Editorials

A Forum to Discuss an Important Subject

ELSEWHERE IN THIS ISSUE is what the editors hope will be just the beginning of a forum to discuss the "Aim of American Medicine Within the Constraints of Today's Society." American medicine is enjoying unprecedented technologic success, while at the same time it is undergoing unprecedented stress. In many ways the stresses now seem to be taking precedence over the successes, at least as far as the medical profession as a whole is concerned. And, surprising though it may be, there seems to be no real consensus or agreement, within or without the profession, about just what should be the basic aim of the medical profession in today's changing social, economic, political and even technologic health care environment. Clearly, as a nation we are entering a period of social transformation that is as yet poorly understood, and just as clearly health care is in the forefront of much that is taking place in the larger environment.

Success and sometimes even survival in any unsettled, stressful or even hostile situation often depend on whether there is a clear purpose and a firm resolve. What was formerly a friendly and supportive environment for medicine and the medical profession is now not always so friendly or supportive. As is already pointed out in the forum, the time-honored and well-proved internal constraints within the medical profession must begin to find ways to work within (or perhaps even to change) the external constraints being imposed by society. This will not be easy, but it will be easier if there can be agreement on what should be the aim of American medicine and if there can be a firm resolve within the profession to achieve that agreed-upon aim. The forum will have served its purpose if it initiates a discussion of this important subject.

MSMW

The Pathogenesis and Prevention of Diabetic Glomerulopathy

SCLEROSING GLOMERULOPATHY develops in approximately 40% of patients with diabetes mellitus. This life-threatening complication becomes clinically manifest a decade or more after the onset of the diabetes and is heralded by the development of persistent proteinuria. Glomerular morphology is altered by an expansion of the extracellular matrices of both the mesangium and the peripheral basement membranes of the glomerular capillary loops.[1] In addition, the functional properties of the glomerular filter exhibit increasing derangement. Progressive impairment of the size-selective properties of the filtration barrier results in increased transmural shunting into Bowman's space of large plasma proteins, leading ultimately to nephrotic-range proteinuria.[2] Simultaneously, the remarkable ability of the glomerular capillary wall to function as a high-capacity ultrafiltration membrane is compromised. Either a reduction of hydraulic conductivity or progressive curtailment of the surface area available for filtration (or a combination of these factors) results in a progressive loss of ultrafiltration capacity by the glomerular capillaries. The rate at which glomerular ultrafiltrate is formed declines predictably, leading eventually to end-stage renal disease.[3]

As discussed by Omachi elsewhere in this issue, diabetic glomerulopathy has emerged as the leading discrete cause of end-stage renal failure in the Western world. During the past decade a substantial investigative effort has been joined to ameliorate its progressive course. Effective control of the arterial hypertension that invariably complicates diabetic glomerulopathy has been shown to slow the inexorable decline in the glomerular filtration rate. Control of hypertension, however, does not arrest, much less reverse, progressive glomerular capillary wall dysfunction.[4,5] Even more ambiguous have been the results of attempts to normalize chronic glycemia by the use of continuous subcutaneous infusion of insulin. This approach has resulted in little or no beneficial effect on progressive glomerular capillary dysfunction in patients with established diabetic glomerulopathy.[6,7] Accordingly, investigations have been intensified to identify a preclinical or occult stage of preproteinuric diabetic glomerulopathy. The hope is that early treatment of latent glomerular capillary dysfunction might prevent the inevitable downhill course that follows in the wake of persistent proteinuria.

A possible precursor to overt proteinuric glomerulopathy in diabetes is the finding that the glomerular filtration rate is sometimes elevated to supernormal levels in patients with type I diabetes of recent onset.[8,9] Since first demonstration of this phenomenon 30 years ago, it has been shown that glomerular hyperfiltration may be accompanied also by a subtle increase in the urinary albumin excretion rate that is not measurable by conventional techniques for detecting proteinuria.[10] Using a sensitive radioimmunoassay, it has been found that healthy nondiabetic subjects excrete albumin in their urine at rates of up to 15 μg per minute. Among persons with diabetes of short duration, by contrast, a proportion excrete immunoassayable albumin at rates below those detectable by conventional techniques (approximately 100 μg per minute) but in excess of 15 μg per minute.[10] To distinguish this phenomenon from overt proteinuria, it has been termed microalbuminuria. Because it has been associated with the most striking degrees of hyperfiltration, it is inferred that an underlying elevation of either the glomerular perfusion rate or pressure leads not only to enhanced formation of filtrate, but also to an increase in transglomerular albumin filtration.

In light of these abnormalities early in the course of diabetes, it has been proposed that either glomerular hyperfiltration per se, an underlying glomerular capillary hyperperfusion or hypertension, an associated increase in traffic of proteins across the glomerular capillary wall or some combination of these factors is the forerunner of sclerosing glomerulopathy in diabetes.[11] This hypothesis is lent credence by observations in rats with streptozocin-induced diabetes. As in humans, newly diabetic rats with moderate hyperglycemia have elevated glomerular filtration rates. Micropuncture studies have shown the diabetic state to be associated with a fall in resistance of cortical microvessels, with the result that

both glomerular capillary perfusion rate and pressure become elevated, thereby accounting for the increased flux of water across glomerular capillaries.[12] Moreover, glomerular ultrafiltration pressure and, hence, nephron glomerular filtration rate can be elevated even further in diabetic rats by surgical reduction of the renal mass or by a diet rich in protein (50%).[13,14] The increment in glomerular capillary perfusion rate and pressure is followed by heavier proteinuria and more severe glomerulosclerosis than observed in diabetic rats with a normal complement of nephrons and fed conventional rat chow (12% protein). The notion that persistent elevation of glomerular perfusion rate, pressure or both is implicated in the genesis of an accelerated sclerosing glomerulopathy is supported by the protective effect of measures that prevent glomerular hyperemia and hypertension in these rodents. Lowering glomerular capillary perfusion pressure by either partial constriction of the renal artery with a clip[15] or the administration of an angiotensin-converting enzyme inhibitor[13] or by restriction of dietary protein intake[14] largely prevents the development of proteinuria and the histopathologic damage found in animals not so protected.

The precise cause of the altered renal vasomotion that attends the diabetic state has yet to be determined. Hyperglycemia per se or elevated levels of vasodilator glucoregulatory hormones such as glucagon and growth hormone may be implicated. There are in the diabetic state also abnormalities of production and activity of several vasoregulatory hormones that are not directly related to glucose metabolism. The renin-angiotensin system, thought by many to be the main regulator of glomerular perfusion rate and pressure, is a notable example. Persons with diabetes who have a tendency for microangiopathy appear to exhibit a progressive inability to convert inactive renin precursor to active renin.[16] Notwithstanding a similar tendency towards hypoangiotensinemia, diabetic rats fail to upregulate glomerular receptors to angiotensin II.[17] Thus, the constrictor influence of this important hormone on the glomerular microcirculation appears to be blunted in the diabetic state. The imbalance in favor of vasodilatation may be compounded by excessive production of prostaglandins E_2 and I. In vitro production of these vasodilator eicosanoids by glomeruli or mesangial cells isolated from diabetic rats has been shown to be enhanced.[18,19]

The postulate that diabetic glomerular injury is hemodynamically mediated has proved very attractive to clinicians, not least because it holds promise of a therapeutic strategy that might prevent the development of sclerosing glomerulopathy. Irrespective of the precise abnormality of vasoregulation that leads to the glomerular overperfusion, the aforementioned observations in rats suggest that any measure that lowers the glomerular perfusion rate and pressure will protect the animal in a nonspecific fashion from the ravages of diabetic glomerulopathy. However, several unresolved issues merit careful consideration before this hypothesis is extrapolated to humans. Still to be determined, for example, is whether streptozocin-induced diabetic glomerulopathy in rats is indeed a precise analogue of the human disease. Whereas mesangial expansion has been described in persons with diabetes to be generalized and global (hence the term diffuse intercapillary diabetic glomerulosclerosis), the corresponding glomerular lesion in rats is focal and segmental.[13,14,20] Also, the large acellular mesangial nodules, described half a century ago by Kimmelstiel and Wilson and thought to be pathognomonic of human diabetic glomerulosclerosis, do not occur in rodents. Furthermore, there is to date no study that has shown renal plasma flow to be elevated in persons with diabetes of recent onset, notwithstanding coexistent hyperfiltration.[8,9,21] Given the consistent finding of glomerular enlargement in early diabetes, it is conceivable that an increase in surface area for filtration results in an enhanced ultrafiltration capacity of glomerular capillaries and that this phenomenon, rather than an elevated glomerular ultrafiltration pressure, is the proximate determinant of hyperfiltration.[1]

It is also worthy of emphasis that unlike the clearly delineated course from early hyperfiltration to sclerosing glomerulopathy in diabetic rats, this linkage in humans is, at best, tenuous. To date, two groups of workers have reexamined patients with type I diabetes 8 to 16 years after hyperfiltration or microalbuminuria or both were first documented.[22,23] Their findings suggest that those who at reexamination exhibited proteinuric glomerulopathy were the subjects with the highest levels of microalbuminuria (and perhaps hyperfiltration) at the time of initial examination. It is important to realize, however, that the total population subjected to such sequential examination numbers only 107 and, of these, proteinuric glomerulopathy developed in fact in only 21. Clearly, before every person with newly diagnosed diabetes mellitus is subjected to decades of therapy designed to lower glomerular pressures and flows, whether by dietary or pharmacologic manipulation or by continuous subcutaneous insulin infusion, it is necessary that the pathogenetic sequence from early hyperfiltration and microalbuminuria to sclerosing glomerulopathy in humans be more convincingly documented.

In our quest to understand better the pathogenesis of the diabetic glomerulopathy, it is important that we not indulge in oversimplification by ascribing entirely the glomerular injury to elevated glomerular pressures and flows. There are a number of compositional changes that distinguish the glomerular basement membrane in diabetic persons from normal. Either glycosylation of its structural proteins[24] or a reduction of the negatively charged, sulfated proteoglycans that normally reside in the basement membrane[25] could alter its permeability properties, thereby accounting for microalbuminuria. Such metabolic and/or structural alteration of the intrinsic properties of the diabetic glomerular capillary wall need not, of course, be an exclusive explanation for the subsequent development of diabetic glomerulopathy. Indeed, coexistent glomerular capillary overperfusion and hypertension could be unusually noxious to a capillary wall whose composition had been altered by the diabetic state. Clearly, a great deal of investigation remains to be done before the pathogenesis of diabetic glomerulopathy is elucidated. In the meantime, circumspection needs to be exercised by the clinical community before, based on the hemodynamic theory of the genesis of diabetic glomerulopathy, it embarks on extraordinary therapeutic efforts in diabetic patients aimed at lowering the glomerular filtration rate. Such therapy must, of necessity, be administered over many years and may prove in the final analysis to be futile.

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Of Physicianship and Patienthood

IN A RECENT ISSUE of the journal *Daedalus,* Eric Cassell makes a number of insightful points.[1] He is discussing the changing concept of the ideal physician and the changing character of physicianship and patienthood. He notes that medicine's embrace of science has been almost total, that physicians have been seduced (my term) by the "disarming simplicity and certainty of technology" and that over time, power in the medical establishment has shifted from clinician to scientist—that is, the physician role model is now more the medical scientist rather than the clinician. While more or less at the same time, the words "person" and "individual" have taken on new meaning as the public has become more aware and self-assertive. Cassell contends that all of this has had profound effects on physicianship and patienthood, and indeed he may be right.

None of the above is likely to change, at least right away. But there are flaws in some of what is going on. There is much more to physicianship than a mastery of science and technology, and there is much more to patienthood than personal awareness and self-assertiveness. Certain things are important to remember. For one, all science is value free. It is amoral. It deals primarily with general laws. It is impersonal. Medicine, on the other hand, has a long tradition of values, and it deals with persons as individuals whose personal needs and ailments are not often described or measured in scientific terms. While medicine and science have become inextricably bound, as Cassell says, they are not and cannot be one and the same. The assumption by some younger physicians (and even some medical educators), and much of the public, that medicine is now all science, is simply not valid. And as for those who espouse the modern view of patienthood, they often seem to forget that patients come to physicians or to the medical establishment seeking help. They seek something they cannot supply themselves, to relieve or cope with their real or perceived pain, fear, discomfort, anxiety or whatever. These needs are individual, personal and value laden. Physicianship that depends only on impersonal and value free science and technology will not and cannot fill this need. Nor will patienthood that relies entirely on awareness and self-assertiveness succeed in filling this need for something beyond that which a patient can supply on his or her own.

Today physicianship and patienthood are both on trial. Physicians are jumpy, living with inadequacies inherent in their science, third party pressures on what they do or do not do, and with the current conventional wisdom that patient care is some sort of impersonal commodity to be bartered at the cheapest price in the marketplace. Patients are trying to make their own health care decisions as much as they can, and looking for someone to blame if there is any failure. And, too often, the doctor-patient relationship may be virtually nonexistent or, if present, may be more adversarial than truly collaborative.

But there are some countervailing trends. There is a new emphasis on primary care in training programs for general internal medicine, pediatrics and particularly in the family practice movement. In these and some other programs the art is being taught as well as the science. In the practice arena there is a recent and now perceptible interest in better payment for the cognitive services of physicians in whatever specialty, services that are so essential for meaningful physicianship and patienthood. And then there is a growing academic, practitioner and public interest in many of the personal, human, ethical and judgmental aspects of patient care. It is even possible that if and when the art and science become better balanced in patient care, there might just be some favorable effect on the cost. But all this will take some time.

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