnight water restriction for a concentration test or an intravenous urogram may initiate a serious chain of events. A decrease in extracellular volume leads to a reduction in filtration rate and a decrease in urine flow, thereby compromising still further the excretory efficiency of an already damaged kidney.

Factors such as those in Table 1, if present, must be identified promptly and corrected judiciously. Once this is accomplished, the efforts of the physician can then be directed toward the specific management of other uremic signs and symptoms.

In simplified fashion, Figure 2 depicts an essential characteristic of the functional response of the diseased kidney to variations in the excretory load of water, nitrogenous products, or electrolytes. Although the functional response of the residual nephron population may be perfectly normal in a qualitative sense, it may be lacking in another important respect—namely, in the flexibility of its response. The diseased kidney is unable to compensate rapidly and efficiently for associated changes in the volume or composition of the body fluids. As illustrated by the solid arrows, the normal kidney can rapidly and effectively adjust its rate of excretion to dispose of a wide range of excretory loads, so that excretion can equal intake plus production minus internal degradation. If the excretory load is large, the healthy kidney quickly increases excretion to equal the load; if the excretory load is reduced, renal excretion is reduced efficiently and appropriately. In contrast, as shown by the dashed-line arrows, the range of excretory adjustments by the diseased kidney to similar loads is restricted severely. When the load is large, the excretory capacity may be insufficient to effect complete disposal; when the load is reduced sharply, the capacity to reduce excretion (conservation) may be insufficient to prevent the appearance of a body deficit. Excretory adjustments cannot be increased to the usual maximum or decreased to the usual minimum. As a consequence, both excess and deprivation are tolerated poorly. It then becomes the responsibility of the physician to adjust the intake to equal the excretory capacity instead of depending on the functional response of a damaged organ to make the necessary excretory adjustments.

Specific Management Problems

An incomplete list of specific management problems or considerations that must be entertained is given in Table 2. Those items followed by an asterisk can be approached at least partially by appropriate adjustment of dietary intake. Their very number offers mute testimony to the fact that dietary therapy affords a major foundation for the management of chronic uremia.

First, let us consider the adjustment of water intake in nonoliguric patients with severe chronic uremia. In such patients, water excess with dilutional hyponatremia is
a frequent consequence of aggressive fluid therapy. This phenomenon may be seen when a conscious patient with chronic uremia is asked to force fluids for the performance of an ill-advised P.S.P. test. Occasionally, excessive fluid intake is prescribed because of the mistaken impression that renal function can be improved. The modest reduction in azotemia that may occur as a consequence of such a maneuver may be viewed as the net effect of hemodilution and a modest increase in urine flow; it does not reflect an improvement of glomerular filtration. Dilutional hyponatremia may also appear, simply because the intake of water has been increased above the excretory capacity of the damaged kidneys. In many patients, a suitable intake of water is that which is dictated by thirst. In other patients whose filtration rate may be reduced more severely, certainly below 5 ml/min, the intake of water may have to be adjusted so that it exceeds an already near-maximal urine output by no more than 300 to 400 ml per day. In such patients, water retention may occur if the total daily fluid intake, perhaps even including dietary water, is increased to a value no higher than 1500 ml. Consequently, an arbitrary and ideal fluid intake that is suitable for all patients cannot be identified. Rather, maximal fluid intakes can be ascertained only by serial observations of body weight, urine output, and fluid intake. Conversely, despite the fact that gross water wasting is rare in chronic renal failure, one may find patients with obligatory minimal urine volumes consequent to an endogenous solute diuresis which may be as high as 2 liters/day. Such patients may rapidly become water-depleted if intake is restricted for any ill-advised reason. Drugs that cause nausea must be used with caution, and hospital procedures that promote dehydration should not be employed. Obviously, a water deficit, if present, should be treated appropriately.

The existence of chronic renal disease should not be equated with a necessity for sodium restriction. In fact, in the absence of edema and, perhaps, severe hypertension, rigid dietary sodium restriction is contraindicated. As renal failure progresses, the diseased kidney loses its normal capacity to alter sodium excretion over a wide range. In contrast to the usual sequence during good health when renal sodium conservation is extremely efficient (Fig. 3), the diseased kidney cannot reduce urine sodium excretion maximally, even after a relatively long period of dietary deprivation. Although the daily quantitative deficit is small, a larger and significant cumulative deficit may occur over a more protracted period. Sodium may be lost in the urine in small amounts even in the presence of a falling concentration of serum sodium. Hyponatremia will occur if the patient drinks excess electrolyte-free water or loses sodium in excess of water via other routes. The loss of GI secretions by vomiting or diarrhea represents another important cause of sodium depletion. Replacement of fluids with salt-free solutions such as 5% dextrose in water may restore extracellular volume at the cost of hyponatremia. Sodium depletion may be facilitated further by the injudicious use of potent diuretics in patients whose dietary sodium has been rigidly restricted. It is important to remember that the residual nephron population can effect a significant increase in fractional sodium excretion in response to the use of potent diuretics such as furosemide, even when the filtration rate is as low as 1 ml/min. Once again, the quantitative daily deficit may be small, but long-term diuretic therapy may contribute to the appearance of a significant sodium deficit.

Conversely, when the dietary salt intake is increased, the patient with renal disease may be unable to excrete the same sodium load that could have been handled with ease.

### Table 1

<table>
<thead>
<tr>
<th>Reversible Causes of Filtration Rate Depression in Patients with Underlying Renal Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Congestive heart failure</td>
</tr>
<tr>
<td>2. Infection</td>
</tr>
<tr>
<td>a. Genitourinary</td>
</tr>
<tr>
<td>b. Systemic</td>
</tr>
<tr>
<td>3. Urinary tract obstruction</td>
</tr>
<tr>
<td>4. Salt and water depletion</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Management Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Salt and water requirements*</td>
</tr>
<tr>
<td>2. Control of azotemia and maintenance of nitrogen balance*</td>
</tr>
<tr>
<td>3. Hyperkalemia*</td>
</tr>
<tr>
<td>4. Acidosis*</td>
</tr>
<tr>
<td>5. Anemia</td>
</tr>
<tr>
<td>6. Infection</td>
</tr>
<tr>
<td>7. Other:</td>
</tr>
<tr>
<td>a. Hypertension</td>
</tr>
<tr>
<td>b. Edema and/or heart failure*</td>
</tr>
<tr>
<td>c. Bone disease</td>
</tr>
<tr>
<td>d. Uremic syndrome: nausea, vomiting, pruritus, malaise, CNS irritability, etc.*</td>
</tr>
</tbody>
</table>

Fig. 2—Renal response to complete dietary sodium restriction in health and renal disease.
by a patient with normal renal function. Sodium intake must be kept sufficiently low to avoid sodium excess. Ideally, one would prefer to maintain the sodium intake at a level that is somewhat below that amount which is capable of inducing sodium excess. In practice, the upper limits must be defined individually for each patient, since they are not predictable with confidence. Most importantly, one must also realize that both the upper and lower limits of sodium excretory adjustments may change with the passage of time and the progression of disease. In the absence of edema or congestive heart failure, it is our own practice to initiate therapy with a 5 gm or 85 millimol salt (NaCl) diet. If sodium bicarbonate is required for the treatment of systemic acidosis, the dietary intake of sodium chloride may have to be reduced equivalently. In other patients, even greater amounts of sodium chloride may be tolerated safely. On admission, some patients may exhibit unrecognized salt depletion with plasma volume contraction and filtration rate reduction. The judicious administration of salt and water, with subsequent stabilization of the body weight somewhat above the admission weight, as well as a measurable increase of creatinine clearance strongly suggest that salt depletion was present. After replacement, the maintenance salt intake is prescribed at a level somewhat below the defined upper limits of excretory capacity.

Important complications of, or contraindications to, an excessive intake of sodium are hypertension or the appearance of a congestive state. With certain exceptions, there is general agreement that the treatment of hypertension can be accomplished satisfactorily with drugs in the usual nonoliguric patient. In such patients, the hazards of rigid dietary sodium restriction would seem to weigh the small contribution of dietary sodium restriction to the control of diastolic hypertension. Of course, in patients whose renal function is so reduced that repetitive dialysis is required, rigid limitation of the dietary intake of salt and water may well be necessary to control hypertension and prevent salt and water excess. The choice of anti-hypertensive drugs rests largely on the experience of the physician. Apresoline, alphamethyldopa, and guanethidine have all been used successfully.

The data in Table 3 reflect an average expression of the traditional views of most physicians regarding dietary protein restriction. Theoretically, dietary protein restriction might be expected to minimize the intensity of systemic acidosis, and there is good evidence to support the notion that the reduction of azotemia may restore a sense of well-being to patients who complain of malaise, anorexia, nausea, and vomiting. There is somewhat less agreement as to just when dietary protein should be restricted in patients with early renal failure. Certainly, there is little evidence that azotemia, itself, is harmful to the asymptomatic patient with mild and uncomplicated renal failure, and in such a patient there may be little basis for rigid dietary protein restriction. The indications for dietary protein restriction in Table 3 admittedly are arbitrary, but they are in agreement with common practice at many institutions. The usual low-protein hospital diet necessitates a protein intake at the indicated level, if negative nitrogen balance is to be avoided. Overall, the goal of protein restriction is to reduce protein catabolism while simultaneously avoiding the hazards of nitrogen depletion. To this end, dietary protein restriction should be coupled with the provision of adequate protein-sparing calories such as carbohydrate and fat, the prevention and treatment of infection, the encouragement of maximal tolerable ambulation, the avoidance of unnecessary surgery and manipulation, the provision of anabolic steroids, and the avoidance of inhibitors of protein anabolism such as tetracycline and adrenal glucocorticoids.

Recently, two European investigators, Giordano (1967) and Giovannetti (1967), have been associated with an increased interest in the control of uremic symptoms by dietary management. Their own clinical results have been impressive, and most would agree that the morbidity of chronic uremia appears to have been lessened significantly by their dietary efforts. Basically, these investigators have demonstrated that nitrogen balance can be maintained and that protein depletion can be avoided by the provision of remarkably low nitrogen diets if the dietary protein is comprised of proteins of high biological value. Nitrogen balance has been maintained in patients with chronic uremia on a dietary protein intake as low as 15 to 20 gm per day. Marked clinical improvement has been observed simultaneously. Anorexia, nausea, vomiting, fatigue, twitching, and mental changes have disappeared completely or decreased significantly. The severity of anemia has been ameliorated in a few patients. Fundamentally, low-protein diets are directed toward control of the

---

R. R. ROBINSON

---

**TABLE 3**

<table>
<thead>
<tr>
<th>Dietary Protein Restriction in Renal Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rationale:</strong> 1) Diminished accumulation of metabolic acid, urea, and other nitrogenous products</td>
</tr>
<tr>
<td><strong>Indications:</strong> 1) Azotemia (BUN &gt; 50 mg/100 ml) 2) Hyperphosphatemia 3) Acidoses</td>
</tr>
<tr>
<td><strong>Amount:</strong> 1) 0.5 to 0.6 gm per kg plus urinary losses</td>
</tr>
</tbody>
</table>
serious nutritional defects that are characterized by weight loss, profound weakness, and gross evidence of decreased muscle mass. In the past, concern over the nutritional status of the uremic patient was often considered futile, because the presence of severe nausea and vomiting appeared to prevent adherence to an effective nutritional regimen. Obviously, if malnutrition is to be avoided, a diet for uremic patients should contain sufficient calories to exert a maximal protein-sparing action and sufficient amino acids of appropriate quality and quantity to promote optimal protein synthesis without increasing the degree of azotemia.

In patients whose creatinine clearances were as low as 5 ml/min, Giovannetti has shown that the institution of a basal diet containing small amounts (12 gm) of high biological protein can be associated with a simultaneous decrease in both azotemia and the negativity of overall nitrogen balance. The further addition of essential amino acids in amounts sufficient to increase the total protein intake to between 15 and 20 gm was followed by the appearance of slightly positive nitrogen balance without an attendant increase in azotemia. Similar results were achieved when egg protein was utilized instead of individual essential amino acids. For practical purposes, the additional nitrogen, as essential amino acids, appeared to be utilized completely without inducing a measurable increase in overall protein catabolism. Furthermore, the urease-induced elaboration of ammonia nitrogen in the gut provided a pathway for the re-utilization of endogenous urea nitrogen for protein synthesis. One important fact that emerges from these studies is the realization that it is possible to improve the nutrition of the uremic patient via the provision of extremely low-protein diets of high biologic value, and that their use may be associated with striking clinical improvement, even in individuals with severe filtration reduction.

Unfortunately, the diets of Giordano and Giovannetti are much better suited to Italian than American tastes. Recently, however, a variety of similar low-protein diets have appeared in this country and seem to offer great promise. Monotony, rather than palatability, constitutes the major barrier to their acceptance by the patient. Basically, these diets consist of appropriate fruits and vegetables, other sources of carbohydrate and fat, and egg protein. Recently, lactalbumin from electrodialyzed whey has been utilized as a protein source of high biologic value. It can be offered to the patient as a reasonably palatable, albeit monotonous, milkshake-like drink. These diets prohibit the use of flour in any form, and special baking recipes have proliferated, each of which utilizes pure wheat starch. Low-protein bakery products of wheat starch can be quite satisfactory, although baking with wheat starch does pose many culinary problems for the housewife. These products are fast-rising, and housewives must learn to initiate the baking process in a cold oven rather than one that has been prewarmed, if they are to avoid a product that has a consistency resembling castiron. At present, at least one commercial company with national distribution is experimenting with a ready-mix baking product of wheat starch that may prove to be satisfactory and originative. As long as facilities are so limited that the patient’s admittance to repetitive dialysis must be delayed, the extra effort involved in these dietary manipulations would appear to justify their time and expense.

Acidosis (Table 3) is a constant feature of chronic uremia that should be controlled, because it may lead to such adverse events as an extracellular shift of potassium and the appearance of hyperkalemia, increased respiratory effort, anorexia, somnolence, bony demineralization, and even, perhaps, reduction in the effectiveness of endogenous insulin. Efforts directed toward minimizing protein catabolism also decrease the endogenous production of fixed acid, and the provision of an additional buffer such as sodium bicarbonate helps to neutralize the effects of excess metabolic acid. We prefer to utilize sodium bicarbo-
nate, rather than sodium lactate, in a daily dose sufficient to maintain the plasma bicarbonate concentration between 18 and 20 mmole per liter. The lactate anion, as you are aware, must first be metabolized, and there is some evidence that the hepatic degradation of lactate may be significantly impaired in uremia. If edema is present and sodium bicarbonate therapy is required, it is obvious that the dietary intake of sodium chloride may have to be reduced in order to keep the total dietary sodium intake within the desired range. Unfortunately, in some patients, one may have to accept an incomplete control of acidosis if aggravation of congestive heart failure by sodium salt administration is to be avoided. Peritoneal dialysis provides a convenient way of correcting severe acidosis without an associated net addition of sodium to the body.

Several therapeutic maneuvers may be utilized in the management of acute hyperkalemia (Table 3). It is true that serious hyperkalemia is uncommon in the usual nonoliguric patient with chronic renal failure. On the other hand, a marginal and persistent elevation of the serum potassium concentration is rather frequent in our experience. The correction of acidosis alone will often facilitate the control of this type of hyperkalemia. An adjustment of sodium intake may also be of importance. We have seen patients on rigid dietary sodium restriction in whom the provision of increased dietary sodium was accompanied by a reduction in modest hyperkalemia, perhaps as a consequence of the increased availability of sodium within those portions of the nephron where sodium-potassium-hydrogen exchange occurs. Sodium-cycle cation exchange resins may be used effectively in small daily maintenance doses. Since their use contributes to the dietary intake of sodium, an appropriate reduction of dietary sodium may be necessary if the control of sodium balance is important. Lastly, the appearance of hyperkalemia can be minimized greatly by moderate dietary restriction, an avoidance of potassium-containing drugs, and prompt control of increased catabolism due to fever, etc.

Anemia is probably best untreated, unless it is symptomatic (undue fatigue, angina, etc.) or unusually severe and complicated by bleeding or excessive hemolysis. The etiology of the anemia of chronic renal failure, in the most general terms, can be related to the net effect of bone marrow suppression, increased hemolysis (perhaps as a consequence of an extracellular hemolysin), defective erythropoietin production by the kidney, and bleeding. Transfusion is the treatment of choice, and maintenance of the hematocrit between 18 and 25 vol% is generally adequate for the relief of symptoms. A further increase serves little purpose, and the short-lived survival time of even fresh red cells in uremic patients often means that repeated transfusions will be necessary. Since the restoration of volume is not a consideration, the use of fresh-packed red cells is preferable. Other types of therapy have been tried (vitamin B₁₂, cobalt salts, etc.), but their use is often impractical, and predictable benefits have not been observed.

Time does not permit detailed discussion of all the items listed in Table 3. However, in closing, I would like to comment briefly on just a few additional therapeutic approaches. The use of anabolic agents has some degree of merit, in my opinion. It is difficult to establish proof in a given individual that agents such as norethandrolone or oxandrolone really contribute to the management of uremia, although, in perhaps a third of the patients, some decrease in protein catabolism and azotemia may be observed. If an anabolic agent is utilized, one with minimal virilizing effects should be chosen. Pruritus can be controlled in some patients by the use of selected antihistamines; symptomatic relief of nausea can be provided by many members of the phenothiazine family. Finally, the control of hyperuricemia is deserving of comment. Whether or not hyperuricemia should be controlled at all is, perhaps, problematic. There is little factual evidence as to whether hyperuricemia per se contributes either to progression of the underlying disease or to uremic symptomatology. Hypothetically, either circumstance is possible. Empirically, we have treated several patients with allopurinol, a potent inhibitor of xanthine oxidase. Therapy has been restricted to patients with marked hyperuricemia (> 12 mg/100 ml), and impressive reductions of the plasma uric acid concentration have been observed. Nevertheless, further investigation is required to establish the real benefits of such therapy.

In closing, I would emphasize that I have failed to discuss many equally important aspects of conservative management. Uremia is a strange disease; it is a difficult illness for the patient, and it is one that requires careful preparation of the family for long-term involvement. If dialysis or transplantation cannot be performed, our minimal objective should be the provision of life that is at least as comfortable as possible. For the most part, this objective can be achieved with proper attention to the selection of tools from our conservative armamentarium.

References
When most clinicians consider problems in renal disease, they think in terms of levels of blood, urea, nitrogen, and creatinine, and the presence of red cells, white cells, or protein in the urine. In essence, they think primarily of disease of the glomerular filter or loss of total nephron mass. Indeed, most of the signs and symptoms of patients with commonly recognized renal diseases are related to retention of various noxious materials which cannot be adequately cleared because of the reduced glomerular filtration rate.

Despite the overwhelming frequency of diseases involving the glomerulus, I would like to discuss a number of interesting clinical renal problems that are primarily characterized by insufficiency of one or more tubular functions in the presence of continuing adequate glomerular operation. These conditions are not common but are of great importance, because several are amenable to therapy and because each is an experiment in nature displaying the profound physiologic consequences of anatomical abnormality or biochemical dysfunction of a particular portion of the renal tubule.

The diseases that I plan to discuss are listed in Table 1 and can be divided into groups according to localization of disorder within the tubule and the specificity of defect. Specific defects localized to the proximal tubule include: renal glycosuria; phosphate diabetes; cystinuria, which until recently was considered to be solely a defect in dibasic amino acid reabsorption; and Hartnup disease, which is a defect in monoamino-monocarboxy amino acid reabsorption. Generalized defects of tubular transport are included under Fanconi syndrome. The distal tubular problems to be discussed include renal tubular acidosis and nephrogenic diabetes insipidus. Study of patients with these disorders has shed much light on the normal function of the renal tubule.

Fig. 1—Schematic representation of a nephron with reabsorptive sites for various substances indicated. The water-impermeable portion of the tubule is indicated by the solid line. The broken line indicates the site of action of ADH.
Review of Renal Tubular Physiology

It is evident that the renal tubule profoundly alters the volume and composition of the 100 cc of filtrate entering Bowman's space before it appears in the bladder as 0.5 cc of urine (Fig. 1). The filtrate, as it enters Bowman's space, contains large quantities of glucose, amino acids, phosphate, bicarbonate, urate, sodium, and many other filterable constituents of plasma. All or most of these substances are reabsorbed by the renal tubules. Most reabsorption of these materials and water occurs in the proximal portion of the nephron with only about 20% of the isotonic filtrate entering the descending limb of Henle's loop. Reabsorption of glucose, amino acids, and filtered protein is virtually complete in the proximal tubule. About 80% of the filtered bicarbonate is reabsorbed there; the remainder is reabsorbed more distally in association with the formation of titratable acid, ammonium and a maximally acid urine. It is also in the more distal portion of the tubule that the remaining filtrate is initially made hypotonic by sodium extraction from the tubular fluid as it passes through the water-impermeable,

**TABLE 1**
Disorders of Renal Tubular Function

1. Specific Disorders of Proximal Tubular Function
   A. Renal Glycosuria
   B. Phosphate Diabetes (Vitamin D-Resistant Rickets)
   C. Cystinuria
   D. Hartnup Disease

2. Generalized Disorder of Proximal Tubular Function (Fanconi Syndrome)

3. Disorders of Distal Tubular Function
   A. Renal Tubular Acidosis
   B. Nephrogenic Diabetes Insipidus

Since glucose and amino acids are reabsorbed by movement from a lower tubular concentration to a higher peritubular concentration, their transport must be considered to be "active" and require an energy-dependent transport mechanism. It has been learned that the capacity

![Fig. 2](image-url)  
*Fig. 2—Schematic representation of the reabsorptive titration curve for glucose. (From Physiology of the Kidney and Body Fluids, 1st edition, by Robert F. Pitts. Copyright © 1963, Year Book Medical Publishers, Inc. Used by permission of Year Book Medical Publishers.)*

![Fig. 3](image-url)  
*Fig. 3—Schematic representation of the mechanism of bicarbonate reabsorption and H⁺ ion secretion in the proximal tubule.*
of the transport systems for these substances is limited, and that, when the reabsorptive load of material in the filtrate reaches a certain value, no more can be reabsorbed, the excess being excreted in the urine. This limiting quantity is expressed as the tubular maximum (Tm) for a given substance. A typical Tm curve for glucose is shown in Figure 2. Such a curve is obtained by progressively increasing the filtered load of glucose by raising the plasma level. Reabsorption is complete until a threshold level is reached, at which point a little glucose appears in the urine. As the load is raised further, the transport mechanism becomes saturated at the Tm level. The deviation of the reabsorptive curve from the line of theoretical complete reabsorption is known as the spary of the reabsorptive curve.

Reabsorption of bicarbonate is also characterized by a Tm limitation, but its origin is somewhat different. Bicarbonate reabsorption in both the proximal and distal tubules is linked to and dependent upon H⁺ ion secretion into the tubular lumen. Thus, as seen in Figure 3, bicarbonate reabsorption in the proximal tubule depends on adequate production of H⁺ ion by carbonic anhydrase catalytic hydration of CO₂ within the cell, followed by movement of H⁺ ion into the lumen. Such activity in the proximal tubule represents most of the total H⁺ ion secretory capacity. Bicarbonate is regenerated in the distal tubular cell as hydrogen is secreted into the tubular lumen, where titratable acid and ammonium are formed (Fig. 4). It is evident that maximal excretion of these substances is dependent on the establishment of an H⁺ ion gradient across the tubule of sufficient magnitude to lower the urine pH and allow for formation of titratable acidity and ammonia diffusion from the tubule cell. Figure 5 shows a normal Tm curve for bicarbonate. Such a curve is a reflection of the total H⁺ ion secretory capacity of
both proximal and distal tubules of the kidney.

Clinical Clues to Diagnosis of Tubular Disorders

There are seven practical clinical clues to the presence of a renal tubular disorder (Table 2).

First, the presence of renal stones or nephrocalcinosis should alert one to the possibility of renal tubular acidosis or cystinuria.

Second, abnormalities of bone, such as rickets, osteomalacia or pseudo fractures, may be the first indication of a defect in tubular secretion of $H^+$ ion or reabsorption of phosphate.

Third, visual problems, particularly in infancy or early childhood, should suggest the possible precipitation of cystine crystals in the cornea. This, we shall see, may occur in generalized cystinosis with Fanconi syndrome.

Fourth, a pellagra-like rash should suggest the possibility of an abnormality of tryptophan metabolism, as seen in Hartnup disease.

Fifth, the presence of glycosuria should suggest the possibility of renal glycosuria. When associated with an alkaline urine and proteinuria in a patient without a family history of diabetes mellitus, glycosuria should suggest a generalized defect in renal tubular reabsorption, as seen in Fanconi syndrome.

Sixth, unexplained hyperchloremic acidosis along with an alkaline urine should suggest a defect in bicarbonate reabsorption or $H^+$ ion secretion, as seen in Fanconi syndrome or renal tubular acidosis.

Seventh, an unexplained low serum phosphate in the presence of adequate food intake and a normal serum calcium should raise the possibility of Vitamin D-resistant rickets or Fanconi syndrome.

TABLE 2
Clinical Clues to Renal Tubular Disorders

<table>
<thead>
<tr>
<th>Clue</th>
<th>Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Renal Stones or Nephrocalcinosis</td>
<td>Cystinuria or Renal Tubular Acidosis</td>
</tr>
<tr>
<td>2. Rickets, Osteomalacia, Pseudo fractures</td>
<td>Phosphate Diabetes, Fanconi Syndrome, Renal Tubular Acidosis</td>
</tr>
<tr>
<td>3. Visual Difficulty in Childhood</td>
<td>Fanconi Syndrome with Cystinosis</td>
</tr>
<tr>
<td>4. Pellagra</td>
<td>Hartnup Disease</td>
</tr>
<tr>
<td>5. Glycosuria</td>
<td>Renal Glycosuria or Fanconi Syndrome</td>
</tr>
<tr>
<td>6. Hyperchloremic Acidosis</td>
<td>Fanconi Syndrome or Renal Tubular Acidosis</td>
</tr>
<tr>
<td>7. Low Serum Phosphate</td>
<td>Phosphate Diabetes or Fanconi Syndrome</td>
</tr>
</tbody>
</table>

Renal Glycosuria

Renal glycosuria, depending on definition, is a relatively common clinical disorder. When defined in broadest terms, it may be characterized by an increased splay in the Tm titration curve, by a lowered Tm for glucose, or by both. It is usually noticed by finding a random positive urine sugar. It is primarily of importance to be differentiated from true diabetes mellitus in order that hypoglycemic agents not be given. Renal glycosuria may occur in patients with true diabetes mellitus, in which case it may make management more difficult, with a tendency to hypoglycemic reactions.

Phosphate Diabetes (Vitamin D-Resistant Rickets)

Phosphate diabetes is a well-defined clinical entity. It characteristically presents in early childhood as rickets, unresponsive to Vitamin D. Figure 6 shows the typical bone changes of rickets including widening of the epiphysis with cupping and ragged mineralization of the metaphyseal plate. Such changes may lead to severe residual deformities in adolescence and adulthood. Typical serum chemistries include a normal calcium, low phosphate, and normal or high alkaline phosphatase, depending on the activity of disease. The low serum phosphate is caused by an increased phosphate clearance. This condition is inherited as a sex-linked dominant trait with a varying propensity for bone disease in the heterozygous female. Mother-to-son and son-to-daughter transmission but no father-to-son transmission is seen, as is characteristic of X-linked inheritance.

The etiology of this condition remains doubtful. There is controversy as to whether there is a primary defect in calcium absorption from the gut, with secondary hyperparathyroidism and parathyroid stimulation of phosphate urinary excretion, or a primary defect in renal tubular reabsorption of phosphate. Recent evidence of Avioli et al. (1967) suggests that Vitamin D metabolism may be defective with production of water soluble metabolites which are ineffective in enhancing calcium absorption from the gut and have no effect on bone. Whether or not such metabolites have a renal effect that blocks phosphate reabsorption is unknown. Recent studies (Wilson et al., 1965) have suggested that the bone disease may be healed by a vigorous and sustained combination of moderate daily doses of Vitamin D (50,000 units) in conjunction with frequent administration of buffered phosphate supplements.

Cystinuria

Cystinuria is an unusual renal tubular defect that usually presents with the passage of a renal stone or gravel. The course is variable, and the first stone may be passed at any time of life from early childhood.
to old age. Untreated cases may suffer all the complications of renal calculi, including urinary tract obstruction with the development of hydronephrosis, chronic pyelonephritis, and progressive renal insufficiency.

Defective epithelial transport of the amino acids arginine, ornithine, and lysine in this condition results in both diminished absorption from the gut and decreased reabsorption in the renal tubule, leading to increased concentrations in the urine. Until very recently, cystine transport was also felt to be defective in both the gut and the kidney, but new data (Thier et al., 1965) have demonstrated that transport of this amino acid is normal in the kidney and may be so in the bowel. The high levels of cystine in the urine seem to be a result of intra-urinary oxidation of abnormally large quantities of excreted cysteine to cystine. Because of the limited solubility of cystine in the urine, particularly when it is acid, precipitation of cystine in characteristic hexagonal-shaped crystals occurs. Observation of such crystals should alert the clinician to the possible presence of this condition.

Cystine crystals are radiopaque, and cystinuria should be considered in any stone-forming patient. The cyanide-nitroprusside screening test for cysteine can easily be done in any lab. Analysis of a stone will usually reveal the presence of some cystine, although calcium and phosphate may be integral parts of the calculus.

Recent studies (Rosenberg et al., 1966) have indicated that cystinuria is a hereditary disease. Stone formation is seen in patients homozygous for one of three possible genes which may or may not be alleles.

Moderately good results with prevention of stone formation have been reported in the past in some cases with a low methionine diet, chronic alkalinization of the urine, and production of a continuous water diuresis. The therapy of cystinuria has been revolutionized, however, by the introduction of penicillamine, which chelates the urinary cystine, making it more soluble in the urine. In addition, by some unexplained mechanism the penicillamine also decreases total cystine excretion. Thus, optimal therapy in the chronic cystine stone-former would seem to combine penicillamine with a copious fluid intake, alkalinization of the urine, and low methionine diet to decrease the intake of cystine precursors.

Hartnup Disease

This is an extremely rare but interesting abnormality of mono-amino-monocarboxy amino acid transport. Clinically, it is characterized by the occurrence of a pelagra-like skin eruption, cerebellar ataxia, and, in some cases, mental deficiency appearing early in life and remitting in late adolescence or adulthood. The basic pathogenic mechanism is considered to be abnormal absorption of tryptophan from both the bowel and the renal tubule. As a consequence of these abnormalities, serum tryptophan levels are low, leading to a decreased production of its important metabolites nicotinamide and serotonin. It may be a deficiency of these metabolites that leads to the integumen-
tary and central nervous system disorders. Hartnup disease is inherited as an autosomal recessive gene.

Therapy is directed to avoidance of sunlight and administration of large supplements of nicotinamide during the years of rapid growth. With such measures, improvement has been noted in several patients, leading to sustained remission in adulthood.

**Generalized Defects in Proximal Tubular Function**

The generalized defects in proximal tubular function are usually grouped under the heading of Fanconi syndrome. This syndrome frequently presents clinically by the occurrence of severe rickets or osteomalacia with fractures and pseudofractures. Laboratory findings include the characteristic hyperchloremic acidosis with a low CO₂ and high Cl content in the serum; low serum phosphate; low serum uric acid; and alkaline urine with proteinuria, aminoaciduria, and glycosuria. Table 3 demonstrates the diffuse aminoaciduria in a patient with adult Fanconi syndrome. Determination of the total amino acid content can be done by measuring the alpha amino nitrogen; individual acids must be separated by chromatography. A typical glucose tolerance test with persistent glycosuria in the face of normal blood sugars is shown in Table 4. Despite the frequent presence of an alkaline urine, occurrence of renal stones in this syndrome is distinctly unusual.

Much evidence points to either an anatomic or functional defect in the proximal tubule as the primary source of difficulty in patients with Fanconi syndrome. Microdissection studies have revealed anatomical damage to the proximal tubular region in patients with both the childhood and adult form of the disease. Recent work of mine (unpublished data) demonstrating a decreased bicarbonate Tm (Fig. 7) indicates that total H⁺ ion secre-

### TABLE 3

<table>
<thead>
<tr>
<th>Patient with Adult Fanconi Syndrome</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino Acid</td>
<td>mg/24 hr</td>
</tr>
<tr>
<td>Lysine-Ornithine</td>
<td>962</td>
</tr>
<tr>
<td>Histidine</td>
<td>650</td>
</tr>
<tr>
<td>Glycine</td>
<td>756</td>
</tr>
<tr>
<td>Alanine</td>
<td>786</td>
</tr>
<tr>
<td>Serine</td>
<td>766</td>
</tr>
<tr>
<td>Glutamine</td>
<td>2489</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>430</td>
</tr>
<tr>
<td>Threonine-Leucine</td>
<td>961</td>
</tr>
</tbody>
</table>

### TABLE 4

| Results of Glucose Tolerance Test in an Adult Patient with Fanconi Syndrome |
|-----------------------------|----------------|
| Period | Blood Sugar | Urine Sugar |
| Fasting | 96 | 3+ |
| 1 Hour | 62 | 3+ |
| 2 Hours | 107 | 3+ |
| 3 Hours | 87 | 3+ |
| 4 Hours | 95 | N.S. |
| 5 Hours | 87 | N.S. |

### TABLE 5

<table>
<thead>
<tr>
<th>Causes of the Fanconi Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Adult: A. Heavy Metal Intoxication B. Multiple Myeloma and Other Tumors C. Wilson's Disease D. Outdated Tetracycline Ingestion E. Transplanted Renal Allograft F. Lysol Ingestion G. Idiopathic</td>
</tr>
<tr>
<td>3. Experimental: Maleic Acid</td>
</tr>
</tbody>
</table>
amino acids lost in the urine and the demands of gluconeogenesis. Recent unpublished data of mine suggest that the renal abnormalities may be markedly improved by administration of hydrochlorothiazide and potassium supplements.

Renal Tubular Acidosis

As mentioned in our review of renal acidification mechanisms, the distal tubule reabsorbs the small amount of bicarbonate remaining in the tubular lumen and establishes a high H⁺ gradient across the tubular wall, allowing for the formation of titratable acid and trapping of large quantities of ammonia. In the absence of establishment of such a gradient, neutral phosphate is excreted, and ammonia diffusion into the tubular lumen is limited. Such an abnormality is seen in renal tubular acidosis, with the result that patients with this syndrome are unable to form an acid urine and, consequently, develop a hyperchloremic metabolic acidosis. Thus, the defect in this disorder lies not in the limitation of total H⁺ ion secretion but in the inability to transfer H⁺ out of the distal tubular cell into the urine against a very low H⁺ gradient.

Presumably because of the systemic acidosis, calcium is leached from the bones as H⁺ ion is buffered by the alkaline bone salts. Osteomalacia develops, and the liberated calcium is excreted in a persistently alkaline urine. Under such circumstances calcium phosphate precipitation occurs, either within the collecting ducts leading to nephrocalcinosis (Fig. 8), or in the renal pelvis producing renal stones. Most patients with this syndrome present with either renal calculi, bone disease, or progressive renal insufficiency secondary to nephrocalcinosis or pyelonephritis.

Because of the important occurrence of renat stones in renal tubular acidosis, it is essential that it be seriously considered in the patient with renal calculi or unexplained hematuria. The presence of a urine pH that is persistently 6.0 or greater indicates that investigation of the systemic acid-base status should be undertaken. The presence of hyperchloremic acidosis in the absence of other tubular abnormalities confirms the diagnosis. Partial defects may occur, however, and, in the questionable case, the response to an acid load of ammonium chloride or a sodium sulfate infusion should be determined. Under such stimuli, the urinary pH in the patient with renal tubular acidosis will not be lowered to the normal range of 5.0 or below.

Renal tubular acidosis occurs in children without apparent genetic cause. An association between adult renal tubular acidosis and a number of disease processes—including a variety of dysglobulinemic states, lupus erythematosus, phenacetin nephropathy, and amphotericin toxicity—has been documented.

Treatment is usually effective in the full-blown case and consists of the administration of sufficient sodium bicarbonate orally to correct the systemic acidosis. Under such circumstances, decalcification is inhibited and hypercalciuria disappears. The urine remains alkaline, but further nephrocalcinosis or stone formation usually does not occur as long as an adequate water diuresis is maintained by large oral intake.

Nephrogenic Diabetes Insipidus

As we noted previously, a concentrated urine is produced by action of antidiuretic hormone on the collecting duct cell, allowing back diffusion of water into the interstitium.

Polyuria unresponsive to vasopressin administration has been described in a number of clinical situations. Infant males may present with severe dehydration and fever and, on investigation, be found to have a persistently hypotonic urine in the face of an elevated serum osmolality. Administration of vasopressin does not correct the defect. Polyuria with a subnormal ability to concentrate the urine may be seen in patients with hypercalcemia, hypokalemia, sickle cell disease, or amyloidosis as well as in patients with any type of severe chronic renal insufficiency.

![Bicarbonate Titration Curve](image-url)
The male infants mentioned above are afflicted with an X-linked genetic defect that causes them to be unresponsive to either exogenous or endogenous antidiuretic hormone. If their problem is recognized, and adequate hydration is maintained, life can be sustained.

In some older individuals with a recognizable cause for vasopressin-unresponsive polyuria, correction of the underlying disorder, such as lowering the serum calcium or raising the serum potassium, will result in return of ability to adequately concentrate the urine. In those patients whose nephrogenic diabetes insipidus is idiopathic or genetic, improvement in the polyuric state may be seen following a decreased dietary solute load or the administration of hydrochlorothiazide. After the diuretic produces an initial saline diuresis, reduction in the extracellular fluid volume occurs. This in turn reduces glomerular filtration, causing enhanced reabsorption in the proximal tubule with consequent reduction in the amount of solute presented to the loop of Henle and the distal tubule. As a result, less dilute urine is formed and excreted. The patient must strictly adhere to a low sodium diet while on this regimen in order that the glomerular filtration rate not be increased.

Summary

I have tried to briefly outline aspects of the presently recognized disorders of tubular function that are of clinical importance. I would like to stress again that, although such disorders constitute a minute portion of the total health problem in this country, they are of great importance as experiments of nature, study of which is opening the way for a clearer understanding of fundamental transport mechanisms in the renal tubule. Additionally, for those individuals afflicted with any of the disorders I have mentioned, the availability of relief is of paramount importance. Such relief can be obtained in some cases by correct diagnosis and proper application of physiologically oriented therapy.

References


Focal Glomerulonephritis

ROBERT H. HEPTINSTALL

Department of Pathology, The Johns Hopkins University
School of Medicine, Baltimore, Maryland 21205

Definition

Focal glomerulonephritis is a form of glomerulonephritis in which only a certain number of glomeruli show lesions, the others being normal. It is a feature of most cases that the glomeruli affected show an involvement of only a portion of the tuft, a change that will be referred to as a local lesion. In general, focal glomerulonephritis can occur as a manifestation of well-recognized entities such as systemic lupus erythematosus, polyarteritis nodosa, subacute bacterial endocarditis, or Schönlein-Henoch syndrome; it can also occur apart from these diseases with a variety of clinical pictures (Heptinstall and Joekes, 1961).

Focal Glomerulonephritis as Part of Systemic Disease

In its early stages, systemic lupus erythematosus affects the glomeruli in a focal way. The affected glomeruli show a predominantly local involvement in which one or two adjacent lobules show necrotizing or proliferative changes. In the later stages of lupus nephritis, most of the glomeruli are affected, but the tendency to localized involvement of individual glomeruli is often apparent even in advanced cases.

Polyarteritis in the classical form shows no glomerular changes apart from those of ischemia, but, in what is often referred to as the microscopic form (Davson, Ball and Platt, 1948), the glomeruli are involved. The changes here are essentially focal, and, even in advanced cases, one frequently sees a significant number of glomeruli not showing involvement. The glomerular lesion is, almost invariably, a necrotizing change usually affecting only part of the tuft, which is rendered eosinophilic and structureless. A proliferative change may be seen in the affected part of the tuft, and the epithelium lining Bowman's capsule is frequently excited, producing crescents. In some cases, the glomeruli show extensive proliferative changes in both tuft and cells lining Bowman's capsule, giving a picture that resembles rapidly progressive glomerulonephritis.

Subacute bacterial endocarditis has long been recognized as a cause of focal glomerulonephritis, the appearance of which is no different with this condition than when it appears apart from systemic disease. This will be described later. The way in which the lesion is produced in endocarditis is unknown, but the two main possibilities are either that it is embolic from the valvular vegetations, or that it reflects some immunologic mechanism.

Schönlein-Henoch purpura has long been known to give rise to a form of nephritis. Up to the time of the renal biopsy, the only picture recognized was that of a florid proliferative glomerulonephritis accompanied by extensive crescent for-
mation in the patient with a rapidly progressing azotemic course. However, the more usual renal manifestation is much milder, with complete recovery occurring, as a rule. This form has been shown on biopsy to have either no recognizable lesion or a picture of a mild focal glomerulonephritis of the type to be described.

**Focal Glomerulonephritis not Associated with Systemic Disease**

The majority of cases diagnosed as focal glomerulonephritis on biopsy do not present clinically with the above-mentioned systemic illnesses. Their presentation is varied. Some patients are first seen with a nephrotic syndrome having no clinical features distinguishable from other causes of this syndrome; others have recurrent attacks of hematuria which may take place over periods of years; some may have hemoptysis and an abnormal urine noted on urinalysis; still others have urinary abnormalities or other symptoms or signs referable to the kidney. Skin rashes and joint pains have been noted in a good proportion of patients. The prognosis in most of these nonspecific cases is good, the exception being the group with hemoptysis, the so-called Goodpasture's syndrome. In this, the patients develop a rapidly progressive glomerulonephritis with death in uremia. In such cases the renal pathology changes drastically over a relatively short time from a focal glomerulonephritis to a widespread florid glomerulonephritis with extensive crescent formation (Johnson and McGovern, 1962; Benoit et al., 1964).

The pathology of focal glomerulonephritis not associated with systemic disease consists of a certain number of the glomeruli showing changes that are usually localized to one or two lobules of the tuft, although in exceptional cases the tuft is diffusely involved. The usual localized change consists of an increase in cell nuclei, often accompanied by necrosis, although one may occur without the other. There is sometimes proliferation of adjacent epithelium lining Bowman's capsule, and adhesions may form. Localized areas of solidification are the main features of certain cases, and these appear to be later lesions, as judged by studies utilizing sequential biopsies. It is of interest that necroses have not been seen in personally studied cases of the nephrotic syndrome. The tubules are frequently unaffected, but focal loss may be found in those cases with most extensive glomerular change. Lymphocytes and plasma cells may be seen in the interstitium, and increased fibrosis is present in those cells with tubular loss. In my own experience, arterial changes have not been very impressive.

**Discussion**

Very little has been written about focal glomerulonephritis not associated with systemic disease. This is almost certainly because it is either an early manifestation of disease or because it represents a mild illness and, therefore, has never been encountered in an autopsy service. Its recognition is largely a result of extended use of the renal biopsy.

It is important that conditions which might be confused with focal glomerulonephritis be excluded by the pathologist dealing with renal biopsies. In the first place, it is essential that some of the glomeruli be normal, and this obvious fact should always be borne in mind. This is important in the differential diagnosis from resolving acute diffuse glomerulonephritis. In this latter condition there is a widespread proliferative lesion in all glomeruli; during resolution, the number of cells decreases at a fairly even rate in all glomeruli, the cells in the mesangium decreasing more slowly than others. In certain cases of acute diffuse glomerulonephritis, some glomeruli show one or two lobules to be more severely affected than others. These lobules have greater numbers of nuclei than their neighbors. It is reasonable to assume that such glomeruli might resolve more slowly than others, so that an appearance resembling a focal glomerulonephritis could be produced. The contrast between these more severely affected glomeruli and the others would become accentuated during resolution, but mesangial hypercellularity would still be present in those with less severe initial involvement. We still cannot be certain, however, of the antecedent picture in the kidney of those cases showing partial solidification of an occasional glomerulus on biopsy. It is conceivable that some of these might be the end result of what was originally a diffuse process, the affected glomeruli representing those that were irreparably damaged during the acute phase. For this reason, it seems best to include in the diagnosis of focal glomerulonephritis only those cases showing proliferative or necrotizing lesions.

Proliferative changes in both the tuft and the cells lining Bowman's capsule may be seen around the periphery of infarcts. These changes could be confused with focal glomerulonephritis if this area were to be sampled by the biopsy needle. It is of interest that these changes may be a likely cause of the glomerular lesions of subacute bacterial endocarditis in which infarcts of the kidney are commonly encountered.

In cases of chronic pyelonephritis with hypertension, it is not unusual to see what has been referred to as alterative glomerulitis. In this condition certain glomeruli show localized nuclear proliferation with pyknosis of some of the nuclei, and sometimes necrosis occurs in the tufts. Loss of surrounding tubules and other stigmata of chronic pyelonephritis should help to exclude a diagnosis of alterative glomerulitis.

In malignant hypertension, the glomeruli may show necrosis of part of the tuft with an occasional
cellular increase. The necrosis in this case is usually in continuity with a necrotic arteriole, and other vascular changes of severe hyper­tension are present.

In many renal biopsies, scattered, completely hyalinized glomeruli are frequently found. The question invariably arises as to how this finding should be interpreted. This is often impossible to determine, especially in the older age group where aging and ischemic changes are present. In a young person, hyalinized glomeruli are more likely to be of significance, but, even here, their presence in small numbers should not be taken as indicative of old glomerulonephritis, nor should focal glomerulonephritis be diagnosed solely on the basis of their presence.

Course of Focal Glomerulonephritis

In general, it has been my experience that, in focal glomerulonephritis not associated with systemic disease, the prognosis has been good. In sequential biopsies I have observed that healing of the localized glomerular lesions takes place with the production of localized scars. The exception to this is the group of cases associated with hemoptysis (Goodpasture's syndrome), in which an apparently benign-looking focal glomerulonephritis has changed into a widespread florid glomerulonephritis with rapid death from renal failure. Some of the cases associated with recurrent hematuria may, after many years, develop permanent renal impairment, but the proportion of such is not great.

In focal glomerulonephritis occurring as a manifestation of poly­arteritis or systemic lupus, the progress of the lesion is quite different.

Etiology

Little can be said of the etiology of focal glomerulonephritis, but the varied circumstances under which it is encountered make it unlikely that there is any common etiologic factor.

References


Some Issues in Human Development

VICTOR C. VAUGHAN, III *

Department of Pediatrics, Temple University School of Medicine and St. Christopher's Hospital for Children, Philadelphia, Pennsylvania 19133

It is a great pleasure and privilege to address you in memory and honor of Dr. Lee Sutton, who was for many years a friend of the Vaughan family, and, as you know, a devoted, able and thoughtful physician who gave much to the care of Virginia's children as Professor and Chairman of the Department of Pediatrics and as Dean of the Medical College of Virginia.

In discussing certain issues in human development, I would like to touch on three phenomena. On two of them we have information chiefly from animal studies; the third is a more immediate part of our lives and the lives of our children.

The first phenomenon is imprinting, which was described about 30 years ago by Konrad Lorenz, who first observed it in geese. Lorenz has summarized some of his studies in a remarkable little book entitled King Solomon's Ring. In it he describes the experience of hatching goose eggs in an incubator, watching these little creatures for a day or two, and then shooing them out into the yard to join their mother. Thereafter, whenever Lorenz appeared in the yard, the little geese who had lived in his presence for the first two or three days ran to him instead of their natural parent. As a thoughtful biologist, Lorenz, instead of dismissing this as mental retardation in goslings, studied the matter in detail. He determined not only that this behavior is characteristic of newly hatched geese, but that ducks and a variety of birds behave in a similar manner.

In further study of this behavior, it has been determined that newly hatched ducklings will follow any moving object, with maximal drive or urgency at about 11 to 14 hours of age. The moving object can be a mother duck, another animal, or even a little block of wood on wheels pulled by a piece of string. If the object emits sound, the duckling will follow a little more effectively. Depending upon the duration or intensity of his following reaction, later in life in a situation where he is exposed to the imprinting object, to his own mother, and to an anxiety provoking stimulus, the duckling will run to the imprinting object for refuge.

During the initial following reaction, an electrified grille may be put in front of the duckling, so that as he follows, he gets shocked. Any normal adult duck would stop following. During the imprinting period, however, the duckling follows even more urgently, and the intensity of the imprinting is made more powerful by the painful stimulus.

This misidentification of one's natural refuge or parent turns out not to be limited to birds. Most of us first heard of imprinting with the story of Mary's little lamb, plainly imprinted to Mary.

* Sutton Memorial Lecturer, Third Annual Pediatrics Day, December 8, 1967, Medical College of Virginia, Richmond.
Other studies of this phenomenon indicate that dogs, too, have a critical period in which they will become accustomed to human handling. If you mean to make a puppy a lap dog, a house dog, a close friend of the family, you will best bring him into the house at five to seven weeks. If you put this off until 12 to 14 weeks, you will not ultimately have the same kind of dog; for the dog that has lived in a kennel for that period of time has a different social orientation. He doesn't become a big, friendly pup like our family's current watch-dog, who came to us at seven weeks, and who might kill a stranger—by licking him to death. An earlier dog came to our house at about 14 weeks. We tried for nearly two years to make a friend out of her, but she truly earned the name "Bitch" in the way she used to greet not only strangers but the rest of the family. She was snappish, irritable, unpredictable, and downright mean. Her pups, on the other hand, born in the house and raised by hand by our own children, were domesticated in just the way one would expect house pets to be domesticated. They had none of their mother's evil temper.

One of the most remarkable examples of imprinting is given in the book Born Free. You will remember that Elsa, the lioness, was found with two siblings in a cave, before her eyes were opened and shortly after her mother was shot. She was brought into human company and grew to adult lionhood absolutely free-living in a human family. Her foster parents put a rope around her neck when they went to town, but Elsa was apparently quite able to generalize her identification of the human species, and in her short life, although she roamed quite free in human society, she never made an attack upon a human being.

Within various families of animals there are variations in imprinting. It is apparently necessary to domesticate a wolf, for example, much earlier than a dog in order to make a house pet out of it. It is said that if one brings a wolf into human company before its eyes are open, as Elsa came to the Adamsons, it is relatively easy to raise him as a domestic animal. This is done with increasing difficulty after the wolf has lived for even a short period in the company of his natural parents. It ultimately becomes virtually impossible to make a house pet out of a wolf.

Further observations add to the mystery and wonder of imprinting and related phenomena. In goats a relationship is established between mother and infant in the first day of life which is quite essential to the nutrition of the infant goat. When the kid is taken away from the mother for a period of 40 minutes during the first day, the bond between the two may be irrevocably fractured. After this separation, the mother receives the kid with butts, pushing it away and refusing to nurse it. In contrast, the normal nanny goat, immediately after delivery, will accept any small goat as her own (Hersher Moore and Richmond, 1958).

Something very important, then, is going on in the first day of life in goats, geese, and ducks—something which is very important for the socialization of the animal with other members of its own species.

Have these phenomena anything to do with the human condition? We really don't know. But studies undertaken at Wisconsin and elsewhere are beginning to tell us something about early socialization in other primates. The studies of Harry Harlow have become famous. He has raised small monkeys with chicken-wire mothers, some of them covered with terry cloth and some of them not. The infant associates with these inanimate mothers without much in the way of feedback from his own input to the mother. Harlow has shown that if he gives the infant a choice between a bare chicken-wire mother and one covered with terry cloth—both of which have a bottle attached and an electric light bulb inside, so that they give both nutrition and warmth—the infant will attach himself to the terry cloth-covered mother. There is something in the feel of the available parent that profoundly conditions the behavior of infant monkeys in the area of socialization.

Now what do monkeys have to do with people? We don't really know. There are likely to be differences between monkeys and people, just as there are between birds. Here it might be of interest to examine the difference between a precocial and an altricial bird. When precocial birds are hatched, they are able to feed themselves, follow their mothers, and so on, within minutes of the time of delivery. The altricial bird, on the other hand, is fed in a nest for a considerable period. The ring-necked dove, for example, is fed in the nest for 14 days, then mounts to the side of the nest, and in 21 days flies away. If a human handler is to come into the life of a ring-necked dove with an optimum chance of creating conditions under which this dove will accept human company as belonging to its natural state of living, the human handler has to come in at nine days. Increasingly, prior to nine days and after nine days, up to the time when the dove leaves the nest, one loses the capacity to socialize the dove to the human experience.

The human infant is probably much less precocial and much more altricial than the rhesus monkey. A monkey is able to fend for himself pretty well in a few days; the human infant not for many months or years. If imprinting as a kind of socialization has any counterpart in the human animal, it probably goes through stages somewhat as follows. The human infant begins to smile, as a rule, sometime between three and five weeks of age. If he hasn't begun to smile by eight weeks, we begin to be
troubled. If he hasn't smiled by three months, we know there is trouble; we don't necessarily know the kind of trouble, but we can be sure it is there. When the human infant first smiles, his mother, if she is a healthy person, is likely to smile back at the infant; and immediately a bond of feeling which is the forerunner of socialization is set up between the mother and the infant. Even before this there have been arrangements made between mother and infant for nutrition and the like. These are being very actively studied in many places now, but we don't quite know yet what it is that these arrangements contribute to socialization.

At three to four months the youngster begins to make some adjustments of his body anticipatory to being picked up. As his mother reaches down for him, he becomes active; his muscle tone improves; he is ready to be picked up; and he may show his pleasure at the social contact. At this point his response is not very differentiated. Anyone who comes close to an infant at this time can elicit a smile. But by six months the child responds to his mother differently than to any other living person. This can be shown in a number of ways. For example, the child cries when his mother leaves the room but not when other people do.

It seems quite likely that the period of primary socialization to the human species or to the parent has had a number of important steps taking place within the first six months. Between six months and a year the infant goes through another interesting phase, which is a reaction of fear to the approach of strange people. I entered pediatrics with the naive notion that if I made friends with four-, five-, and six-month-old infants as I gave them shots and various treatments, our friendship could continue, so that we would never enter a period where the child was afraid of the physician. This was nonsense. At eight to ten months every child is afraid of a stranger. Infants may show this in a variety of ways, but we can be sure that there is anxiety both on the introduction of a stranger and on separation from the parent and that this anxiety represents a phenomenon in socialization.

Interference with man's socialization has not been studied in a systematic or controlled way. None of us is going to purposely interfere with normal socialization of the infant, although we may ask what it does to the relationship between mother and infant when, in the neonatal period, we anesthetize the mother, remove both the mother and the baby from the experience of giving birth and being born, take the baby immediately to a nursery remote from the mother, bring him out to her for short periods at long intervals without relationship to his physiologic need for the mother or hers for him, and then, at the end of five days, send these strangers home together to build a social unit. This kind of experience has not been given the name of experimentation; but its impact is something we must begin to study.

Another kind of early experience of unplanned impact has been described by Sally Provence and Rose Lipton in a little volume called *Infants in Institutions*. Here we learn what may happen when the opportunities of the human infant for socialization are denied. The authors describe an institution in an East Coast city which operated as a foundling home, in which most infants who were admitted came for adoptive placement, born out of wedlock. They were from predominantly lower middle class or upper lower class strata of society, but possessed relatively little that would differentiate one from the other. The institution had a number of nurseries for these children, each containing as many as 20 to 30 infants. Cribs were generally set around the wall, and the infants were in the care of two to three people in the daytime and of, perhaps, one person at night, who spent the night changing them and feeding them with propped bottles because there was relatively little time to do anything else.

Some curious things were observed when Provence and Lipton began to watch these infants. As early as two months of age it was quite evident that they had less vocalization than the normal infant. The growth of two groups of these infants was further studied, as measured on the Gesell scale. Both groups fell into a reasonably normal pattern of distribution with respect to developmental quotients at three to four months of age. Children in the first group were put into adoptive or foster home placement prior to four months, and at the end of a year they were restudied. Again, they had a normal distribution of developmental quotient. The second group of infants remained in the institution a year or more for reasons that are not at all clear, though it appears that random selection determined which youngsters were going to stay in this institution for that period of time. Testing at the end of a year in this second group showed these youngsters to be defective. Without exception they scored below the infants who had been placed in adoptive or foster home care. The best of them scored below the least adequately functioning child in the other group. Other observations indicated they had been slower to develop use of gross muscular activity. They were able to stand, but they didn't have much to stand for; so they were likely to lie in their cribs and show relatively little interest in their surroundings except to look at them. As a result they became very visually oriented.
of the measured deficiency by Gesell standards. By three years the children in the two groups were not far apart in gross intellectual function.

At six years it was still difficult to find intellectual differences between the two groups, but differences now emerged in the area of behavior which are quite striking. The children who spent the early period of life in the institution now seemed to be relatively impulsive in their behavior, have a short attention span, have difficulty in forming really warm human relationships with others, and, in these and other respects, resembled the so-called brain-damaged child. We don't really know what the brain-damaged child is, but we do know that there are homes in which the quality of care the child gets much more resembles the institutional quality of care than the quality of care given by loving foster, adoptive or natural parents.

These observations raise many questions. We are reminded that the monkeys raised by Harlow with those surrogate chicken-wire mothers presented possibly counterpart disabilities in socialization. When such animals are raised to adult life, they appear totally unable to make places for themselves in monkey society and live both sexually and socially incapacitated. Interestingly enough, in monkeys, and possibly in man, too, some contact with siblings or other animals of the same species and same age can sometimes substitute to a remarkable degree for mothering.

The concept of primary socialization, then, determines what kind of moving objects an animal is going to relate to as members of its own species. We may ask whether the relationship that schizophrenic children have to objects which they have set into motion may somehow reflect experiences in this early period which we don't fully understand as yet.

So much for imprinting or primary socialization. It has some very powerful effects. How powerful and how durable the effects are for man we don't know. How durable they are for some birds we do know. There is a story told of the jackdaw, which, having been raised by Konrad Lorenz in his backyard, fell in love with Lorenz. The courting behavior of the male jackdaw in mating season is to feed his ladylove mealworms. He lights on the branch next to her and stuffs mealworms into her mouth, while she accepts all this with carefree disdain. Lorenz became aware of the affection of this jackdaw when it lit on his shoulder and began stuffing mealworms into his mouth. Needless to say, he was anything but happy about this, but he loved the bird in return in his own way and didn't want to do the animal violence. In his gentle way he tried to persuade the bird that something was wrong, and we are told that on at least one occasion, when Lorenz got a mouthful of mealworms and jackdaw saliva, the whole episode came close to coming to an end. But the bird survived and got the message. With the discovery that something was wrong, the jackdaw desisted from trying to put mealworms in Lorenz' mouth, but, for the reminder of this courting season, lit on his shoulder and tried to stuff them into his ear.

Imprinting, then, is a very powerful and very persuasive phenomenon in the socialization of animals. We need to know very soon and in very great detail what its counterpart is in man, because we have no reason to feel that we are so different that there isn't somewhere a phenomenon that has like meaning for us.

A second powerful phenomenon in socialization has been given the name "territoriality." It has been celebrated in recent literature by Robert Ardrey's book Territorial Imperative: A Personal Inquiry into the Animal Origins of Property and Nations. Territoriality shapes the interpersonal relations or intergroup relations that will exist in a society of animals socialized to each other.

One of the remarkable experiments dealing with territoriality is that which was carried out off the coast of Puerto Rico some 30 years ago by C. R. Carpenter. Several hundred rhesus monkeys in a state of total social disorganization—they didn't know each other, came from all parts of India and Africa—were put on the island. Carpenter made sure they had enough food and patiently watched the way in which the island became organized as a home for monkeys. It took the monkeys about a year to get the situation under control. At the end of that time they had an island which they had divided into various territories; each had a home tree where its monkey colony tended to rest at night; each territory had borders; and each had its own activity. The supreme activity on the island was the defense of territorial borders by the various groups of monkeys. Each group was organized under a male leader, with a pecking order among subordinates similar to that which exists among barnyard chickens. The wives had a somewhat similar pecking order, corresponding in some measure to that of their husbands.

When a monkey from one group came close to the border of another group's territory, monkeys in the other group would run over and scream to him to go home. Indeed, monkeys gathered at the border sometimes in such masses that the border was pushed in a little bit, whereupon all the monkeys in an "invaded" group would stop whatever they were doing and defend their territory. We do mean whatever they were doing. The call to defense of territory took precedence over feeding, over sexual activity, over grooming, over anything else that was going on in the monkey colony except the care of infants. Everybody would run out and push the border back to where it was or
a little farther. These borders, then, were somewhat fluctuant.

The one thing that did not occur, generally, was that a moving border overran a home tree; as invaders came close to the home tree, the defenders became invincible.

We don't really know what would happen if you threw a bunch of human beings onto a medium-sized planet in a state of social disorganization; but the planet might look a bit like this one, and if history hasn't taught us that the defense of home and territory is an extremely powerful biologic organizer of social action in primates, including man, then we haven't yet learned our lesson. I, for one, think the lesson we are learning in Viet Nam is that when one invades peoples' territory from the air or by any other route, they become fantastically courageous and angry. To find peace in this kind of setting is extraordinarily difficult. I am sure that we are reaping the failure to anticipate this kind of biologic lesson in our difficulties there.

There are many, many examples of this kind of thing that we might touch on. Let us examine one that is closer to home. We now have children growing up in a state of relative or massive social disorganization in many of our big cities. What happens when this occurs? "West Side Story" is our most graphic description. The territory is known as "turf"; the borders of the territory are certain streets or avenues; and the defense of the borders of the territory takes precedence over other activities. The real tragedy is that this game is played out with switchblade knives and zip guns rather than with the howls and screams of monkeys.

We have symbolic representations of this, too. I offer you a game. It is played on a rectangle with a symbolic object which is put into play in the center of the rectangle. There are 11 primates opposing 11 other primates, the object of the game being for one group to move the symbolic object into the home territory of the other group. You know that the object moves relatively easily in midfield, but that when defenders get their backs to the goalposts, they often draw on reserves of strength, courage, or whatever that throw back the invaders. There are 102,000 other primates gathered around vicariously, enjoying this struggle. The name of the game has to be "Territoriality."

The game can be played in another way which makes the territorial nature of the game a little more obscure. Here the territory has a corner, and in the corner there is a little plastic device having a symbolic meaning which will become clear. The symbolic object is thrown by a primate from a point known as "the mound" past another primate who stands holding a stick. If the second primate is able to hit the symbolic object as it goes past in such a way as to have it land in the territory being defended, then he has the privilege of entering the territory along one margin, where he comes to occupy a symbolic spot, a small rectangular canvas bag. According to certain rules which I won't go into now, he may further invade the territory to occupy another safe spot and possibly even come to a third point. Then, if he is a winner, he goes—where? It cannot be an accident that we call it "home" plate. He has made an invasion of enemy territory, and he has come home.

This game is played in another setting and is in this form disappearing, for which we can be everlastingly grateful. The territory in this case is a restaurant in a nameless Southern town, defended by white diners and proprietors against the anxieties created in them by black people who want to use the facilities. Black people have, in fact, used the facilities for a good long while, according to the rules of the game. The rules permit one of this group to enter the restaurant along the first base line (the front door), but he can remain safe only if he goes directly to second base (the kitchen). If he enters the front door with any other intent, there is panic. At second base he can disappear, and no one will care. If he re-enters from the kitchen, he can only be safe if he goes out the door (the third base line), the two doors being topologically equivalent.

It helps me, and I think it would help us all, to understand the deep biologic meaning of the anxieties and anger that take place in settings like this, to know what they symbolize and how they serve to trigger feelings and actions. Such an understanding is our best hope of finding controls or acceptable vicarious outlets for feelings of anxiety that lead to hostility, aggression, defensive responses, mounting violence, and so on—feelings which constitute the greatest threat to the world at this time.

There is another noteworthy aspect to territoriality, and that is the personal dimension of territory. All of us walk along surrounded by a certain space which we don't like people to invade. If somebody is too close to us or touches us under the wrong circumstances, we tend to back off. Styles in personal space tend to vary in various parts of the world. We don't use the embrace between men that is so common in Latin countries. We react to it unusually and think it funny, for example, that Frenchmen embrace each other. The Latin American transacts business several inches closer than we do. When we find him that close, we back off and get a reputation for being cold, for not liking people, for being difficult to get along with.

People who transact business even more closely are the Middle Easterners. In Kahlil Gibran's poem, "The Prophet," you may recall that the prophet says, in taking leave of the people among whom he has lived, that he has felt their breath upon his face. In the Middle East, there is no conversation among friends really unless they feel each
other’s breath upon their faces. It has been suggested that the distance at which various societies transact business around the world is inversely proportional to the amount of garlic consumed in the society. Whether garlic permits a closer relationship because everybody eats it, or is simply a defense against such a relationship, I don’t know.

The personal dimension of space is very important, and it is felt by animals other than man. If you stride along the boardwalk at Atlantic City through a group of pigeons, a circle will open up around you that accurately measures the distance within which a striding man can approach a pigeon before the animal takes evasive action. As another example, visualize a heron sitting on a nest of eggs. You can move to a distance of about 27 inches before the heron will leave the nest. At a distance of 28 inches you can stay there and look at the bird all day.

Lion tamers know about this setting of distance. When the lion tamer enters the cage, if he is bright, he will enter when the lion is far from the door. Then he will move toward the lion. The lion will generally move away until, as the tamer follows him, the tamer gets close enough to transgress the lion’s definition of the critical distance. At this point, the lion will turn and start stalking the trainer. Now the trainer maneuvers in such a way that the pedestal on which he wants the lion to stand is between him and the lion. The tamer stays just within the critical distance. The lion sees no obstacle to seizing the man and moves straight toward him, climbing over the pedestal. As the lion reaches the top of the pedestal, the tamer immediately steps back outside the critical distance, and the lion remains fixed there on the pedestal, looking rather silly. The gun, the chair, the whip—these are all props. The lion tamer is using the lion’s critical distance to evoke behavior in him. I would not, myself, give up the props.

We can see territoriality operating in another area. This could be in a streetcar, a subway car or a bus, but, for our purposes, take an empty subway car. There are only two people involved. One man gets in at one station and sits a few feet from the door. At the next station, the second person gets on. If he goes to the other end of the car to sit, no new problem is created. But the second man has an old problem. He has had a bad day. A number of things have not gone well; he is sick and unhappy, or something of that sort. Normally he would sit on the side opposite the first man, not directly across from him, though, people having an uneasy feeling about things directly opposite them. His comfortable location would indicate, “I notice you here; we’re friends, but we are not going to have much to do with each other.”

If, on the other hand, the second person gets on the car and sits immediately beside the first man, bringing about the possibility of bodily contact between them, the second man’s need to situate himself thusly, has, in turn, created a problem for the first man.

It has been fun watching an auditorium like this fill up. As it fills up with people who don’t know each other, you will find that the density with which people sort themselves out is a measure of their personal space, and not necessarily of their desire to be close to the speaker. As a matter of fact, most people, if I am to judge the empty front row correctly, prefer not to be conspicuously close, but to be in the second, third, or fourth row, for example. Late-comers sit in the back.

The way in which people move themselves and locate themselves in space, reflecting a personal dimension in territoriality, has its counterpart in feelings of families about territory. This, too, is something that we need to study in the human condition. Some of the most violent altercations people have are those which involve property lines. Let a man’s property come to a given point. If he imagines that something has been built or hangs six inches over his property, a situation develops which, lawyers tell us, makes for most unpleasant feelings and violent quarrels between neighbors. Territoriality, then, is something we need to be more aware of; we need to see not only how it affects children but adults as well.

There is a third phenomenon I would like to comment on as an issue in human development which flows rather naturally from the first two. We have indicated that aggression—as impulsive action in reaction to anxiety or as an expression of hostility—has biologic roots in socialization, important elements of which are imprinting and territoriality. Aggression takes a peculiar form in man. Man is the only animal that routinely destroys other members of his own species. In most other species of animals, destruction of other members occurs only in response to population pressures. In rats, destruction occurs with the introduction of new members into an already ordered group. If a group of rats is reasonably well established on a plot of ground and a few new rats are introduced, those on home territory will destroy the outsiders. Population pressures of other sorts have been shown to be responsible for fatal warfare within species. However, among the various species, aggression and violence tend mostly to disperse the species, rather than destroy the individual members.

Violence, like territoriality, has two dimensions—the personal and the social. Our experiences as individuals breed tendencies to act out impulsive behavior. These are a result of hostilities engendered by our unique personal lives as we grow up in our homes or neighborhoods. While speaking of neighborhoods, I cannot help but reflect upon how difficult it is for children in a crowded slum to develop loving and gentle attitudes toward others or toward life in general.
The personal dimension of violence is unique for the individual, but there is a social dimension, too.

In our own society we may ask, "Is this really an issue? How much violence is there?" I was struck by, and would like to share with you, the words of Jessamyn West on violence. She has indicated, rather more plainly and better than many writers, what aspects of our present society we need to consider as we plan a future for our children.

Miss West says:

Never in the history of man has any generation been as free of pain as ours. We lose teeth, have babies and undergo five-hour operations, all without pain. We are not only pain-free, we are comfortable. The air is conditioned, in home and cars; the bed preheated when we get into it; and the rocking chair, if we like, wired to oscillate without any effort of ours. And never has any generation, without knowledge of pain or experience of discomfort, spent so much time watching others experience pain and suffer discomfort. Never has any generation tried harder to hide from itself the fact of death—and at the same time been so absorbed in watching others die.

We do not call what we see on the movie and television screens "death." We call it "violence"—and the way in which we use the word "violence" today is new in the world. We all know what is hidden beneath its parlor-proper syllables; but by using it we let into our parlors and our family rooms what, rightly named, we would not care to be seen inviting in, let alone feasting on, evening after evening.

Death on the screen is so easy a matter. The fast draw, the quick collapse. We are never permitted to see very much of the man who is going to die. We must not learn to care for him, to feel that his death matters; otherwise our enjoyment of his violent end will be weakened. We must never see him as a fellow who planted radishes, made kites for his kids or patted a dog on the head. We must not, in fact, see him as anything but a dirty dog himself, who deserved all he got and more. Excite and enthral the customers with violence, but don't upset them. Let's not make it tragic. Lots of death and disaster, but for fun...

By dehumanizing the action (real persons don't die, only the "bad men"), by never giving the proper name to what we see, are we blinded to reality? Is a generation of Americans being prepared for the routine and casual killings of concentration camps and gas chambers, of death marches and saturation bombings, of mass evacuations and 100-megaton explosions? Violence is a big word with sonorous syllables. Do we never see behind it the small boy with his face blown away? The child without hands? The men with dreams and promises oozing from their broken skulls, along with the gray matter that gave rise to dreams and promises? Are these facts forgotten?

There are many intelligent, thoughtful people who believe that there is too much violence on our movie and television screens and that it is particularly bad for children to see it. But what is really wrong is that the children do not see it. They see only the pleasure of landing the blow without ever imagining the pain of receiving it, without even imagining that the one who receives the blow is capable of suffering pain.

The TV screen whereon only bad men die, and then neatly and with dispatch, dulls and kills the imagination—and whatever destroys the imagination limits and ultimately destroys man. "When there is no vision, the people perish." It is doubtless sad that children must learn of pain, suffering, and death. But it is tragic for them to believe that bullets and blows do not cause suffering and death. The child who is conditioned by screen and parent to identify only with the one who lands the blow, never with the victim, loses the humanizing power of compassion.

With these dramatic words, Jessamyn West gives us a slightly different picture of our television screens and of what we are offering our children. The picture is not unique; but I think it describes phenomena in our lives and the lives of our children which are part of our scene, and which we recognize. Jessamyn West is not alone in calling attention to them. H. Rap Brown says that violence is as American as apple pie. I don't know whether he is talking about the Ku Klux Klan or riots in the ghettos, but the impact of all this on the individual is just now beginning to be assessed. In the assessment of it, I don't care whether it is violence of the right or of the left. There are a great number of people in the middle who are moved more or less by this without taking action. I suggest that perhaps those of us who are concerned with the growth and development of children ought by now to be moved to action which we haven't taken in the past.

I am reminded here of the cover of the December 9, 1967 Saturday Review on which appears the following quotation by Abdul Rahman Pazhwak, past president of the U.N. General Assembly: "If fools and folly rule the world, the end of man in our time may come as a rude shock, but it will no longer come as a complete surprise." That's a pretty pessimistic view of things. But for all that I may sound pessimistic, I am in fact optimistic about what we can do and what we are going to have help in doing.

For example, in closing I would again like to refer you to the Saturday Review. Its October 7, 1967 issue contains an article by Urie Bronfenbrenner of Cornell entitled "The Split-Level American Family." He points out some of the difficulties that we are up against and discusses some of the studies being made of which we should be aware. He points out that there has been movement from the agrarian to the urban society and that it
causes enormous constriction in the lives of children. The separation between the lives of children and the lives of adults is greater than it has ever been. Our neighborhoods have become homogenized; the suburbs are residential, and the things that people do to live there are lost upon children growing up where there are only homes, lawns, and people who are quite similar. As far as the children are concerned, their mothers and fathers tend to be less familiar and less available to them than was once the case.

We now have a society in which one-third of the mothers work. The father's absence has already been shown—especially in boys—to correlate with low motivation for achievement, inability to defer gratification, low self-esteem, susceptibility to group pressures, and juvenile delinquency. In the absence of parents, and in the homogenized neighborhood, whether in a suburb or in the urban core, children turn to devices as substitutes for parents. One is the peer group; the other is the television set. Some parents consciously foster the child's choice of the TV set as a babysitter. Studies almost ten years old indicate that children five years of age spend two hours a day watching TV. Jessamyn West has told us what they see on it. By 12 years of age, the average child spends three hours a day watching TV. He sees, again, the "Great American Story" that combines noble elements of territoriality and personal space. Typically, the story is played by two men, one known as Good and the other known as Bad, who face each other at noon on a dusty street. As they approach each other, with guns at their hips, the rules of play are such that the critical distance is always a little longer for the bad man than for the good, so that the bad man draws first and the good man kills him—in self defense. This is the Great American Story, the legend of our time. The bad man dies; he doesn't suffer.

And what of our children? Do they learn courage, compassion, affection, empathy, love, from identification with the "goodie"? Healthy kids with other socializing experiences may have a chance. But the image of the bad man is as vivid as that of the good, and for many children it is a good deal more exciting. Many youngsters with low self-esteem, susceptibility to group pressure, inability to defer gratification, low motivation for achievement, and delinquent tendencies have learned from western or crime shows how to behave like the "baddies" they feel they are.

Well, what does all this do? It worries us, and has done so for a long time. Numerous studies have appeared, such as those of Albert Bandura, Richard Walters, Leonard D. Eron and Muzafer Sherif discussed by Bronfenbrenner in the Saturday Review. Bandura of Stanford exposed a group of children—as they entered a playroom—to the sight of someone in the corner battoning around a doll called Bobo. All of us know Bobos; one pushes or smashes them down, and they bounce up to be hit again. The children were uncommitted to any particular activity in the playroom, which had all kinds of opportunities for creative activity. If someone was engaged in violent activity as these children entered the room, they engaged in significantly more violent activity than a control group. When the TV people heard about it, they objected that the situation was unnatural. But Bandura has shown that films work as well, that even cartoons will set the tone of children's activity, and that a ten-minute experience of this sort has an impact that can be measured for at least six months.

It has been shown by Walters at Waterloo University in Canada that exactly the same things are true for adults. The evidence mounts. Eron, at Iowa, showed in a study of 600 children that the most aggressive children watched the most violence on TV. Which is cause, and which is effect? Is it because they are the most aggressive children that they watch the most violence? The answer has to be no, because aggression can be turned on and off. The Robbers' Cave Experiment conducted by Sherif at the University of Oklahoma reaffirms this.

Two groups of children, known as the Eagles and the Rattlers, were set up in a summer camp experience near Robbers' Cave, Oklahoma, and, under the control of the counselors, deliberately exposed to conditions designed to create animosity between the two groups. With relatively simple techniques emphasizing competition between the two groups, these youngsters were at each other's throats at the end of two or three weeks of camp, hating each other, calling each other names, and seizing on every opportunity for an imagined slight to emphasize the difference in the two groups—"we" were the "goodies"; "they" were the "baddies."

Now when this gut hate was well established, the counselors tried to undo it. They found that they could, with procedures whose effectiveness was predicted by them.

What they did was exemplified by two crises which they created and which involved the whole camp—not one group or the other. A leak in the water line that brought water to the camp was fabricated somewhere in the mile and one-half that this line ran, and the camp was organized to go out and find the leak and repair it. The truck that was going to get the food developed a lesion and wouldn't move. The whole camp went out and took turns pushing the truck to where it could get help. With these and other cooperative activities, the tensions between these two groups began to diminish. They ended up being the very best of friends through what was finally termed joint activity in superordinate goals.

There are many superordinate goals in our society to which we could address the attention of
adults and children alike. There are needs in health, education, and other areas which afford enormous opportunities for greater involvement of adults in the lives of children and greater opportunities for involvement of children in the problems and tasks of adults and of a larger society. I think that such programs as Head Start, the Peace Corps, VISTA, and VISA are only the beginning and are not just for the poor.

In summary, then, there are deeply rooted biological forces upon which we draw unwittingly for attitudes and behavior. There are pressing problems before us, ranging from war and slum riots to the misery and hopelessness of hundreds of thousands of infants and children leading empty and desperate lives in an unproductive way without society ever noticing that something preventable and irrevocable is happening. All of us, as citizens devoted to the healthiest kind of childhood and adulthood for our children, know that this represents an appalling tragedy for the individual. Multiplied by the hundreds of millions, it may represent a catastrophe for mankind. As physicians, we and other students of human behavior have unique opportunities and responsibilities in these matters. We must make our concerns widely known and be ready to fight vigorously not only for the formulation of public education programs but the implementation of public policy, to the end that all children have the best possible opportunity for fulfillment—fulfillment through behavior which manifests the altruistic qualities of sharing, caring, giving, loving, and, if need be, of sacrificing.

References


Present-Day Psychiatry*

HENRY D. LEDERER

Department of Psychiatry, Medical College of Virginia
Richmond 23219

Introduction

As part of the excitement and challenge of our times, psychiatry shares with the rest of human activity a soul-searching, candid questioning of principles and practices and a responsibility for developing new perspectives and patterns of action. During these times when there seems to be a strong swing toward conformity and stereotypy in our society, there is also an intense counteraction—especially in those under 30—of questioning all tradition, respecting no sacred cows. These phenomena lead to heated debates, voices raised in anger, and hot letters to editors; but, through all of the dust raised, I believe we can see encouraging prospects and clearing of the atmosphere—possibly because there has been open disagreement. The late John Courtney Murray is credited with having said, "One of the great difficulties of our time is to ensure disagreement." In present-day psychiatry, we have assured ourselves not only of many unresolved disagreements, but also of ferment from which we can expect a burst of further growth.

Not many years ago it would have been easy to define psychiatry as the medical discipline concerned with diagnosis and treatment of the mentally ill. In the past decade almost every part of this definition has been challenged and, by some, largely rejected. There is the extreme position taken by Dr. Thomas Szasz, who rejects the very notion of mental illness. Less unusual objections either question our systems of diagnosis or look coldly upon our treatment procedures.

At present we find ourselves having to accept an operational definition of psychiatry as the work activity engaged in by a wide range of physicians who are concerned with problems of human existence that present any of the following conditions or any combinations thereof:

1) personal discomfort;
2) behavioral deviation leading to social rebuff and isolation;
3) failure to realize personal and group potentiality for creativity, productiveness, and perceptiveness.

I should be the first to express dissatisfaction and uneasiness about this definition, but I believe that it describes broadly what is meant today by psychiatry.

Another approach to what constitutes psychiatry might use operational definitions describing the locales in which the psychiatric physician practices: for example, state hospitals; private sanitoria; out-patient clinics offering somatic liaison and child guidance in addition to contributing to forensic, industrial and student health, etc. Such designations, however, only tell us where psychiatry is, not what it is.

An urgent dialogue has developed among psychiatrists as well as between psychiatrists and other professionals over the question of whether or not a medical background is necessary for accomplishing all of the activities, particularly psychotherapeutic, now attempted by psychiatrists. We recognize the problems of deciding whether or not nonmedical psychotherapists should be certified and licensed, thereby being severely limited by state laws. A related question is whether or not nonmedical therapists should be legally required to be supervised by board certified psychiatrists. Some state legislatures already have licensed clinical psychologists as psychotherapists. Moreover, many federal and state mental hygiene clinics are staffed by clinical psychologists who regularly conduct various psychotherapies. Despite these legislative and practical sanctions granted nonmedical psychotherapists, it may be of some profit to reexamine the rationale for a general medical training for psychiatrists. What, if any, are the benefits to the psychiatrist derived from his medical background? After considering this question, I should like to discuss some of the peculiarities of psychiatric medicine as distinguished from the other branches of medicine.

The Value of Medical Education for Psychiatrists

One can identify three types of advantages to the psychiatrist accruing from his medical education. These are: (1) substantive knowledge; (2) technical skills; and (3)

* Presented September 15, 1967 to the Georgia Psychiatric Association.
ethical and attitudinal orientation. In terms of some of his substantive knowledge, the psychiatrist is in a position to evaluate and advise in psychosomatic disorders. His general medical training provides a base for appreciating and understanding the intricacies of psychophysiological reactions. Moreover, he knows through direct observation the impact and effects of various medical and surgical procedures on patients and their families. In addition, a general medical background is a necessity for prescribing and administering drugs and evaluating new psychoactive agents.

Recent advances in neurophysiology and neurosurgery point toward future treatment possibilities that may involve electrode placements or other interventions in discrete brain regions. The psychiatrist’s medical background will be much needed in the event of these treatment procedures.

As far as technical skills are concerned, the methods of medical problem solving are important in the practice of psychiatry. I am referring to the repeated experiences of exploring the presenting complaint; assembling the history of the present illness as well as the development and past history of the patient; combining these data with direct observation and examination of the patient’s immediate functional status; supplementing this information with special tests; logically correlating all such information into a formulation which summarizes stress, response to stress, special strengths and vulnerabilities; and then predicting the immediate future course of events. Obviously, medical problem solving is a special application of general logical thinking and is not the sole property of physicians. However, the experience gained in repeated exercise of this approach to problem situations is of tremendous value to the psychiatrist. He obtains this skill through his training as a physician.

Other technical skills are those related to the conduct and evaluation of scientific research, both in laboratories and in clinics. Again, these technical skills are not limited to, or even best presented in, general medical education. However, the prolonged exposure to methodology in medical school equips the future psychiatrist with a general scientific orientation which in some ways may extend his effectiveness both as a practitioner and as an independent investigator.

In regard to ethical and attitudinal matters: medical school, internship and medical practice, when honestly pursued, indoctrinate anyone with a sense of responsible commitment to sufferers requesting his assistance; with the realization that such commitments take priority over all other relationships; and with the recognition that life truly presents serious problems that demand the full use of one’s intelligence, self-control, and steadiness. Furthermore, the ancient responsibility of all physicians not only to minister to human suffering, but also to observe it, record it, and share unreservedly any new insights with colleagues, is an ethical charge that psychiatrists assume as physicians. As members of the medical profession, they have voluntarily accepted roles and status which involve accounting to their colleagues and being judged, if necessary, by these colleagues as to the proper or improper discharge of their responsibilities. It is in this latter area that nonmedical therapists cannot provide a truly professional attitude, since there is to date no mechanism for their policing their own activities.

Divergencies of Psychiatry from General Medicine

Let us now consider some difficulties in our medical affiliation. After almost a century of struggling to establish psychiatry as a medical discipline and having achieved a modest degree of acceptance as “card carrying” members of the medical fraternity, we are faced with the disturbing prospect of challenging the accepted medical model.

In the latter half of the 19th century, psychiatry based its claim for medical legitimacy on a family connection with neurology. The very term neuropsychiatry indicated and stressed the medical nature of psychiatry. The advantages of this emphasis were obvious. Inmates of asylums were accorded the status of patients, which, at least hypothetically, entitled them to such privileges as compassionate acceptance, non-judgmental diagnosis, and tolerance of deviant behavior as being evidence of sickness rather than lax morality.

On the other hand, this emphasis on the medical nature of psychiatry resulted in attempts to apply to the study of psychiatric conditions the methods that had been productive in the rest of medicine. For example, the success of cellular pathology in general medicine led to elaborate searches for brain lesions as underlying factors in the mentally ill. The most positive results were those gained through the study of neural changes in general paresis. However, this same approach failed to yield any reliable findings in patients exhibiting schizophrenic, depressed or neurotic behavior. Another mixed blessing stemming from the use of the 19th century medical model was the concentrated attention on the individual patient. The positive result of this was the development of refinements in interviewing and, even more important, in the clarification of transference processes. The negative result of the one-to-one doctor-patient approach was the failure to recognize the weight of family and group dynamic influences as determinants of behavior.

In recent years there has been serious questioning of treatment methods directed toward the pa-
tient abstracted from his milieu. The original concept of mental illness, constructed on the classical medical model, focussed on disturbances in the inner economy, either in terms of defense mechanisms or regression to early levels of personality integration. This point of view reasonably calls for a therapeutic approach directed toward reestablishing healthier emotional equilibria and more mature levels of integration. It assumes that the major impact of therapy must be on the patient himself. Therefore, the treatment maneuvers of hospitalization, individual psychotherapy, drug therapy and shock therapy are viewed as the core of essential and sufficient treatment.

Probably the first breakaway from this approach began in the 1920's in the child guidance clinics. Just as pediatricians found it impossible to treat child patients in isolation from their families, so child psychiatrists learned the futility of an exclusive one-to-one doctor-patient relationship as sufficient therapy for their patients. Successful therapy seemed to depend upon much attention to the actions, strengths, biases, etc., of the parents and other persons in close contact with the child patient. Often the child designated as the patient became symptom-free when the major intervention was directed toward the parents, even when directed by a nonmedical person such as a psychiatric social worker. This radical departure from the medical model did not penetrate the medical profession, possibly because of the isolation of child guidance clinics from other medical centers.

It is interesting that, in the field of non-psychiatric medicine during the first quarter of the 20th century, there was a parallel movement away from the classical medical model in the therapeutic practices offered in tuberculosis sanatoria. In some ways the TB sanatorium represented one of the first therapeutic communities in which the total activity of the hospital was geared to treatment purposes; all persons—physicians and non-physicians alike—were engaged in assisting the patient to overcome his illness. Isolation, often in high mountains and rural areas, kept this approach from influencing the rest of medicine.

Freud's Position vis-à-vis Medicine

In basing psychoanalysis on a theory of instinct, Freud remained well within the 19th century medical model; however, when he extended this theory to include the vicissitudes of instinctual expression, he directed attention to social and psychological dimensions outside traditional medical purview. Moreover, in stressing early family experience as the breeding ground of neurosis, Freud was introducing a new schema for conceptualizing disease. Now, almost 70 years later, psychiatry is more fully accepting the implications of this idea by seriously attempting family psychotherapy.

Another early break with the classical medical model which marked the psychiatrist as a different sort of physician from all others was the view of certain symptoms as symbols, i.e., as having communicative and emotionally expressive meanings. The psychiatrist became a new breed of physician when Freud proposed in his monograph, *Studies on Hysteria*, that the symptoms of hysteria were not the end result of nerve dysfunction but, instead, were the symbolic statement of a conflict between the patient's wishes and his conscience, and, still further, that this conflict was obscured by a meaningful amnesia. Any physician who accepted this thesis was committing himself to a new path in theory and in therapy that has led far from traditional medical practices.

In his own professional life Freud seems to have tried to retain as much of the medical model as possible, especially in such matters as intense stressing of the one-to-one doctor-patient relationship, the ultimate in strict confidentiality, and the attempt to maintain high objectivity. He departed considerably from general medical practice by assuming a very passive role—eschewing the laying on of hands, avoiding giving medications or advice, restraining the impulse to reassure, and insisting that the patient take a responsible role in his own treatment. In the area of theory Freud tried valiantly to remain true to the medical science of his day and devised the libido theory as a psychological extension of the mechanistic approach of the Helmholtz School of Physiology. Moreover, by his dogma of strict determinism he also kept psychoanalysis and dynamic psychiatry within the same philosophy as that underlying the rest of medicine. However, Freud's eventual stress on the primacy of the resolution of the transference neurosis as the necessary therapeutic maneuver transposed psychiatry into a dimension different from any other in medicine; that is, in stressing the doctor-patient relationship as the chief element in therapy, Freud departed from the older medical model, which saw the doctor-patient relationship as the art through which scientific methods could be applied.

To some degree all dynamic psychiatrists who engage in individual psychotherapy differ, as did the pioneer Freud, in the aforementioned ways. One either must extend the concept of the physician's work to include these psychotherapeutic innovations or must recognize that psychiatrists, although similar to other physicians, are also significantly dissimilar.

The Existential Analysts

In very recent years the group of psychiatrists who variously call themselves existentialists or onto-
analysts have openly rejected the suggestion of compromise with classical medicine made not only by their colleagues, but also by Freud. To stress in their psychotherapy the matters of decision making and choice places them quite counter to the thesis of strict determinism. They object to the dehumanizing effects of the medical model on both the patient and the doctor. They strive for a therapy in which the issue of authenticity of character is seen as the central goal rather than the resolution of a transference neurosis. They claim a concentration of attention on the unique existence of each patient and are not concerned with such medical matters as diagnostic classification and cataloging of symptoms. Moreover, their insistence upon the singularity of each patient leads logically to a studied ignoring of statistics. Some representatives of this group do not hesitate to express indifference to charges of being unscientific, because they claim that medical and scientific analyses impede their understanding the person as being and becoming.

It is quite interesting that their insistence on an unbiased view of the raw material of human existence, that is, their attention to subjective phenomena, has actually cleared up certain diagnostic problems such as differentiating varieties of depression.

Behavior Therapy

At another pole from the existentialist, one finds a group of psychiatrists who approximate the medical model far more than most. These are the behavior therapists who concentrate their attention on symptoms, who are satisfied with modest treatment ambitions such as the relief of phobias, and who base their work on a modified Pavlovian neurophysiology. They seem little concerned with symbolism and accept symptoms at face value. Their approach and theoretical stand are almost as simplistic as those of their medical colleagues' common sense psychology. This group remains more faithful to strict scientific methods, for example, in their statistical conservatism, than most other psychiatrists.

To return to our tentative definition, we can see a wide range of physicians who engage in psychiatric work. But, at the same time, it becomes clear that most psychiatrists do stray from the usual paths followed by other doctors.

An Extended View of Suffering

In the definition offered, I mentioned personal discomfort as one of the problems of human existence about which psychiatrists are concerned. Now, to some extent this discomfort is very similar to that which engages the efforts of other physicians. Unusual and painful sensations, as well as physical dysfunction, may represent the end products of certain existential problems. Clinically, there is an overlap in diagnostic work associated with many of the symptom complexes of conditions such as hypochondriasis and depression. However, psychiatrists have pushed far beyond usual medical concern into areas of human discomfort experienced as lack of self-confidence, self-disgust, masochism, despair, disillusionment, apathy, etc. These matters are distressing and uncomfortable as ongoing features in any human life experience, and psychiatric concern about them parallels that of the clergy, educators, moralists, artists, and humanists, rather than that of medical men. In other words, those physicians whom we call psychiatrists frequently share their concern in an intellectual and social community with nonmedical professionals. It is over these issues that Dr. Szasz seems exercised. His claim that it is logically incorrect to equate mental illness with physical discomfort stems from his recognizing fundamental differences in kind in the varieties of human suffering.

In fully accepting as factual these differences—that is, fundamental qualitative differences between mental and nonmental illness—we must honestly reflect on our own attempts to establish a professional monopoly on the treatment of mental suffering.

The Social Aspects of Emotional Illness

In reflecting on the nature of psychiatry, it seems to me that one must repress his awareness of many aspects of mental and emotional illness if he is to adhere to a strict biological and medical point of view. In sharp contrast to other forms of illness, mental illness is always a social matter; that is, it always involves other persons in addition to the designated patient. As the members of the interpersonal school of psychiatry have demonstrated, some of the most troublesome aspects of psychiatric illnesses are communicative disturbances. The patient's deviance is in one way or another expressed as difficulty in transmitting, receiving, and decoding messages to and from others. Psychiatrists, perforce, must depart from a medical base and associate themselves with social scientists and communication theorists until the time when nonpsychiatric physicians adopt a general systems theory in their thinking and action.

Because of the social facet of psychiatric disturbances, psychiatrists treat many patients through a process of social and legal intervention rather than voluntary contract. Our medical and surgical colleagues rarely, if ever, undertake the treatment of a patient on legal injunction. In fact, aside from a few laws requiring immunizations, society does not prescribe medical procedure except in our field. This matter has again been considered by Dr. Szasz, who misinterprets it as a conspiracy joined.
by psychiatry and the law to penalize the social deviant and strip him of his civil liberty. Although this interpretation seems extreme and false, nonetheless, it has pointed up a very fundamental difference between much of psychiatric practice and that of other physicians.

On a far less dramatic level than that concerned with commitment policies, there has been increasing psychiatric concentration on the dynamics and derivative therapies of various social groups: the hospital ward population, the family, and even neighborhood networks. The tremendous thrusts toward community mental health approaches as well as the growth of milieu, group and family therapies seem to have exploded forever the exclusive one-to-one doctor-patient relationship as the *sine qua non* of treatment. With these changes, psychiatry finds itself either far ahead of or far away from the rest of medicine. There is very little in the general medical curriculum that involves medical teachers and students in community networks such as those into which we are moving. Consequently, for the average physician, psychiatry may become even more strange and difficult to comprehend than it was only a decade ago.

Who Should and Could Do Psychiatric Work

I should like to digress at this point for a few moments to consider the inherent difficulties in teaching psychiatry under present-day circumstances and the associated problems of recruiting present-day graduates into our field. Despite the pious pronouncements in the catalogs of most medical schools which claim to present a comprehensive approach to patients, in actual practice this is not the case. In fact, with the tremendous accumulation of substantive information in most fields of medicine, there is much anxiety about finding curriculum time to teach these new facts to each student. This attempt leaves little time or program for a comprehensive approach. In addition to this difficulty we find that, with the development of full-time medical school faculties, much of the teaching devolves upon highly sophisticated clinical researchers whose work divorces them from the view of the patient as a total human being in his environment. With few exceptions, faculty psychiatrists seem to be the only medical school teachers presenting a comprehensive approach. In other words, we are struggling against the main current and, consequently, appear as non-conformists on medical faculties. When we add to this the facts which Dr. Harold Lief has described—that the majority of medical students are intellectually and emotionally conservative persons—we should not be surprised that the comprehensive point of view recommended by psychiatric faculties is ignored in favor of an overwhelming disregard by other teachers.

After 20 years of earnest attempts to have psychiatry incorporated as a major part of the undergraduate curriculum, we continue to meet disheartening resistance and rejection by most students. This fact has been detailed in a recent survey in which it was found that only 3% of recent graduates thought that psychiatry was a relevant subject in their studies.

Consequently, one can see the serious problems of recruiting new blood into our ranks. These sobering facts impel me to share some thoughts with you about who can and should do psychiatric work. This question becomes almost painful to those of us responsible for residency training programs. On the one hand, we are faced with the necessity of offering training experience to as many young physicians as we can gather from a population of medical graduates who lack motivation for, interest in, curiosity about, or the capacity to assimilate a psychiatric point of view. On the other hand, we must assume the responsibility for not accepting candidates who cannot actually learn to function as psychiatrists must.

Fundamentally, any physician in the last third of the 20th century who elects to be a psychiatrist should possess or acquire most of the following characteristics. Along with an ability to maintain an objective point of view toward the accumulating data in our field, he must be flexible enough not to be afraid to use empathic, imaginative, and subjective hunches about his work.

Because of psychiatry's immaturity as a discipline and its high state of ignorance about human behavior, one aspiring to practice psychiatry must be mature enough to live and work with considerable uncertainty. No one who requires the high degree of certainty which one obtains from standardized laboratory tests should enter psychiatric work, for we have not arrived at a point of closure in our knowledge. On the other hand, the young physician who can work comfortably while uncertain will find great opportunity for original creative work in the open-ended field of psychiatry. To put it in our own clinical jargon, psychiatry is no place for a compulsive character, since he will be threatened repeatedly by doubt and indecision arising from the lack of firm guidelines.

Anyone aspiring to be a psychiatrist has an advantage if he can move intellectually with fair ease in humanistic studies and the social sciences as well as in basic biology. Now, this broad span of intellectual interest is not commonly found among the majority of medical graduates. A fine example of the universal, intellectual man was Freud, who combined humanistic interests in language, the Greek classics, and mythology with a good working knowledge of the British social philosophers from Hobbes.
through Mill, and yet managed to become a master in his researches in microscopic neuroanatomy. Since psychiatry must take as its objective the study of man as man, then psychiatrists must be acquainted with man’s works in the humanities, his various methods of social affiliation, as well as the physiological apparatus by which he lives. This is a vast and at times almost overwhelming task, particularly in a world in which the accumulation of knowledge is accelerating in an exponential manner. A recent brief note by a psychiatric resident in *Psychiatric Opinion* expressed rather plaintively the shock experienced by many young physicians upon entering psychiatric studies. He asked that his teachers try to confine themselves to biologic and medical approaches and to present other matters in as gentle a fashion as possible. In reading his complaints I thought the author lacked the intellectual stamina called for in psychiatry, since he was asking for a watered-down version of necessary training.

Because it is not centrally located in the medical “establishment,” psychiatry is a field in which one can continue to be curious and skeptical about man, entertaining all kinds of notions about human behavior. Emotionally, if not physically, one can experience the satisfactions of the life of an explorer rather than of a comfortably settled inhabitant. Something of the qualities of a pioneer are valuable assets in any candidate aspiring to psychiatry. Those who, figuratively, want to sleep soundly in well-made beds of theory and practice should avoid the wide open spaces in which psychiatrists must roam.

It seems to me that anyone who is electing psychiatry must have the courage to be a minority member of the medical fraternity. He must face the displeasure of his medical colleagues when his ideas and practices jar their composure. That is, he must be man enough to stand up for his convictions even though this costs him considerable popularity. (I always warn applicants for psychiatric residency that they will enter a field in which they will not gain great popularity, but in which it is quite real and possible to obtain respect and self-respect.)

Ideally, the candidate for training in psychiatry should be able to accept the social and professional responsibilities of being a physician while renouncing, as far as humanly possible, the special privileges associated with membership in a guild. Specifically, I am referring to the responsibilities of caring for distressed persons regardless of their position in society; maintaining a non-censuring and non-judgmental attitude toward patients and their families; evaluating social change in terms of its benefits for the preservation and improvement of health; and conducting oneself in a way that may serve as an example of mature and healthy action; at the same time not exploiting the misfortunes of another for one’s personal gain in terms of prestige, power, and/or possessions.

The ideal psychiatrist should be one who does not feel alarmed by the knowledge, ideas, or criticisms offered by professionals outside his own group. He should be able to recognize the value of information gathered by neurophysiologists, psychologists, social scientists, poets, and all persons concerned with the vagaries of human behavior. To cite an example: the open-minded psychiatrist will find delight in the work of the ethnologists, particularly those who are making fresh observations on the behavior of our close primate relatives. The ethnologist Konrad Lorenz has joined us in concern over the issue of aggressive behavior. His monograph on aggression has been informative and interesting to most psychiatrists who study human violence. I cite this as an example of the rewards that come to those psychiatrists who can respect and examine the thoughts and opinions of knowledgeable persons in fields other than psychiatry.

With the movement toward community mental health services, it will be especially helpful to train in our own field those men who can work productively with other professionals and still maintain their own identity. To accomplish a team approach, future psychiatrists will have to occupy leadership positions without becoming dictatorial. Only a combination of humility and true respect for the integrity of other team members will accomplish community mental health goals.

To continue, in thinking about who should do psychiatric work, it seems to me highly important that a psychiatrist be a person capable of independent study which he can organize and sustain throughout his entire career. In any intellectual pursuit as incomplete and unfinished as psychiatry, one must remain a student forever. If we consider the history of psychiatry over the past 20 years, we can see how necessary it is for a psychiatrist to pursue unrelentingly his studies of behavior. During these 20 years, we have been deluged with information about many new concepts: group dynamics; group psychotherapy; psychopharmacology; a new neurophysiology which has introduced us to the reticular activating system, motivational physiology, sensory deprivation and physiology of sleep; family process and family psychotherapy; behavior therapy; communication theory, etc. I doubt that in a comparable time practitioners in any other medical field have had to master so many new concepts and so much substantive information. It is a most valuable asset to any psychiatrist to conduct independent study in a critical and benevolently skeptical fashion. Again, the experience in medical school until very recently has not been one to encourage such scholarship, since most medical teaching is of a lockstep variety.
of anyone doing psychiatric work is the ability to study oneself as an object. Almost 2400 years ago Socrates stated, "The unexamined life is not worth living." Few persons systematically undertake a continuing examination and evaluation of their own lives. There may be some grounds for contesting Socrates' statement, although I believe no one can be considered truly mature who has not devoted great effort to self-understanding. In a psychiatrist, continuing self-scrutiny is imperative. Many of the reasons for this necessary introspection have been detailed for years in the psychiatric literature. It is still debatable whether or not all psychiatrists should personally undergo some form of psychotherapy. Certainly most psychiatrists who have undertaken personal psychoanalysis have found this experience of extreme value in their individual and professional development.

To be introspective is not typical or characteristic of most physicians; they are usually oriented outwardly, and their training, aside from a touch of psychiatry, has in no way encouraged introspection. So, again, we find a significant difference between the psychiatrist and the non-psychiatric physician.

Closely related to the introspective study of oneself is the understanding of symbolism. There is a need to comprehend the symbolic qualities of human life. Most psychiatrists agree that Freud's greatest contribution was his classic on symbolism, The Meaning of Dreams. Each of us in psychiatry has known some physician whose attempts to master our field foundered on the rocks of symbolic communication. The successful psychiatric resident is the one who, in some way or other, has managed to maintain responsiveness to symbolism despite the great emphasis of his medical education on literal-mindedness.

In addition to possessing the ability to understand symbolism, the psychiatrist must continue to cultivate it throughout his career. He must increase the acuity of his third ear. To do so involves him in exposure to such nonmedical influences as poetry, novels, the graphic arts, and other symbolic expressions of human existence. Again, he must have the courage to follow these stars, although they may at times estrange him from his medical colleagues.

Finally, those who would do psychiatric work should be those who recognize both the tragic and comic aspects of life and can focus on these rather than on the banality of pathos. Again, we can reflect on the history of Freud, who clearly distinguished between what was tragic and what was pathetic but did not lose his capacity for laughing with the comic. Perhaps the greatest reward of introspection is the discovery that one can laugh with oneself about one's own absurdities. No patient is more unfortunate than he who has to trust himself to a humorless psychiatrist, and none more fortunate than he who finds a therapist who can join him in a tolerant and delighted chuckle over our human comedy.
Recent Advances in Pediatric Allergy*

F. STANFORD MASSIE

Department of Pediatrics, Medical College of Virginia, Richmond 23219

In 1923 Coca and Cooke, two of the most important pioneers of allergology in the United States, enumerated a number of postulates defining an allergic or, more specifically, an atopic individual (Coca and Cooke, 1923). Atopy, a term coined by Coca, literally means "atypical," referring to a series of differences from the normal individual, partially proved and partially postulated. Today, I would like to examine those postulates with you in light of relatively recent clinical and experimental data which are fostering some changes in our understanding of the nature of the atopic state. Much of the information for discussion has been recently reviewed by Frick (1966; unpublished data).

Postulates

1) Atopy is an immediate hypersensitivity reaction limited to man;
2) There is a genetic predisposition to atopy;
3) Atopic individuals become sensitized "spontaneously" after the same natural exposures to antigens which are innocuous in most humans;
4) Atopic individuals form peculiar types of antibodies—skin-sensitizing antibody, or reagin, and blocking antibody.

* Presented at the Third Annual Pediatrics Day, December 8, 1967, Medical College of Virginia, Richmond.
The Ishizakas (1968) have also redefined a new class of immunoglobulins, which they have named IgE. This class has physicochemical and antigenic properties distinct from all the other recognized immunoglobulins—IgG, IgA, IgM, and IgD. The Ishizakas (1968) have also reported evidence that the normal individual has IgE fixed to his skin. Hence, it appears that the atopic individual may have a quantitative abnormality in skin-sensitizing antibody production.

Salvaggio (Salvaggio et al., 1964; Salvaggio, 1966) showed that 60%-80% of a group of allergic individuals but only a few of the nonallergic controls developed positive immediate skin tests after being exposed, for a period of six months, to aerosol nasal inhalations of two unnatural antigens, beef ribonuclease and dextran. He suggested that this was because of increased nasal membrane permeability in the atopics. In addition, Rothenberg and Farr (1965) demonstrated that adult allergic patients have a much higher incidence of antibodies to milk than controls, which suggests increased gut permeability to milk protein. Perhaps this increased permeability is genetically determined.

The third postulate, that atopic individuals become sensitized “spontaneously” after the same natural exposures to antigens which are innocuous in most humans, can be viewed in light of recent reports of asthma epidemics. These epidemics have raised the question of whether all humans, under sufficient allergen exposure, could be made to form atopic antibodies, thereby mediating clinical disease.

In one rural South African community, over 200 individuals living in the environs of a castor bean processing factory developed asthma, and many had positive skin tests to castor bean. Air pollution with castor bean waste appeared to sensitize a large number of the population (Ordman, 1955).

Epidemiologic studies of asthma and allergic rhinitis have suggested another intriguing question: Is asthma an infectious disease? Smith, at the University of Iowa, has performed two surveys. In the first, she studied 1,760 rural families (Smith and Knowler, 1965a). In the second, every fourth household in Iowa City was canvassed, all socioeconomic groups being included (Smith and Knowler, 1965b). She found that when one member of a family pair with a negative family history for allergy married an allergic individual, there was a fourfold to fivefold or 20% increase of allergic disease in the nonatopic spouse within five years after marriage. Furthermore, when the mother was the allergic individual, there was a five times greater incidence of allergy in the children than when the father was originally allergic. Previous genetic studies mentioned earlier in my paper revealed that approximately 50% of the children in the family with one affected parent are potentially allergic. According to Smith’s epidemiologic data, when the mother was the original allergic family member, 50% of the later allergic spouses developed allergy at about the same time as the offspring. This would suggest transmission of the atopic condition by an infectious agent of low virulence and communicability, with intimate contact over a long period of time being required for transmission.

The physicochemical nature of allergens is currently under intense investigation. It appears that there are some striking similarities among rather diverse naturally occurring substances which produce skin-sensitizing antibody in man (Frick, 1966). In general, their molecular weight is between 10,000 and 40,000. They have a low nitrogen content, usually between 1% and 13%, but a high carbohydrate content. Berrens, in Holland (Berrens and Bleumink, 1965; Bleumink and Berrens, 1966), has purified several common allergens, including horse dander, tomato atopen and milk. He has found that they all contain an N-glycosidic protein-sugar linkage and that, with aging or browning, as in the case of tomatoes, a particular rearrangement occurs in the sugar moiety of the carbohydrate-protein complex. An enol form results, producing the allergic component of the mole-
cule. This, then, raises the question of whether atopic persons are deficient in handling this kind of molecule. Do they have a genetic enzyme defect, as in the inborn errors of metabolism, and does the previously mentioned increased membrane permeability relate to this?

The fourth postulate deals with the formation of peculiar types of antibodies—skin-sensitizing and blocking. Atopic sensitization develops following natural exposure to allergens in patients with an atopic constitution; allergic disease develops following repeated exposure to the allergen after skin-sensitizing antibody has formed (Boyden, 1963). The demonstration of a similar mast cell-sensitizing antibody in the rat by Becker and Austen (1966) and the production of a heat labile, gamma 1, anaphylactic-type antibody in the Hemophilus pertussis-treated mouse (Fishel, Szentivanyi and Talmage, 1964) have suggested the presence of reagin-like antibodies in other species. The mechanism which triggers the formation of this kind of antibody is being vigorously sought.

Specific treatment of allergic disease with immunizing injections of allergens has been shown to produce a blocking gamma G type of antibody. This type of antibody subsequently prevents allergen-reagin interaction (Boyden and Roth, 1963). Studies have not shown a close correlation between the titer of blocking antibody and the absence of clinical disease. Sherman (1968) has shown that the skin-sensitizing antibody titer itself significantly diminishes in patients receiving allergy injections for a number of years. The decrease in skin-sensitizing antibody content correlates with clinical improvement, suggesting either the production of immune tolerance or an actual desensitization (Claman, 1964). The latter hypothesis is supported by the diminishing in vitro release of histamine from sensitized leukocytes in treated allergic patients as compared with controls (Lichtenstein, 1968).

**Altered Autonomic Reactivity**

As a final consideration I would like to review with you a theory proposed by Cookson and Reed (1963), suggesting that asthmatics have an imbalance of sympathetic nervous system adrenergic receptors with a partial beta-adrenergic blockade.

In 1948 Ahlquist described two types of adrenergic receptors, which he named alpha and beta on the basis of their responses to various amines. Endogenous mediators for alpha receptors are epinephrine and norepinephrine; for beta receptors, epinephrine. Thus, epinephrine has both kinds of activity. Acetylcholine stimulates the cholinergic receptors of the parasympathetic system. Norepinephrine has been shown to be a pure alpha stimulator; Isoproterenol, a beta stimulator; and methacholine, a cholinergic stimulator (Innes and Nickerson, 1965).

The action of these receptors on different organs depends upon their concentration in a given organ—e.g., the blood vessels of the skin have alpha receptors primarily, and stimulation causes constriction. Skeletal muscle blood vessels, on the other hand, respond by dilation in response to beta stimulation. The heart is largely regulated by beta receptor stimulation for increase in heart rate, stroke volume and force of contraction. Slowing of the heart rate occurs with vagal cholinergic stimulation. The lungs respond to beta stimulation by bronchodilation, and there are few alpha receptors present except in blood vessels. Vagal cholinergic influences would bring about bronchoconstriction. Thus, there is a neat balance between the adrenergic alpha and beta receptors and the cholinergic parasymathetic receptors. Alpha receptors may be blocked by Dibenzyline and Regitine with resulting imbalance of the adrenergic system due to beta enhancement. The beta receptors may be blocked by agents such as Dichloroisoproterenol, propranolol and pronethanol, leaving the alpha system unchecked. Atropine blocks the cholinergic receptors (Innes and Nickerson, 1965).

As an experimental model for anaphylaxis, the H. pertussis-treated mouse has heightened sensitivity to histamine and other amines of importance as mediators in allergic asthma (Fishel, Szentivanyi and Talmage, 1964). The response seems to be mediated through a partial blockade in the beta receptors, with alpha receptor overactivity or enhancement (Fishel, Szentivanyi and Talmage, 1962, 1964; Fishel and Szentivanyi, 1963). This is supported by beta blockade with Dichloroisoproterenol increasing histamine sensitivity in the untreated mouse and alpha blockade with Dibenzyline decreasing sensitivity to histamine in H. pertussis-treated mouse. Various metabolic effects, including flattening of the glucose tolerance test, are also noted after beta blockade in the normal mouse and the H. pertussis-treated mouse. The latter fails to respond to epinephrine with hyperglycemia (Fishel and Szentivanyi, 1963). Whereas, as mentioned previously, normal mouse and man produce IgG antibodies in response to most antigens, an additional antibody is produced by the mouse after treatment with H. pertussis; it is a 7S gamma 1 anaphylactic type of antibody and is comparable to IgE or reagin in man (Mota, 1967). The relationship between production of this antibody and the apparent imbalance in the adrenergic receptors is not clear at this point.

Various investigators have shown that the asthmatic man is much more sensitive to bronchospastic effects of histamine and acetylcholine administration than the normal control is (Curry, 1946; Curry and Leard, 1948; Tiffeneau, 1958). Compared with normal controls,
this response in asthmatics may be variably enhanced by beta-adrenergic blockade with agents such as propranolol (Zaid and Beall, 1966). Ouelleite and Reed (1965) have further shown that asthmatics have marked increase in response to methacholine after influenza vaccine. They suggest that this is an endotoxin-like toxic effect of the vaccine acting through the autonomic nervous system and propose this as a mechanism whereby acute respiratory infections provoke asthma. Clearly bacterial products do alter autonomic nervous system reactivity, and such mechanisms may be operative in conjunction with antigen-antibody reactions in allergic individuals (Szentivanyi and Fishel, 1965).

A number of altered metabolic effects have also been noted in asthmatic man consistent with a partial beta-adrenergic blockade, but absolute proof is lacking that this mechanism is of fundamental pathophysiological importance in asthmatics, and, in view of other conflicting data (Zaid and Beall, 1966), it must remain only an attractive hypothesis.

Summary

Evidence has been presented to indicate that atopic disease is not limited to man but occurs in subhuman primates. The genetic transmission of allergy may relate to altered membrane permeability or an enzymatic defect, with inability to handle certain N-glycosidic protein-sugar linkages occurring in the atopens of nature. The suggestion that an infectious agent transmits allergic disease has been examined. Finally, in vitro and animal experimental models of anaphylaxis closely akin to atopy and the effects of manipulation of the autonomic nervous system in laboratory animals and man have been discussed.

References


F. S. Massie


Histochemical and Fine Structural Studies of Lymphocyte Transformation with Phytohemagglutinin and Pokeweed Mitogen

PETER F. HOFFMAN (M-IIA)

During a study of the effects of pokeweed mitogen extract (PWM) on cultured human peripheral lymphocytes, several distinct morphological differences were noted when these cells were compared with cultures of lymphocytes treated with phytohemagglutinin (PHA). The number of blast cells which appeared in both PHA- and PWM-treated cultures was maximal at 72 hours, not only as seen by light and phase contrast microscopy, but also as determined by the incorporation of tritiated thymidine into DNA, which reached its peak at this time. Giemsa- and acetic orcein-stained preparations of the 72-hour cultures showed that the transformation induced by PWM differs from that induced by PHA, in that cell nuclei are more eccentric, nucleoli are fewer, and heterochromatin is more prominent in the former. PWM-transformed cells showed maximum PAS staining after 72 hours, while the PAS staining of the PHA cells was diminished by this time. Both PHA- and PWM-treated cells showed similar ability to bind rabbit anti-human gamma globulin conjugated to fluorescein isocyanate, which cross-reacts with IgG, IgA, and IgM. Histochemical and electron microscopic studies revealed a significant increase in the number of lysosome-like bodies in PHA- and PWM-stimulated cells when compared to control cultures at 72 hours. A comparative fine structural study of the cells present in culture after 72 hours revealed differences in the populations of cells in PHA- as compared to PWM-treated cultures. In PHA cultures, there was a predominance of large blast-like cells, with smaller numbers of normal-appearing small lymphocytes, as described previously. In PWM cultures, three cell types were distinguishable: normal appearing lymphocytes of varying size, large blast-like cells, and a distinct type of intermediate-sized cell. The latter type of cell contained significantly more rough-surfaced endoplasmic reticulum than PHA-transformed cells or 72-hour control cultures. In addition, the cells of intermediate size contained numerous ribosomes in various stages of aggregation. These fine structural features were comparable to those of cells which have been described by other investigators as early antibody-producing cells.

Preceptor: STEVEN D. DOUGLAS, JAN BORJESON, LAWRENCE N. CHESSIN, National Institute of Arthritis and Metabolic Disease, National Institutes of Health


Plasma Pressor Activity in Normal and Stressed Newborns

KENTON R. HOLDEN (M-III B)

Plasma pressor activity (PPA) was measured in umbilical plasma of 29 full-term infants using a modified in vitro bioassay which reflected, primarily, plasma levels of epinephrine and norepinephrine. Of this group, seven infants with asphyxia neonatorum demonstrated significant hypercapnia (pCO₂ = 78.3 ± 5.2 S.E.M.), acidemia (pH₇.₄ = 7.06 ± 0.05), elevation of PPA (42.7 ± 19.9 µg/ml), and lowered Apgar scores (one minute = 4.4 ± 0.7; five minutes = 7.6 ± 0.7) as compared to 14 normal newborns (pCO₂ = 49.8 ± 2.2, pH₇.₄ = 7.27 ± 0.01, PPA = 1.6 ± 0.4 µg/ml), Apgar scores (one minute = 8.6 ± 0.1; five minutes = 9.9 ± 0.1). Eight newborns of mothers with mild pre-eclampsia showed a trend similar to the newborns with asphyxia neonatorum. Pooled data on all infants revealed a highly significant correlation between umbilical artery PPA and pCO₂ and pH₇.₄, respectively, as well as Apgar scores at one and five minutes. However, no correlation of umbilical artery PPA could be demonstrated with pO₂ free fatty acids, blood glucose or maternal PPA at time of delivery. All infants and their mothers were discharged in normal condition except for one infant with asphyxia neonatorum who had persistent tracheomalacia on discharge.

Preceptor: REUBEN B. YOUNG, Department of Pediatrics, Medical College of Virginia

Adrenal Cortical Responsiveness in Patients with Renal Homotransplants Receiving Prednisone

JOSEPH D. LINEHAN (M-II)

It is known that large doses of prednisone, taken daily, produce adrenal atrophy and inhibit the adrenal response to ACTH or insulin-induced hypoglycemia. All the patients in the MCV transplant series received daily doses of prednisone from the time of transplantation. Because these patients were subjected to normal stresses as well as stresses peculiar to transplantation, such as multiple surgical procedures, infection, and rejection, the adrenal responsiveness was tested in these patients on various dosage
schedules and at relatively stable periods up to five years following transplantation. Plasma levels of 17-hydroxy-corticosteroids were determined by the Nelson-Samuels method before and after a four-hour infusion of 25 units of ACTH. The following results were obtained in 38 patients: The responsiveness of the adrenal was related to the dose of prednisone given, to the extent that seven out of nine patients on 5 mg/day responded normally, while only seven out of 29 patients on 7.5 mg/day or more responded normally. There was no correlation between the presence or the absence of a response and the resting levels of 17-hydroxy-corticosteroids, nor was there any correlation with the presence or the absence of obvious changes as described by Cushing. There was no statistically significant correlation between the response and the length of time the patients had been on corticosteroids, as nine out of 29 patients on prednisone for over two years responded normally. These rather surprising results indicate that the majority of patients receiving doses as low as 7.5 to 10 mg per day showed suppression of their adrenal response. As long-term patients in our series were in excess of 5 mg/day, they should be considered adrenal deficient in stress states. It was also concluded that, while small dosages do suppress the adrenal gland, prolonged prednisone treatment at suppressing dosages may not produce permanent adrenal insufficiency.

Preceptor: HYUNG M. LEE, Department of Surgery, Medical College of Virginia

Cortical Influences on Midbrain Evoked Activity in Cat

JOHN H. OSTRICH (M-III A)
DAVID F. POLSTER (M-III A)

This study was designed to investigate cortical influence on evoked afferent activity at discrete thalamic and midbrain loci in cats. Animals anesthetized with nitrous oxide were placed in a stereotaxic instrument. Monopolar electrodes were positioned at two midbrain loci, one in the periaqueductal grey at the level of the superior colliculus, and the other in the ventral tegmentum at a point characterized physiologically by Collins and O'Leary. A third electrode was placed in the nucleus ventralis postero-lateralis of the thalamus. Evoked potentials in these areas, produced by contralateral peripheral nerve stimulation, were monitored by capacity-coupled amplifiers and a triple-beam oscilloscope. Cortical somatosenory areas I (SI) and II (SII), ipsilateral to the deep recording loci, were identified. Physiological saline ice slush was applied to SI, SII, or both areas simultaneously. Following either a demonstration of alteration in evoked responses at the deep loci or an elapsed time of five to ten minutes, the cortical areas were warmed with saline and covered with warm mineral oil. During the experiment, the animal was immobilized with Flaxedil and maintained by positive pressure ventilation through a tracheostomy. Rectal temperature was monitored and was kept above 36 °C, using electric heating pads. Systolic blood pressure, recorded continuously by an indwelling arterial catheter, stayed above 120 mm Hg at all times. Animals were sacrificed with barbiturate overdose, and recording loci were marked by electrolytic deposition of iron at the electrode tips. Subsequent arterial perfusion with Potassium Ferrocyanide solution allowed microscopic eval-

uation of recording sites to be made by histological brain sections. Data were drawn from 24 experiments which met the criteria of reproducible baseline potentials and accurate electrode tip placement. Evoked activity in the periaqueductal grey was always depressed—never augmented—during cooling of the somatosensory cortex. The thalamic and thalamic responses were always stable. Cooling SII alone produced greater depressions than cooling SI alone. Simultaneous cooling of both areas caused the most marked depression of the periaqueductal response. Such results could be obtained as many as four times during a single experiment. These data suggest a physiological substrate for cortical control over discrete areas of the reticular formation. Anatomically separate cortical areas, although sharing a similar input, may exert varying degrees of control at specific sites even in the histologically diffuse reticular brain stem. One can conjecture that subtle cortical malfunctions, not only in the sites we have studied, but also in others, might lead to severe disturbances in the modulation and channeling of sub-cortical information, and that these disturbances, in turn, might be manifested by gross behavioral changes in the animal not satisfactorily explained by a consideration of cortical zonal physiology alone.

Preceptor: WILLIAM F. COLLINS, Department of Surgery, Medical College of Virginia

The Ultrastructure of the Vibratory Muscle of Crotalus horridus

LOUIS T. PASTORE (M-I)

A comparison of the vibratory and epaxial muscles of Crotalus horridus (timber rattlesnake) was made. Muscle fibers, fibrils, filaments, mitochondria and sarcoplasmic reticulum were described in this study. The sarcomeres of the epaxial muscle were almost three times the length of those of the vibratory muscle. The A band was observed to be about twice the length of the I band in the vibratory muscle. As seen in cross section, the vibratory muscle had fibrils arranged in discrete packets with a limited number (less than 100) of thick myofilaments. In contrast, the fibrils of epaxial muscle were less conspicuously separated from each other and contained about six times as many myofilaments. The vibratory muscle was profusely provided with large spherical mitochondria having highly developed cristae. The epaxial muscle had relatively fewer mitochondria; these were ellipsoidal and smaller in size, with less-developed cristae. The sarcoplasmic reticulum of the vibratory muscle was highly developed with numerous tubules, which were continuous between fibrils. A reduced development of reticulum was found in the epaxial muscle. It was concluded that the vibratory muscle is highly specialized in structures related to energy production or dissemination of the contraction impulse to the interior of the fiber.

Preceptors: FRANCIS B. LEFTWICH, Department of Biology, University of Richmond; THOMAS M. HARRIS, Department of Anatomy, Medical College of Virginia
Beta-Adrenergic Receptors in the Human Distal Esophagus*

RICHARD F. PRINCE (M-111)

The body of the esophagus and the lower esophageal sphincter (LES) are thought to be under different neural control. The following study was performed to test the hypothesis that adrenergic receptor activity may be important in control of the motor function of the esophagus. In 11 normal volunteers, three open-tip esophageal catheters were placed 5 cm apart, locating the distal tip in the LES. Each catheter was perfused with microliter quantities of water, and pressures were recorded. Response to degluti-
tion was evaluated by measuring duration and amplitude of contraction, velocity of the peristaltic wave and sphincter tone while BP and EKG were being monitored. Phenylephrine Hydrochloride (alpha stimulant) and Phentolamine (alpha blocker) were administered I.V. to four subjects; no alpha-adrenergic response was observed. Isoproterenol (beta stimulant) and H-56/28 (Astra; beta blocker) were administered I.V. to seven subjects. No effects were noted in the body of the esophagus; in six of seven subjects, beta blockade caused a marked increase in amplitude and duration of sphincteric contraction; beta stimulation caused decrease in sphincteric tone, an effect which was abolished by beta blockade. These findings indicate that beta-adrenergic inhibitory receptors are present in the LES, and blockade of these receptors results in exaggerated sphincteric contraction. Such a mechanism may be operative in the “hypertensive” or “hypercontracting” sphincter.

Preceptor: ALVIN M. ZEASS, Department of Medicine, Medical College of Virginia


In Vitro and in Vivo Activity of Hamycin Against Blastomyces dermatitidis

GILES M. ROBERTSON, JR. (M-111B)

Variable responses to hamycin, a new polyene antifungal agent, have been observed in patients with North American blastomycosis. Possible mechanisms for such differences were studied with five strains of Blastomyces dermatitidis. In vitro studies revealed only a twofold difference in mini-
ma inhibitory concentration values (0.008μg to 0.016μg per ml) for hamycin. In vivo responses were measured in fatally infected mice treated, intraperitoneally, for 28 days with daily doses of 0.001 to 0.033 mg per mouse. Differences in response to treatment were significant among the five strains (p << 0.001), with median protective dose values ranging from 0.001 to 0.033 mg per mouse per day. Surviving mice were further observed, without treat-
ment, for 34 days, and marked relapse rates and renewed deaths were seen with several strains. At the termination of the studies, all remaining mice were killed and grossly examined; cultures of tissues revealed high levels of persistent infections with several strains. Deaths or histopatho-
logical changes due to the drug were not observed. These results suggest that variations in response to hamycin ther-

Preceptor: SMITH SHADOMY, Department of Medicine, Medical College of Virginia

Sinus Arrhythmia in the Canine Cardiac Transplant

MARC D. THAMES (M-111)

The recurrence of sinus arrhythmia was investigated in 13 mongrel dogs submitted to cardiac autotransplantation or homotransplantation. The animals were studied at vari-
ous times postoperatively in an attempt to demonstrate vagal and sympathetic reinnervation and recurrence of sinus arrhythmia. Electrical stimulation of the vagus nerve and stellate ganglion was used to elicit proof of parasym-
pathetic and sympathetic reinnervation, respectively. Further proof of reinnervation was the reflex response to acute, pharmacologically induced changes in blood pres-
sure: bradycardia, following intravenous injection of phe-
nylphrine, and the hypertension thereby produced provided proof of vagal reinnervation; tachycardia, following intra-
venous injection of nitroglycerine, and the hypotension thereby induced provided proof of sympathetic reinnerva-
tion. Simultaneous cardiotachometric and pneumographic recordings were employed to detect sinus arrhythmia. Thir-
ty-two studies were performed on 11 dogs without anes-
thesia, and ten studies were done on ten dogs using chlora-
lose and urethane anesthesia. Most of the 13 dogs were shown to have both vagal and sympathetic reinnervation by four months postoperatively. No sinus arrhythmia was demonstrable during the period prior to cardiac reinnerva-
tion. Sinus arrhythmia was found to recur as early as 100 days postoperatively, ten of the 13 dogs demonstrating the arrhythmia by 455 days postoperatively. Sinus arrhythmia failed to recur in three animals, all of which had demonstrable reinnervation. It is thus concluded that, within a few months following canine cardiac transplantation, cardiac reinnervation is sufficiently developed to elicit sinus arrhythmia.

Preceptor: RICHARD R. LOWER, Department of Thoracic Surgery, Medical College of Virginia
Contributors to this Issue

**William F. Falls, Jr.** (*Clinical Aspects of Renal Tubular Disorders*), assistant professor of medicine at the Medical College of Virginia and chief of the renal section at the Veteran's Administration Hospital, Richmond, received his B.S. and M.D. degrees from the University of Maryland. After completing his internship at the University of Maryland and a tour of duty in the U.S. Navy as a general medical officer, he served as assistant resident in general medicine at MCV. Prior to his present appointments, Dr. Falls spent several years as a fellow in renal and metabolic disease at the University of Texas Southwestern Medical School.

**Lee W. Henderson** (*New Developments in Hemodialysis for Chronic Renal Failure*) is director of the dialysis unit and assistant director of the clinical research center at the Hospital of the University of Pennsylvania. He received his B.S. degree from Harvard University and his M.D. from the University of Pennsylvania, completing his internship and residency at the Pennsylvania Hospital. Before assuming his academic positions at the Hospital of the University of Pennsylvania, Dr. Henderson spent several years as a renal fellow and research associate at the Peter Bent Brigham Hospital and as an assistant in medicine at Harvard University. He is currently a Markle Scholar in academic medicine.

**Robert H. Heptinstall** (*Focal Glomerulonephritis*), a native of England, is acting director of the department of pathology at the Johns Hopkins University School of Medicine and acting pathologist-in-chief at the Johns Hopkins Hospital. He received his undergraduate education at King's College, London, and his medical degree from Charing Cross Hospital Medical School, London University. After serving several years as a medical officer in the R.A.M.C., he returned to London and became a member of the pathology department at St. Mary's Hospital. Dr. Heptinstall has held an Eli Lilly travelling fellowship at the Johns Hopkins Hospital and has been a visiting professor of pathology at Washington University School of Medicine, St. Louis, Missouri.

**Henry D. Lederer** (*Present-Day Psychiatry*), chairman of the department of psychiatry at the Medical College of Virginia, received his premedical education at the University of Chicago and his M.D. degree from Rush Medical College of that school. After completing his internship at the Cincinnati General Hospital and his residency at the University of Cincinnati School of Medicine, he served in the U.S. Army as a psychiatrist and neurologist. Before coming to MCV, he was a member of the faculty at the University of Cincinnati for 16 years and then of Georgetown for two years. Among his main interests are the areas of psychosomatic medicine and psychotherapy of ambulatory patients.
F. Stanford Massie (Recent Advances in Pediatric Allergy) is director of pediatric allergy and immunology at the Medical College of Virginia. He received his A.B. and M.D. degrees from Duke University, Durham, N. C., and completed his internship in pediatrics at Duke Hospital. After spending one year as assistant resident in pediatrics at the University of California Medical Center in San Francisco, he served two years as a pediatric medical officer at the U. S. Naval Hospital in Camp Pendleton, California. Returning to the University of California Medical Center after his tour of duty, Dr. Massie was chief resident in pediatrics and a USPH allergy fellow there prior to joining the MCV faculty. His special research interests are isolation and characterization of allergic antibodies.

Roscoe R. Robinson (Conservative Management of Chronic Renal Failure) is professor of medicine and director of the division of nephrology at Duke University Medical Center, Durham, N. C. He received his M.D. degree from the University of Oklahoma School of Medicine. Following internship and assistant residency in medicine at Duke University Medical Center, he served as a research fellow of the American Heart Association and visiting fellow in medicine at Columbia-Presbyterian Medical Center in New York. Before returning to Duke University as an associate in medicine, Dr. Robinson spent two years in the U. S. Air Force as chief of the renal unit at the Aerospace Medical Center, Lackland Air Force Base, Texas.

Victor C. Vaughan, III (Some Issues in Human Development), a native of Richmond, is professor and chairman of the department of pediatrics at Temple University School of Medicine and medical director of St. Christopher's Hospital for Children. After receiving his A.B. degree from Harvard College and his M.D. from Harvard Medical School, he completed an internship at the Massachusetts General Hospital, followed by pediatric residency training at Yale University School of Medicine. Dr. Vaughan held academic positions at Yale and the Medical College of Georgia, as well as an earlier appointment at Temple University, prior to assuming his present position. His research interests lie in the areas of growth and development, hemolytic disease of the newborn, and pediatric allergy.
ABDOMEN
  pain in . . . , due to liver cirrhosis, 10

ABORTION, CRIMINAL
  abortion: legal aspects, 86

ABORTION, LEGAL
  abortion: legal aspects, 86
  abortion: medical and moral aspects, 83

ABORTION, THERAPEUTIC
  abortion: legal aspects, 86
  abortion: medical and moral aspects, 83

ACIDOSIS, RENAL TUBULAR
  clinical aspects of renal tubular disorders, 162

ACID PHOSPHATASE
  a histochemical study of skin wounds, 81

ADENOSINE TRIPHOSPHATE
  pathogenesis of hepatic encephalopathy, 32
  mechanism of energy transformations in biological membranes, 96

ADRENAL GLANDS
  adrenal cortical responsiveness in patients with renal homotransplants receiving prednisone (abstracts), 194

AGGRESSION
  some issues in human development, 173

AIR POLLUTION
  the ambient air, 58

ALANINE
  amino-acid absorption, 21

ALCOHOL, ETHYL
  cirrhosis: what is it?, 10
  pancreatitis, 4

ALKALINE PHOSPHATASE
  a histochemical study of skin wounds, 81

ALLERGENS
  recent advances in pediatric allergy, 189

AMINO ACIDS
  amino-acid absorption, 21

AMMONIA
  pathogenesis of hepatic encephalopathy, 32

AMYLASE
  pancreatitis, 4

ANAPHYLAXIS
  recent advances in pediatric allergy, 189

ANGIOGRAPHY
  the use of a computer in the diagnosis of intracranial tumours, 114

ANTIBODIES
  recent advances in pediatric allergy, 189

ANTIFUNGAL AGENTS
  in vitro and in vivo activity of hamycin against Blastomyces dermatitidis (abstract), 196

ANTIGENS
  recent advances in pediatric allergy, 189

ANTIHISTAMINICS
  histamine and a possible unity of autonomous microcirculatory dilator responses, 101

ARRHYTHMIA, SINUS
  sinus arrhythmia in the canine cardiac transplant (abstract), 196

ARTERIOVENOUS FISTULA
  new developments in hemodialysis for chronic renal failure, 148

ASPHYXIA NEONATORUM
  plasma pressor activity in normal and stressed newborns (abstract), 194

BIOLOGICAL TRANSPORT, ACTIVE
  amino-acid absorption, 21

BLASTOMYCOSIS
  in vitro and in vivo activity of hamycin against Blastomyces dermatitidis (abstract), 196

BLOOD CHEMICAL ANALYSIS
  changes in, due to liver cirrhosis, 10

BLOOD UREA NITROGEN
  conservative management of chronic renal failure, 156

BLOOD VESSELS
  histamine and a possible unity of autonomous microcirculatory dilator responses, 101

BODY TEMPERATURE
  changes in, due to liver cirrhosis, 10

BRAIN
  cortical influences on midbrain evoked activity in cat (abstract), 195

BRAIN DISEASES
  pathogenesis of hepatic encephalopathy, 32

BRONCHITIS
  the ambient air, 58

CARCINOGENS
  the ambient air, 58

CARDIOVASCULAR SYSTEM
  changes in, due to liver cirrhosis, 10
  circulatory effect of hypercapnia and its role in the production of the vasodilator response to ischemia (abstract), 42

CATS
  cortical influences on midbrain evoked activity in cat (abstract), 195

CELL MEMBRANE
  mechanism of energy transformations in biological membranes, 96

CELLOPHANE
  new developments in hemodialysis for chronic renal failure, 148
CHLOROPLASTS
mechanism of energy transformations in biological membranes, 96

CHOLESTEROL
relationship between fertility and elevated cholesterol levels in rats, 135

CHROMOSOME MAPPING
a linkage map of seven loci in the x-chromosome of Drosophila tropicalis (abstract), 41

CHYMOTRYPSIN
pancreatitis, 4

CLASSIFICATION
a brief history of the taxonomy of mammals, 77

COMPUTERS
the use of a computer in the diagnosis of intracranial tumours, 114

CONSTIPATION
the surgical management of Hirschprung's disease, 38

CRITICAL PERIOD
lasting biological effects of early influences, 52

CYSTINURIA
amino-acid absorption, 21 clinical aspects of renal tubular disorders, 162

CYTOLOGY
cell culture of oral mucous membrane lesions (abstract), 43 histochemical and fine structural studies of lymphocyte transformation with phytohemagglutinin and pokeweed mitogen (abstract), 194 in vitro and in vivo activity of hamycin against Blastomyces dermatitidis (abstract), 196 vaginal cytology (book review), 45

DENTIST-PATIENT RELATIONS
a psychiatrist listens to dental complaints, 73

DENTISTRY
a psychiatrist listens to dental complaints, 73

DIABETES INSIPIDUS, NEPHROGENIC
clinical aspects of renal tubular disorders, 162

DIABETES, PHOSPHATIC
clinical aspects of renal tubular disorders, 162

DIALYSIS
conservative management of chronic renal failure, 156 new developments in hemodialysis for chronic renal failure, 148

DIET THERAPY
conservative management of chronic renal failure, 156

DOGS
respiratory gas tensions and flow of pulmonary lymph in anesthetized dogs (abstract), 41 sinus arrhythmia in the canine cardiac transplant (abstract), 196

DREAMS
a psychiatrist listens to dental complaints, 73

DROSOPHILA
a linkage map of seven loci in the x-chromosome of Drosophila tropicalis (abstract), 41

DRUGS
cirrhosis: what is it?, 10

DYSLEXIA
developmental language disability: adult accomplishments of dyslexic boys (book review), 141

EDUCATION, MEDICAL
present-day psychiatry, 182

ELECTRON TRANSPORT
mechanism of energy transformations in biological membranes, 96

EMPHYSEMA
the ambient air, 58

ENDOCARDITIS, SUBACUTE BACTERIAL
focal glomerulonephritis, 170

ENDOCRINE GLANDS
changes in . . ., due to liver cirrhosis, 10

ENERGY TRANSFER
mechanism of energy transformations in biological membranes, 96

ENVIRONMENT
lasting biological effects of early influences, 52

ESTERASES
a histochemical study of skin wounds, 81

EVOLUTION
a brief history of the taxonomy of mammals, 77

FANCONI SYNDROME
clinical aspects of renal tubular disorders, 162

FERTILITY
relationship between fertility and elevated cholesterol levels in rats, 135

FLUOROURACIL
5-fluorouracil, a tool in the treatment of skin cancer and keratoses, 133

FORENSIC MEDICINE
abortion: legal aspects, 86 a histochemical study of skin wounds, 81

FUNDUS OCULI
potential applications of lasers in ophthalmology, 117

GALACTOSE
amino-acid absorption, 21
GASTROENTEROLOGY
amino-acid absorption, 21
cirrhosis: what is it?, 10
pancreatitis, 4
pathogenesis of hepatic encephalopathy, 32
the relation of the intestinal cell surface to vitamin B_{12} absorption, 18

GASTROINTESTINAL SYSTEM
changes in . . . , due to liver cirrhosis, 10

GENETICS
a linkage map of seven loci in the x-chromosome of *Drosophila tropicalis* (abstract), 41

GLOMERULONEPHRITIS
focal glomerulonephritis, 170

GLUCOCORTICOIDS
histamine and a possible unity of autonomous microcirculatory dilator responses, 101

GLYCINE
amino-acid absorption, 21

GLYCOSURIA, RENAL
clinical aspects of renal tubular disorders, 162

GROWTH
lasting biological effects of early influences, 52

GUINEA PIGS
a histochemical study of skin wounds, 81

HARTNUP DISEASE
amino-acid absorption, 21
clinical aspects of renal tubular disorders, 162

HEMATOPOIETIC SYSTEM
changes in . . . , due to liver cirrhosis, 10

HEMODIALYSIS
new developments in hemodialysis for chronic renal failure, 148

HEPATITIS
cirrhosis: what is it?, 10

HEREDITARY DISEASES
recent advances in pediatric allergy, 189

HISTAMINE
histamine and a possible unity of autonomous microcirculatory dilator responses, 101

HISTOCYTOCHEMISTRY
a histochemical study of skin wounds, 81
histamine and a possible unity of autonomous microcirculatory dilator responses, 101
histochemical and fine structural studies of lymphocyte transformation with phytohemagglutinin and pokeweed mitogen (abstract), 194

HISTOLOGY
the ultrastructure of the vibratory muscle of *Crotalus horridus* (abstract), 195

HUMAN EXPERIMENTATION
amino-acid absorption, 21
beta-adrenergic receptors in the human distal esophagus (abstract), 196

HYDROXYPROLINE
amino-acid absorption, 21

HYPERCAPNIA
circulatory effect of hypercapnia and its role in the production of the vasodilator response to ischemia (abstract), 42
plasma pressor activity in normal and stressed newborns (abstract), 194

HYPERSENSITIVITY
recent advances in pediatric allergy, 189

HYPERTENSION
mechanisms controlling the peripheral circulation of the lung with some clinical correlations, 121

IMPRINTING (PSYCHOLOGY)
some issues in human development, 173

INCEST
abortion: medical and moral aspects, 83

INFECTION
lasting biological effects of early influences, 52

INFLAMMATION
histamine and a possible unity of autonomous microcirculatory dilator responses, 101

INTESTINAL ABSORPTION
amino-acid absorption, 21
the relation of the intestinal cell surface to vitamin B_{12} absorption, 18

INTESTINE, SMALL
amino-acid absorption, 21
the relation of the intestinal cell surface to vitamin B_{12} absorption, 18

INTRINSIC FACTOR
the relation of the intestinal cell surface to vitamin B_{12} absorption, 18

ISCHEMIA
circulatory effect of hypercapnia and its role in the production of the vasodilator response to ischemia (abstract), 42

ISOLEUCINE
amino-acid absorption, 21

JURISPRUDENCE, PSYCHIATRIC
present-day psychiatry, 182

KERATOSIS
5-fluorouracil, a tool in the treatment of skin cancer and keratoses, 133
KETOGLUTARIC ACID  
mechanism of energy transformations in biological membranes, 96  
pathogenesis of hepatic encephalopathy, 32

KIDNEY  
adrenal cortical responsiveness in patients with renal homotransplants receiving prednisone (abstract), 194

changes in . . . , due to liver cirrhosis, 10

the potability of sea water, 107

KIDNEY, Artificial  
new developments in hemodialysis for chronic renal failure, 148

KIDNEY FAILURE, CHRONIC  
conservative management of chronic renal failure, 156

new developments in hemodialysis for chronic renal failure, 148

KIDNEY TUBULES  
clinical aspects of renal tubular disorders, 162

KREBS CYCLE  
pathogenesis of hepatic encephalopathy, 32

LANGUAGE DISORDERS  
developmental language disability: adult accomplishments of dyslexic boys (book review), 141

LASERS  
potential applications of lasers in ophthalmology, 117

LEUCINE AMINOPEPTIDASE  
a histochemical study of skin wounds, 81

LEUKOCYTES  
a histochemical study of skin wounds, 81

LIGHT COAGULATION  
potential applications of lasers in ophthalmology, 117

LIVER CIRRHOSIS  
cirrhosis: what is it?, 10

LIVER DISEASES  
cirrhosis: what is it?, 10

pathogenesis of hepatic encephalopathy, 32

LONGEVITY  
lastling biological effects of early influences, 52

LUNG  
changes in . . . , due to liver cirrhosis, 10

mechanisms controlling the peripheral circulation of the lung with some clinical correlations, 121

LYMPHOCYTES  
histochemical and fine structural studies of lymphocyte transformation with phytohemagglutinin and pokeweed mitogen (abstract), 194

MALNUTRITION  
cirrhosis: what is it?, 10

MAMMALS  
a brief history of the taxonomy of mammals, 77

MATHEMATICS  
the use of a computer in the diagnosis of intracranial tumours, 114

MESENCEPHALON  
cortical influences on midbrain evoked activity in cat (abstract), 195

MICE  
lastling biological effects of early influences, 52

MITOCHONDRIA  
mechanism of energy transformations in biological membranes, 96

MITOCHONDRIA, MUSCLE  
the ultrastructure of the vibratory muscle of Crotalus horridus (abstract), 195

MORALS  
abortion: medical and moral aspects, 83

MUCOUS MEMBRANE  
cell culture of oral mucous membrane lesions (abstract), 43

MUSCLES  
the ultrastructure of the vibratory muscle of Crotalus horridus (abstract), 195

MUSCULOSKELETAL SYSTEM  
changes in . . . , due to liver cirrhosis, 10

NEOPLASMS  
the use of a computer in the diagnosis of intracranial tumours, 114

NERVOUS SYSTEM  
changes in . . . , due to liver cirrhosis, 10

NUCLEIC ACIDS  
a histochemical study of skin wounds, 81

NUTRITION  
lastling biological effects of early influences, 52

OPHTHALMOLOGY  
potential applications of lasers in ophthalmology, 117
Pancreatitis
pancreatitis, 4

Parotitis
cirrhosis: what is it?, 10

Pediatrics
plasma pressor activity in normal and stressed newborns (abstract), 194
recent advances in pediatric allergy, 189
some issues in human development, 173

Periarteritis Nodosa
focal glomerulonephritis, 170

Phagocytosis
the initial destruction of intracellular Salmonella typhimurium (abstract), 43

Phenylalanine
amino-acid absorption, 21

Phenylketonuria
amino-acid absorption, 21

Physician-Patient Relations
present-day psychiatry, 182

Prednisone
adrenal cortical responsiveness in patients with renal homotransplants receiving prednisone (abstracts), 194

Proline
amino-acid absorption, 21

Proteolysis
pancreatitis, 4

Psychiatry
a psychiatrist listens to dental complaints, 73
present-day psychiatry, 182

Psychotherapy
present-day psychiatry, 182

Pulmonary Circulation
mechanisms controlling the peripheral circulation of the lung with some clinical correlations, 121

Pulmonary Embolism
mechanisms controlling the peripheral circulation of the lung with some clinical correlations, 121

Pyridoxal Phosphate
amino-acid absorption, 21

Radiography
the use of a computer in the diagnosis of intracranial tumours, 114

Rape
abortion: medical and moral aspects, 83

Rats
relationship between fertility and elevated cholesterol levels in rats, 135

Receptors, Neural
beta-adrenergic receptors in the human distal esophagus (abstract), 196

Rehabilitation
new developments in hemodialysis for chronic renal failure, 148

Respiratory Distress Syndrome
mechanisms controlling the peripheral circulation of the lung with some clinical correlations, 121

Respiratory System
respiratory gas tensions and flow of pulmonary lymph in anesthetized dogs (abstract), 41

Salmonella Typhimurium
the initial destruction of intracellular Salmonella typhimurium (abstract), 43

Schoenlein-Henoch Purpura
focal glomerulonephritis, 170

Serine
amino-acid absorption, 21

Shock
histamine and a possible unity of autonomous microcirculatory dilator responses, 101

Skin
a histochemical study of skin wounds, 81
changes in . . . , due to liver cirrhosis, 10

Skin Neoplasms
5-fluorouracil, a tool in the treatment of skin cancer and keratoses, 133

Skull Neoplasms
the use of a computer in the diagnosis of intracranial tumours, 114

Socialization
some issues in human development, 173

Socioeconomic Factors
abortion: medical and moral aspects, 83

Stains and Staining
a histochemical study of skin wounds, 81

Starch
a study of some factors affecting starch swelling and their relationships to tablet disintegration (abstract), 41

Stasis
cirrhosis: what is it?, 10

Statistics
the use of a computer in the diagnosis of intracranial tumours, 114

Surgery
the surgical management of Hirschsprung's disease, 38

Tablets
a study of some factors affecting starch swelling and their relationships to tablet disintegration (abstract), 41

Taxonomy
a brief history of the taxonomy of mammals, 77

Territoriality
some issues in human development, 173
THALAMUS
cortical influences on midbrain evoked activity in cat (abstract), 195

THIRST
the potability of sea water, 107

THREONINE
amino-acid absorption, 21

TISSUE CULTURE
cell culture of oral mucous membrane lesions (abstract), 43

TRANSPLANTATION
sinus arrhythmia in the canine cardiac transplant (abstract), 196

TRYPsin
pancreatitis, 4

TRYPTOPHAN
amino-acid absorption, 21

UREMIA
conservative management of chronic renal failure, 156

VAGINA
vaginal cytology (book review), 45

VAGUS NERVE
mechanisms controlling the peripheral circulation of the lung with some clinical correlations, 121

VALINE
amino-acid absorption, 21

VASODILATOR AGENTS
histamine and a possible unity of autonomous microcirculatory dilator responses, 101

VITAMIN B₁₂
the relation of the intestinal cell surface to vitamin B₁₂ absorption, 18

WATER
the potability of sea water, 107

WOUNDS AND INJURIES
a histochemical study of skin wounds, 81

References to articles are in boldface; references to photographs and biographical sketches are in lightface; references to abstracts are in italics.

BANERJEE, C. M., 41
BURKE, J. D., 77, 90

CARAVATI, C. M., 10, 46
CARVALHO, G., 135, 142

DONALDSON, R. M., Jr., 18, 46
DUBOS, R., 52, 90
DU BOULAY, G. H., 114, 142
DUNN, L. J., 45

FALLS, W. F., Jr., 162, 197
FATTEH, A., 81, 90
FLESHLER, B., 21, 46
FLOWERS, A. M., 141

GEERAETS, W. J., 117, 142
GRADUATE THeses, 1967, AbSTRACTs, 41
GREEN, D. E., 96, 142
GRUBBS, C. G., 41

HENDERSON, L. W., 148, 197
HEPTINSTALL, R. H., 170, 197
HOFFMAN, P. F., 194
HOLDEN, K. R., 194

IGLAUER, E., 58, 90
INGELFINGER, F. J., McGuire Lecture, 1967, 4, 46
INGRAM, J. T., 41

JORDAN, T. D., 86, 91
KONTOS, H. A., 42
KRAHL, V. E., 121, 143

LEDERER, H. D., 73, 91, 182, 197
LINEHAN, J. D., 194

MANN, G. T., 83, 91
MARTIN, L. W., 38, 47
MASSIE, F. S., 189, 198
McGUire Lectures, 1967, 4

OSTRICH, J. H., 195
PASTORE, L. T., 195
POLSTER, D. F., 195
PRINCE, R. F., 196
RADCLIFFE, A. S., 43
ROBERTSON, G. M., Jr., 196
ROBINSON, R. R., 156, 198

SCHAYER, R. W., 101, 143
Snyderman, R. K., 133, 143
STONEBURNER, Lectures, 1968, 148

THAMES, M. D., 196
VAUGHAN, V. C., III, 173, 198
VLAHCEVIC, Z. R., 32, 47
WHITE, R. P., Jr., 43
WOLF, A. V., 107, 143
# TABLE OF CONTENTS

## 1968 • NUMBER ONE

**Thirty-Ninth Annual McGuire Lecture Series: Gastroenterology**

<table>
<thead>
<tr>
<th>Title</th>
<th>Author, City, State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>FRANZ J. INGELFINGER, Boston, Massachusetts</td>
</tr>
<tr>
<td>Cirrhosis: What Is It?</td>
<td>CHARLES M. CARAVATI, Richmond, Virginia</td>
</tr>
<tr>
<td>The Relation of the Intestinal Cell Surface to Vitamin B₁₂ Absorption</td>
<td>ROBERT M. DONALDSON, JR., Boston, Massachusetts</td>
</tr>
<tr>
<td>Amino-Acid Absorption</td>
<td>BERTRAM FLESHLER, Cleveland, Ohio</td>
</tr>
<tr>
<td>Pathogenesis of Hepatic Encephalopathy</td>
<td>Z. RENO VLACHEVIC, Richmond, Virginia</td>
</tr>
<tr>
<td>The Surgical Management of Hirschsprung’s Disease</td>
<td>LESTER W. MARTIN, Cincinnati, Ohio</td>
</tr>
<tr>
<td>Abstracts of Theses for Graduate Degrees</td>
<td>MEDICAL COLLEGE OF VIRGINIA, June, 1967</td>
</tr>
<tr>
<td>Book Review</td>
<td>LEO J. DUNN, Richmond, Virginia</td>
</tr>
<tr>
<td>Installation of Members</td>
<td>THE SOCIETY OF THE SIGMA XI, Medical College of Virginia</td>
</tr>
</tbody>
</table>

## 1968 • NUMBER TWO

<table>
<thead>
<tr>
<th>Title</th>
<th>Author, City, State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasting Biological Effects of Early Influences</td>
<td>RENÉ DUBOS, New York, New York</td>
</tr>
<tr>
<td>The Ambient Air</td>
<td>EDITH IGLAUER, New York, New York</td>
</tr>
<tr>
<td>A Psychiatrist Listens to Dental Complaints</td>
<td>HENRY D. LEDERER, Richmond, Virginia</td>
</tr>
<tr>
<td>A Brief History of the Taxonomy of Mammals</td>
<td>JACK D. BURKE, Richmond, Virginia</td>
</tr>
<tr>
<td>A Histochemical Study of Skin Wounds</td>
<td>ABDULLAH FATTEH, Richmond, Virginia</td>
</tr>
<tr>
<td>Abortion: Medical and Moral Aspects</td>
<td>GEOFFREY T. MANN, Richmond, Virginia</td>
</tr>
<tr>
<td>Abortion: Legal Aspects</td>
<td>THOMAS D. JORDAN, Richmond, Virginia</td>
</tr>
<tr>
<td>Contributors to this Issue</td>
<td></td>
</tr>
</tbody>
</table>

Contributors to this Issue
Mechanism of Energy Transformations in Biological Membranes  
**DAVID E. GREEN**, Madison, Wisconsin 96

Histamine and a Possible Unity of Autonomous Microcirculatory Dilator Responses  
**RICHARD W. SCHAYER**, Orangeburg, New York 101

The Potability of Sea Water  
**A. V. WOLF**, Chicago, Illinois 107

The Use of a Computer in the Diagnosis of Intracranial Tumors  

Potential Applications of Lasers in Ophthalmology  
**WALTER J. GEERAETS**, Richmond, Virginia 117

Mechanisms Controlling the Peripheral Circulation of the Lung with Some Clinical Correlations  
**VERNON E. KRAHL**, Baltimore, Maryland 121

5-Fluorouracil, A Tool in the Treatment of Skin Cancer and Keratoses  
**REUVEN K. SNYDERMAN**, New York, New York 133

Relationship Between Fertility and Elevated Cholesterol Levels in Rats  
**GRIMALDO CARVALHO**, Richmond, Virginia 135

Book Review  
**ANN M. FLOWERS**, Richmond, Virginia 141

Contributors to this Issue 142

---

From the Twenty-First Annual Stoneburner Lecture Series: Diseases of the Kidney

New Developments in Hemodialysis for Chronic Renal Failure  
**LEE W. HENDERSON**, Philadelphia, Pennsylvania 148

Conservative Management of Chronic Renal Failure  
**ROSCOE R. ROBINSON**, Durham, North Carolina 156

Clinical Aspects of Renal Tubular Disorders  
**WILLIAM F. FALLS, JR.**, Richmond, Virginia 162

Focal Glomerulonephritis  
**ROBERT H. HEPTINSTALL**, Baltimore, Maryland 170

Some Issues in Human Development  
**VICTOR C. VAUGHAN, III**, Philadelphia, Pennsylvania 173

Present-Day Psychiatry  
**HENRY D. LEDERER**, Richmond, Virginia 182

Recent Advances in Pediatric Allergy  
**F. STANFORD MASSIE**, Richmond, Virginia 189

Student Honors Day: Abstracts of Scientific Presentations  
**MEDICAL COLLEGE OF VIRGINIA, May, 1968** 194

Contributors to this Issue 197

Index to Volume Four 199
"Well, he finally decided to clean the attic. Almost had the job done, too..."

"...Yeah, until he tried to lift me. It sure put his back out of whack. His doctor's got a real job to do—trying to ease both the pain and the strain."
When stress results in muscle strain and pain

When the normally sedentary person suddenly turns active—cleaning the attic, for instance—the outcome is sometimes a strain or sprain in the back, neck or shoulders.

Fortunately, however, most patients with muscle spasm and pain are highly responsive to therapy with Robaxisal. This rationally based formula provides the well-known relaxant benefits of methocarbamol for strained, tense skeletal muscle plus the dependable analgesic and anti-inflammatory effects of aspirin. Investigators have found methocarbamol a well-tolerated agent with “specificity of action.” And methocarbamol potentiates the salicylate levels of aspirin so that, in combination, higher salicylate levels are produced than with equivalent doses of aspirin alone. When the Robaxisal combination was administered to a group of 22 patients with painful musculoskeletal disorders, 20 (91 per cent) showed an excellent or good response.

With Robaxisal you can conveniently fulfill the most important objectives in treatment of muscle spasm: relaxation of skeletal muscle, relief of pain, restoration of mobility and normal muscle tone. And when mild anxiety is a factor in the spasm-pain syndrome, consider Robaxisal®-PH.

*In this investigation, 400 mg. methocarbamol was combined with 300 mg. aspirin.


Robaxisal® brings relief for both

Robaxisal® and Robaxisal-PH are indicated when both analgesic and skeletal muscle relaxant effects are required, as in strains and sprains, painful disorders of the back, “whiplash” injury, myositis, pain and spasm associated with arthritis, torticollis, and headache associated with muscular tension.

Contraindications: Hypersensitivity to any one of the components.

Side Effects: Lightheadedness, slight drowsiness, dizziness, and nausea may occur rarely in patients with unusual sensitivity to drugs, but usually disappear on reduction of dosage.