The exploration of fundamental mechanisms responsible for idiopathic membranous nephropathy (MN) has traced a long, enigmatic, and frustrating history for scientists, clinicians, and patients. The logical beginning of this saga can be traced to its recognition as a distinct clinicopathologic entity by David Jones\(^1\) in 1957 and the most recent chapter defined by the possible identification of an autoantibody-mediated pathogenetic mechanism responsible for the human disease by Beck et al\(^2\) in 2009. The approximately 50-year period encompassed by these bookends delineates a fascinating tale of “short feasts and long famines” of scientific progress.\(^3\) The challenge of idiopathic MN during these 5 decades recalls the tribulations and cunning intelligence of Ulysses in Homer’s epic poem *The Odyssey*, written approximately 28 centuries ago. In this essay, I attempt to capture the high points of this adventure, rather than be comprehensive. The focus is on the idiopathic disease (idiopathic MN). However, the reader should be fully aware that similar glomerular lesions can be produced in humans (and animals) by a wide variety of events, some secondary to recognized diseases, such as cancer, systemic lupus erythematosus, and other autoimmune processes; graft-versus-host reactions; many drugs; and chronic viral, bacterial, and parasitic infections.\(^4\)

DISCOVERY

The term membranous glomerulonephritis was used first by Bell\(^5\) in 1946 to describe a category of glomerular renal disease classified within the spectrum of Ellis type II glomerulonephritis, characterized clinically by a more insidious onset and marked proteinuria and edema. This category also included lipoid nephrosis, lobular glomerulonephritis, and...
chronic glomerulonephritis (not otherwise specified). Thus, membranous glomerulonephritis (later to morph into MN) was “lumped” together with other histologic lesions subsumed by the Ellis classification of glomerulonephritis. In 1957, David Jones, a renal pathologist from Syracuse University in New York, separated membranous glomerulonephritis as a distinct morphologic entity using the special stain periodic acid–silver methenamine (now known as Jones stain), applied to human renal biopsy specimens. In this seminal study, Jones fully illustrated the special features of this lesion not shared by other lesions, such as lobular glomerulonephritis (now known as membranoproliferative glomerulonephritis), lipoid nephrosis (now known as minimal change disease), and chronic glomerulonephritis (now known as focal and segmental glomerulosclerosis). The thickening of the capillary wall and alteration in basement membrane structure, so characteristic of the membranous lesion, were convincingly shown (Fig 1). The electron-dense subepithelial location of the deposits occupying the spaces between the altered glomerular basement membrane (GBM) also subsequently were identified by Movat and McGregor in 1959 using electron microscopic methods applied to renal biopsy specimens pioneered by Farquhar et al in 1957. Mellors et al in 1957 had identified the third component of the unique lesion of membranous glomerulonephritis; namely, the presence of immunoglobulin in the deposits, using the immunofluorescence technique described by Coons and Kaplan in 1950. Thus, in a burst of morphologic investigations using newly developed technology, over the span of just 2 years, the triad of essential (diagnostic) features of the lesion of membranous glomerulonephritis were delineated; namely, alteration in basement membrane structure, subepithelial electron-dense deposits, the latter containing immunoglobulin G (IgG). These are still the fundamental features used today to identify membranous glomerulonephritis (called extramembranous glomerulonephritis or epimembranous nephropathy by some Europeans), henceforth called MN in this essay.

**THE MODELING OF HUMAN DISEASE**

The story of MN then moves from the human arena to the experimental laboratory. Walter Heymann and colleagues discovered in 1959 that active immunization of an outbred strain of rats by intraperitoneal administration of crude homologous rat renal homogenates along with complete Freund’s adjuvant induced a disease identical, both clinically and morphologically, to human MN. This experimental model, subsequently known as Heymann nephritis, was believed to be caused by autoimmunity, although the autoantigen and the injurious autoimmune vector (or vectors) were unknown at that time. Heymann repeatedly stated that he regarded this kidney disease model as an example of “autoimmune nephrosis.” A few years later, Dixon et al identified glomerular lesions very similar to MN in rabbits repeatedly immunized with intravenous heterologous serum proteins (such as bovine serum albumin or bovine γ-globulin) in sufficient quantities to maintain a slight excess of antigen over antibody. They postulated that immune complexes formed in the circulation in this situation ac-
quired properties enabling them to localize in glomeruli and form the deposits located on the outer or subepithelial aspects of the GBM.\textsuperscript{13,14} The circulating immune complexes involving precipitating antibodies theoretically could disassociate, permeate, and re-form in the subepithelial space;\textsuperscript{15} however, evidence for their direct involvement in MN is scarce.\textsuperscript{16} In this chronic serum sickness model of MN, the perpetrators of disease (immune complexes) were derived from the circulation and glomeruli were passive victims.

Not surprisingly, Heymann nephritis became the subject of intense laboratory investigation because it provided a reproducible and useful model to study the possible pathogenesis of human MN. Very quickly, it became clear that circulating autoantibodies developed in the actively immunized animals (active Heymann nephritis) and that a similar disease could be produced by passive administration of a heterologous antibody (made in sheep or rabbits) to the putative autoantigen contained in the crude renal homogenate. We hypothesized that the small soluble antigen present in glomeruli of normal rat kidney using frozen sections and indirect immunofluorescence techniques, whereas large deposits of RTE\textalpha{}5 could be found in small amounts in the circulation of normal rats, but RTE\textalpha{}5 could not be identified in glomeruli of normal rat kidney using frozen sections and indirect immunofluorescence techniques, whereas large deposits of RTE\textalpha{}5 could be found in the subepithelial deposits present in active Heymann nephritis.\textsuperscript{19} Active Heymann nephritis could be transferred to naive rats by lymphoid cells (lymph node and spleen cells) and parabiosis; however, this probably was caused by a small amount of pathogenic antigen contaminating the lymphoid cell preparations because lethally irradiated (in vitro) lymphoid cells also could transfer the disease.\textsuperscript{20,21} A marked strain and species variation of susceptibility to the induction of active Heymann nephritis was established.\textsuperscript{22} The disease could not be induced in rabbits, and some strains of inbred rats were very resistant to induction of disease. Immunization of rats with human-derived FxIA induced the disease; however, the deposits contained only rat-derived RTE\textalpha{}5,\textsuperscript{23} indicative of its autoimmune nature.

All the mentioned information led to the construction of a hypothesis (called autologous immune complex nephritis) by Edgington et al\textsuperscript{23} and Glassock et al\textsuperscript{24} that active Heymann nephritis was caused by the formation of circulating immune complexes by the interaction of anti-RTE\textalpha{}5 autoantibodies with the small amount of RTE\textalpha{}5 constantly supplied to the circulation by the proximal renal tubules. We proposed that the small soluble circulating autoantigen-autoantibody immune complexes escaped rapid removal by the reticuloendothelial system and preferentially deposited in glomeruli (in a subepithelial location, similar to the chronic serum sickness model mentioned previously), provoking MN. Sensitized lymphoid cells (cellular immunity) were not regarded as important to the pathogenesis of the model, although such sensitization was likely to have occurred as the result of the immunization process. Although fully consistent with the available observations at the time, this hypothesis was to have only a short-lived period of validity. The crucial bit of missing data was whether the normal (naive) susceptible rat did or did not have pathogenic antigen present in glomerular structures.

These missing data were resolved by the publications of Van Damme et al\textsuperscript{25} in April 1978 and Couser et al\textsuperscript{26} in December 1978 showing that deposition of antibody to FxIA in glomeruli was independent of circulating antigen (using cell- and blood-free ex vivo organ perfusion). The patho-
genic antigen (FxIA containing RTEα5) was a normal constituent of the clathrin-coated pits found on podocytes. These pivotal observations, which were anticipated by Okuda et al27 working in Heymann’s laboratory in 1965, meant that immune complexes were formed in situ and were not necessarily deposited as preformed immune complexes from the circulation. Subsequent studies using autoantibodies, reactive solely with the in situ autoantigen, eluted from the kidneys of animals with active Heymann nephritis confirmed this hypothesis.28 Thus, the autologous (circulating) immune complex nephritis hypothesis had to be discarded and replaced with an in situ immune complex formation explanation. In retrospect, the difficulty detecting RTEα5 in the normal kidney and the ease of showing RTEα5 in the diseased kidney may have been caused by the enhanced synthesis of RTEα5 by podocytes in the presence of disease.29

The biochemical and molecular characteristics of pathogenic antigen present in or on these clathrin-coated pits of podocytes (and also expressed in microvilli of the brush border of the proximal tubule) became a subject of intense investigation. Makker30 showed it to be a mannose-containing glycoprotein in 1978. Purification of the antigen using lectin affinity chromatography was accomplished by Kerjaschki and Farquhar31 and Makker and Singh32 in 1982. The antigen isolated by Kerjaschki and Farquhar31 was a 330-kDa glycoprotein, whereas the antigen isolated by Makker and Singh32 was a 600-kDa glycoprotein. Both these purified proteins subsequently were called megalin,33 and the molecular mass of megalin is now believed to be 600 kDa. Megalin copurifies with its chaperone, called receptor-associated protein; however, megalin alone is capable of inducing active Heymann nephritis.34 Megalin is a multipurpose cell-membrane receptor capable of binding lipoproteins (such as low-density lipoprotein) and other proteinaceous substances33 and is present on the brush border of proximal tubules and on the glomerular podocyte (the latter only in murine species, eg, rats). Megalin in the proximal tubule participates (along with another protein called cubulin) in the endocytic reabsorption of filtered proteins, including albumin.33 Its exact physiologic function in the podocyte is uncertain. The actual epitopes in megalin responsible for the production of active Heymann nephritis are limited to only a small portion of the molecule.35-37 Megalin is now known to contain many such epitopes,33,36,37 and glycosylation of the epitopes is critically involved in its pathogenicity.38 In the active Heymann nephritis model, intramolecular epitope spreading is observed as the disease progresses.39

An additional new twist appeared in 1980 and 1981 by the novel findings of Batsford et al40 and Border et al,41 who described the production of typical MN in animals by intravenous infusion of cationized foreign serum proteins (such as cationic human IgG, ferritin, or bovine serum albumin). These investigators convincingly showed that the lesion was produced by the electrochemically mediated deposition of the cationized antigen in the subepithelial aspect of the GBM through interaction with electrically negative charged (anionic) components of GBM (possibly heparan sulfate proteoglycans). This led to a “planted” foreign antigen in glomeruli to which circulating antibody could react and form immune complexes in situ, eventually producing the typical MN lesion. In addition, experimental models of MN have been developed by exposure to toxic agents (eg, mercuric chloride). In these models, marked genetically based susceptibility is noted and autoantibodies to nonhistone nucleoproteins are found.42

Thus, by 1982, a quarter century after its initial description, the pathogenetic mechanisms responsible for the formation of subepithelial electron-dense deposits containing immunoglobulin in both active and passive Heymann nephritis were reasonably well understood. Antibodies (IgG) appearing in the circulation (actively induced or passively administered) permeated the GBM and bound to a native antigen (megalin) present on the podocyte surface, forming immune complexes in situ in close approximation to the clathrin-coated pits of podocytes. These immune complexes grew in size and subsequently were shed into the subepithelial space, where they interacted with matrix components of the GBM (perhaps covalently) and accumulated as electron-dense aggregates that persisted long
after the antibody has disappeared from the circulation.43

It was clear even in 1982 that the finding of electron-dense deposits containing immunoglobulin could be a manifestation of more than one pathogenetic mechanism, including the Heymann-type mechanism of in situ formation of immune complexes when circulating antibodies (heterologous or autologous) interact with a native podocyte membrane-derived antigen, the chronic serum sickness-type mechanism in which immune complexes deposit from the circulation, and the planted antigen mechanism in which antibodies in the circulation deposit by interacting with non-native antigens artificially planted in the subepithelial space because of a biophysical or immunologic affinity for GBM structural elements (Fig 2).

The next series of questions, which would prove to be even more controversial, involved a search for better understanding of the linkage between the formation and persistence of the in situ immune complexes to the mediation of proteinuria and whether the Heymann models of disease were relevant to the pathobiological process of human disease.

THE MEDIATION OF PROTEINURIA

Marked proteinuria and nephrotic syndrome are the hallmarks of MN in humans and animal models (including Heymann nephritis). Even at an early stage of development in our understanding of MN, it was clear that proteinuria could not always be taken per se as a sign of the active formation and in situ deposition of immune complexes42,43 because irreversible damage to the glomerular capillary wall could induce changes in the permselectivity barrier that could persist even in the absence of autoantibody to megalin.43 Nevertheless, proteinuria is a regular feature associated with active formation of in situ immune complexes and local complement activation in the developing experimental disease.44,45 Novel experiments conducted by Salant et al46 using the passive Heymann nephritis model (induced by a mixture of polyclonal antibodies to a crude kidney homogenate [FxA]) and using congenital or acquired deficiencies

Figure 2. A representation of the possible immunopathogenetic mechanisms for the formation of immune deposits in the subepithelial space. Reproduced from Glassock66 with permission of the Massachusetts Medical Society.
of later acting complement components, strongly suggested that assembly of the membrane attack complex (C5b-C9) in the subepithelial space was a requirement for abnormal proteinuria in the initial (heterologous) phase of passive Heymann nephritis when the administered heterologous antibodies to FxIA react in situ with the native podocyte-related megalin epitopes.\(^45\) This phase of passive Heymann nephritis may be more akin to the human idiopathic MN situation, when immune complexes are actively being formed in situ. However, the complement dependency and proteinuria in passive Heymann nephritis has been shown only when antibodies to the crude FxIA are used; this is not observed when antibodies to purified megalin\(^47\) or homologous autoantibodies are used.\(^21,48\)

The later (autologous) phase of passive Heymann nephritis is more involved with the interaction of endogenously generated antibody (and perhaps also sensitized T cells) to the deposits of heterologous IgG planted in glomerular structures (subepithelial space).\(^49\)

In the heterologous phase of passive Heymann nephritis, sublytic local concentrations of membrane attack complex were believed to activate podocytes to produce reduced nicotinamide adenine dinucleotide phosphate (NADPH)-oxidoreductase and lead to the elaboration of toxic oxygen radicals with attendant lipid peroxidation, thus altering the cell membrane structure of podocytes essential for maintenance of the glomerular permeability barrier. Antioxidants (such as probucol) were capable of ameliorating proteinuria in Heymann nephritis.\(^50-52\)

Abnormally filtered autoantibody to megalin also could interact with the brush border of the proximal tubule to further interfere with protein reabsorption and produce tubulointerstitial lesions.\(^53\) In this formulation, proteinuria in passive Heymann nephritis (heterologous phase) was complement dependent (C5b-C9) and leukocyte independent because the events were occurring in the subepithelial compartment of glomeruli, presumably protected from intact circulating cells (but not from their soluble and diffusible products). The effects of antibody on neutralizing (or overwhelming) the activity of locally expressed complement-regulatory proteins present on the podocyte cell wall cannot be overlooked.\(^54\)

Binding of antibodies to intrinsic podocyte membrane protein antigens thus might create a microenvironment conducive to alternate pathway complement activation, even if the antibodies themselves do not activate complement (eg, IgG4).

The complement-dependent leukocyte-independent formulation of the mediation of proteinuria in MN subsequently was challenged by investigators who found that in passive Heymann nephritis, the PVG/c- rat totally deficient in the C6 component of complement developed proteinuria identical in severity to the PVG/c+ rat without C6 deficiency.\(^55\) Autoantibody levels to crude FxIA were similar in the 2 groups of actively immunized rats (antibodies to megalin or gp330/600 were not analyzed). In these experiments, the size of the deposits correlated highly (\(r = 0.94\)) with the magnitude of proteinuria. The observations in active Heymann nephritis in PVG/c6- and PVG/c6+ rats also have been confirmed in the passive Heymann nephritis model studied during the heterologous phase (but not the autologous phase), but unlike the active Heymann nephritis model, the size of the immune deposits does not correlate with proteinuria.\(^56\)

In the passive Heymann nephritis model, depletion of CD8+ T cells during the autologous phase leads to abolition of proteinuria in both strains of rats.\(^57\)

In addition, CD8-depleted rats (adult thymectomy plus anti-CD8 monoclonal antibody treatments) with active Heymann nephritis do not develop proteinuria.\(^57\) Moreover, fragments of heterologous IgG (non-C\(^3\)=fixing Fab\(^’\)) anti-FxIA antibodies can induce abnormalities of glomerular permeability when administered to rats.\(^58\) The complement dependence and T-cell independence of the early heterologous phase of passive Heymann nephritis has been amply confirmed in many laboratories, including studies using the isolated perfused kidney system in which T cells are totally lacking.\(^59\)

It seems clear that resolution of proteinuria may be delayed greatly compared with the disappearance of deposits in the capillary wall in both experimental and human MN.\(^43,44\) Thus, proteinuria per se is not a completely reliable indicator of the presence or absence of the active formation of in situ immune deposits. Concomitant deposition of C3c (a degra-
tion product of C3 indicating recent activation of complement) may be a more reliable tool to assess the activity of in situ deposition.44,60

Taken together, these experimental studies strongly affirm the complement dependence of proteinuria during the early phases of the interaction of antibody with the relevant podocyte antigen. They also raise the possibility that the characteristics of the deposits themselves, the deleterious effects of the antibody itself on podocyte function or attendant cellular (CD8+ T cell) responses, also might be involved, particularly in the later autologous phases of passive Heymann nephritis or in the actively induced disease. T-Cell infiltration of glomeruli usually is not conspicuous in experimental (active or passive) Heymann nephritis, but even small numbers of activated T cells transiently trapped in glomerular structures could elaborate soluble diffusible substances that alter the integrity of the podocyte-dependent permselectivity barrier in glomeruli. Active antibody-mediated damage to podocytes may create an environment favoring alternative pathway complement activation. Concomitant C3c deposition may be a convenient way to assess the activity of the disease (ie, the phase in which in situ immune complexes are forming rapidly). Because all these studies have been conducted in the megalin-dependent Heymann nephritis models of MN, we still do not know whether they fully apply to the human situation. Thus, we still face the next challenge of MN; namely, linking the pathophysiologic process of spontaneous human disease and the induced experimental disease models in animals.

THE PATHOGENESIS OF HUMAN IDIOPATHIC MN

For more than 40 years (specifically between 1959 and 2002), the dominant school of thought was that the Heymann models of experimental MN were most likely to represent the pathogenesis of MN in humans. However, despite a diligent search for antimegalin (gp330)-like antibodies in idiopathic MN and attempts to identify megalin as a component of the normal human podocyte cell membrane, no pathogenetic connections could be found between Heymann nephritis and human idiopathic MN.61 However, the Heymann antigen could be identified in a few secondary forms of MN, most notably sickle cell anemia.62 Despite these disappointingly negative findings in idiopathic MN, the striking morphologic and clinical resemblance of Heymann nephritis to human idiopathic MN perpetuated a concept that the pathogenesis of the diseases of rats and humans was similar, if not identical. Then, beginning in 2002, Hanna Debiec and the group of Pierre Ronco and co-workers described an elegant series of studies63-65 in an experiment of nature that in many respects broke the log jam of thinking about the pathogenesis of idiopathic MN.3 They studied the development of neonatal MN in infants born of mothers genetically lacking neutral endopeptidase (NEP), a membrane-associated podocyte antigen that digests peptides. Because the fetus did not lack NEP, fetomaternal alloimmunization occurred and anti-NEP antibodies (often in very high titers) developed in the mothers. These antibodies (often of the IgG4 or IgG1 subclasses, similar to human idiopathic MN) crossed the placental barrier and interacted with the NEP, heavily expressed on the normal fetal podocyte. In situ immune complexes (containing both IgG1 and IgG4) developed in the newborn infant (or soon after birth) and typical MN ensued, along with proteinuria and nephrotic syndrome. Of interest was the finding of the C5b-C9 membrane attack complex in the deposits, suggesting that this spontaneous human alloimmune disease also might be complement dependent, similar to what had been proposed for Heymann nephritis. These breakthrough studies of Debiec and Ronco et al63-65 in the alloimmunization experiment of nature clearly indicated a common denominator concept, clearly enunciated by Kerjaschki,3 “that podocytes and their membrane-associated proteins have a pivotal role in the development of the disease by providing antigenic targets for the circulating antibodies and for the in-situ formation of immune deposits.”3 These studies launched a concerted and ongoing effort to “molecularly dissect the target antigens and nephritogenic antibodies” in human MN.36

Thus, human idiopathic MN evolved from an immune complex-mediated disease into a podocytopathy, and the path
was open for a search for other podocyte-related antigens in the quest for more complete understanding of human idiopathic MN. This search already has dramatically borne fruit with the recent seminal description by Beck et al in David Salant’s laboratory of the role of an anti-M–type phospholipase A₂-receptor autoantibody (commonly of the IgG4 subclass) in the pathogenesis of a very high fraction (≥70%–80%) of individuals with idiopathic MN. The anti-NEP system, first described in an alloimmunization situation, also may be a major player in human idiopathic MN mediated by autoantibodies. Other autoantigen-autoantibody systems also will need to be considered.

The exact frequency of various autoantigen/autoantibody systems in idiopathic MN is likely to be resolved only by confirmatory studies involving sharing of reagent antisera. At this juncture, it seems reasonable to speculate that human idiopathic MN will be caused by a variety of antigen-antibody systems converging on the podocyte cell membrane as the target, but that the classic Heymann antigen (gp330/600; megalin) is not commonly involved in the human disease.

However, the mediation of proteinuria in human idiopathic MN is still shrouded in some controversy (see also the previous discussion of mediation of proteinuria in experimental models of MN). Both IgG1 and IgG4 subclasses are deposited in glomeruli in humans with idiopathic MN. Secondary forms of MN may show different patterns of IgG subclass deposition. Idiopathic MN now is regarded as a prototypical IgG4-mediated disease. In the alloimmune experiment of nature described by Debiec et al, only mothers who produced IgG1 autoantibodies to NEP transmitted disease to the fetus, suggesting that complement-fixing IgG1 autoantibodies are involved in the mediation of proteinuria. In the studies of idiopathic MN reported by Beck et al, the anti-PLA₂R autoantibodies were of the IgG4 and IgG1 subclasses. It is well known that IgG4 antibodies activate complement poorly, if at all. Thus, the IgG1 subclasses of autoantibodies capable of activating complement may be involved directly in causing proteinuria in human idiopathic MN, similar to the animal models of the disease. It also is worth noting that in active Heymann nephritis, the predominant isotype of IgG deposited in glomeruli is IgG1 (the murine equivalent of IgG4 in humans), another facet of the pathobiological process shared between the experimental model and human disease. Other non-complement-dependent (eg, T-cell–dependent) mechanisms also likely come into play in the production of damage to the permselectivity properties of the capillary wall in the human disease, just as they have been suggested to do in some of the experimental models of disease. The decrease or disappearance of proteinuria in human idiopathic MN (after treatment with rituximab) is associated with a decrease in IgG4, but not total IgG, deposition in glomeruli. Complete resolution of proteinuria may occur, although some subepithelial deposits persist using electron microscopy. Repeated kidney biopsies in patients with full or partial resolution of proteinuria usually show a diminution in the intensity of electron-dense deposits, and the remaining deposits acquire a more electron-lucent character as the proteinuria resolves, but deposits may take months or years to completely resolve despite the absence of proteinuria. Concomitant C₃c deposition and increased urinary C₅b-C₉ levels are a good way to assess active immune complex formation (present in only about 70% of patients with idiopathic MN who have long-term proteinuria). Abnormalities of the slit-pore membrane often resolve in parallel with the decrease in proteinuria.

The remaining uncertainties regarding the fundamental biological mechanisms of proteinuria and the lack of a clear understanding of pathways underlying the initiation of autoimmune responses to polymorphic autologous (podocyte-related) antigens and their unique epitopes are major questions for the next 50 years of research in idiopathic MN.

**SUMMARY AND SPECULATIONS**

Idiopathic MN is now in its second half-century of independent existence. A pure morphologic description of the disorder has given way to a pathogenetic explanation of the underlying disease process itself. The target autoantigens/molecular epitopes
(and cellular systems), the effector molecules, both autoantibody, lymphoid cells, and complement for this quintessential autoimmune disease, are well along the way to complete understanding. However, we still have only fragmentary knowledge of what triggers the autoimmune response in the first place. Thus, idiopathic MN remains a disease of unknown cause. However, progress in the precise identification of target autoantigens and autoantibodies likely will provide new insights into the possible roles of environmental agents through molecular mimicry.

The main issues to be resolved in the second half-century of the existence of idiopathic MN are reasonably clear, and a preliminary road map for basic and clinical investigation in idiopathic MN could be reasonably constructed. Perhaps the immensely robust and highly efficient tools of science available today will make the path to resolution of these issues much easier and less frustrating than they have been in the past. It also is a hope and dream that advances in understanding the pathogenesis of idiopathic MN will lead to better diagnostic tools and also a new basis of rational therapeutics.

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