Correspondence

Multiple Sclerosis

To the Editor: We are troubled by the suggestion in the review article on multiple sclerosis by Noseworthy and colleagues (Sept. 28 issue)[1] that hepatitis B vaccine should be administered only to persons at substantial risk for exposure to the virus. The concern that hepatitis B vaccine may cause multiple sclerosis stems from case reports of demyelination beginning within months after vaccination. The World Health Organization and the Viral Hepatitis Prevention Board have reviewed preliminary results from ongoing controlled studies and other evidence. They have concluded that a causal association between hepatitis B immunization and demyelinating diseases of the central nervous system has not been demonstrated and that there is no need to change policies regarding immunization against hepatitis B.[2,3]

Decisions about immunization for patients with multiple sclerosis are best made by the patient and his or her physician. Immune stimulation from vaccination could theoretically exacerbate multiple sclerosis, but this possibility has not been specifically addressed for hepatitis B vaccine. The best available evidence on the safety of vaccination in patients with multiple sclerosis comes from a randomized, controlled trial of influenza vaccination, which found no differences in attack rates or disease progression between patients receiving vaccine and those receiving placebo.[4]

Hepatitis B causes an estimated 4 million acute infections worldwide each year and is responsible for tens of thousands of deaths from liver cirrhosis or primary liver cancer. Hepatitis B vaccines are safe and highly effective. Unsubstantiated concern that hepatitis B vaccine may cause or exacerbate multiple sclerosis must be weighed against the very strong record of vaccines in protecting against disease and death.

FRANK DESTEFANO, M.D., M.P.H.
THOMAS VERSTRAETEN, M.D.
Centers for Disease Control and Prevention
Atlanta, GA 30333

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To the Editor: Noseworthy et al. note that cognitive impairment may become troublesome in patients with multiple sclerosis but do not develop the point further, except to state that prominent cortical signs rarely dominate the clinical picture. In fact, great strides have been made in the past five years in understanding the patterns and severity of cognitive impairment in the various forms of this disorder. Classically, patients with multiple sclerosis have been found to have bradyphrenia, impaired attention and concentration, reduced manual speed and dexterity, and defects in memory retrieval.[1,2] However, recent research has also demonstrated different degrees of cortical language deficits, including impairments in naming, aural comprehension, and letter and category fluency, in patients with the relapsing–remitting and chronic progressive forms of multiple sclerosis.[3]

Another recent study demonstrated that cognitive and other neurologic deficits referable to cortical sites may be caused by lesions at the gray matter–white matter junction and that cognitive dysfunction in patients with multiple sclerosis may progress rapidly, even in the absence of motor deficits or other evidence of clinical deterioration.[4] Finally, a recent study of rates of global and regional cortical cerebral glucose metabolism demonstrated significantly reduced rates in patients with multiple sclerosis as compared with normal controls.[5] These reductions in the rate of cerebral glucose metabolism correlated well with the total area of the lesion, as well as with the degree of cognitive dysfunction, indicat-

ing that the lesion burden in white matter is associated with a deterioration of neural function in the cerebral cortex.[5]

For these reasons, initial and serial neuropsychological assessments of patterns of deficit can have an important supporting role in the diagnosis of multiple sclerosis, as well as in the ongoing assessment of disease progression, and neurocognitive rehabilitation can help patients circumvent their deficits.

J.P. NEWMAN, PH.D.
Hadassah University Hospital
91120 Jerusalem, Israel

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Dr. Noseworthy and a colleague reply:

To the Editor: The letter by Drs. DeStefano and Verstraeten makes several important points. Although there has been controversy with regard to a possible association between the administration of hepatitis B vaccine and multiple sclerosis, studies conducted to look for a relation have found no evidence of an association,[1-3] and this result is further supported by two articles in this issue of the *Journal*.[4,5] The Viral Hepatitis Prevention Board concluded that the data available did not demonstrate a causal association between hepatitis B vaccine and demyelinating diseases of the central nervous system, and that all countries should maintain established hepatitis B immunization programs and develop universal-immunization programs for infants and adolescents.[6] Careful scientific study can almost never completely discount reports of strong temporal associations between a small number of cases of a relatively common illness and widespread exposure to a vaccine. However, we accept that such associations cannot be the basis for alterations in important public health initiatives. Others have concluded that coincidence is the most plausible explanation for any temporal association between vaccination and multiple sclerosis.[7]

We view this as an important clarification, since national health policy in the United States and other countries recommends universal hepatitis B immunization for infants and adolescents. This policy has benefited public health by substantially reducing the considerable morbidity and mortality associated with acute and chronic hepatitis B infection. Readers should, therefore, be aware that the best scientific data available do not demonstrate an association between hepatitis B immunization and multiple sclerosis.

We agree with the statement by DeStefano and Verstraeten that the decision about whether or not to administer hepatitis B vaccine to patients with multiple sclerosis is "best made by the patient and his or her physician." This was the spirit underlying the statement in our article, and we regret that it appeared to question the wisdom of global hepatitis B immunization. The concern expressed in our article should not diminish the importance of hepatitis B immunization for children worldwide. The absence of definitive evidence of an association and the apparent safety of immunization against influenza suggest that hepatitis B vaccine is usually safe for patients with multiple sclerosis. The two reports in this issue of the *Journal* provide reassurance that hepatitis B vaccination is safe in patients with multiple sclerosis.[4,5] If there is continued concern about the apparent development of multiple sclerosis or the worsening of existing inflammatory demyelinating disease, the question might best be studied prospectively with magnetic resonance imaging, as we stated in our review.

Dr. Newman correctly highlights several of the advances that have been made in our understanding of the neurobehavioral consequences of multiple sclerosis.

JOHN H. NOSEWORTHY, M.D.
GREGORY A. POLAND, M.D.
Mayo Clinic
Rochester, MN 55905

Editor's note: Dr. Poland receives funding from Merck Research Laboratories.

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Efficacy of Mycophenolate Mofetil in Patients with Diffuse Proliferative Lupus Nephritis

To the Editor: There are several reasons for advocating caution in generalizing the beneficial findings reported by Chan et al. (Oct. 19 issue)[1] to other patients with proliferative lupus glomerulonephritis. First, mycophenolate mofetil was compared with oral rather than pulsed intravenous cyclophosphamide, which has become the standard of treatment for patients with diffuse proliferative lupus nephritis.[2]

Second, patients with poor prognostic factors with respect to renal outcomes were either not included in the study or were underrepresented.[3,4] In particular, patients with serum creatinine concentrations of more than 3.4 mg per deciliter (300 μmol per liter) were excluded, and many had only minor degrees of renal impairment. Only 3 of the 42 patients were men, presumably none were black, and there was little evidence of chronic renal parenchymal injury on biopsy. These base-line characteristics of the patients may well explain the higher rate of remission found in this study (79 percent, if only complete remission is taken into account) than in previous studies (46 percent).[4,5]

Third, the follow-up was short, considering that cyclophosphamide does not appear to provide any advantage over oral glucocorticoid therapy alone until the fifth year of fol-

low-up.[2] The fivefold higher rate of relapse in the mycophenolate mofetil group than that in a recent study of bolus doses of cyclophosphamide[5] also arouses concern about the long-term efficacy of this treatment.

DAVID A. ISENBERG, M.D.
FONTINI B. KARASSA, M.D.
Royal Free and University College Medical School
London W1P 9PG, United Kingdom

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Dr. Chan replies:

To the Editor: The objective of our study was to examine the efficacy and tolerability of mycophenolate mofetil as compared with oral cyclophosphamide, each combined with prednisolone, in the treatment of patients with diffuse proliferative lupus nephritis. We studied only Chinese patients, and the size and duration of the study were not designed to examine the prevention of relapse. With regard to the control therapy, both pulsed intravenous cyclophosphamide and short-term oral cyclophosphamide have been used effectively in patients with diffuse proliferative lupus nephritis, and the data to date suggest that the risk of cyclophosphamide-related complications may be related more to the duration of treatment and the cumulative dose than to the route of administration.[1-3]

The severity of lupus nephritis in the patients we studied was evidenced by the histologic class, the activity score, and the clinical manifestations and was not defined by renal function alone. Patients with severe impairment of renal function were not included because we were interested primarily in determining whether the immunosuppressive treatments were effective in controlling immune-mediated acute inflammation. The favorable response to therapy in our study further affirms the importance of early and effective immunosuppressive treatment in achieving optimal outcome in patients with lupus nephritis. In this context, the importance of the induction of remission in ensuring a favorable long-term outcome was highlighted in a recent study.[4] It is inappropriate to compare our study, which focused on the induction of remission, with others that examined the long-term deterioration of renal function.

TAK MAO CHAN, M.D.
Queen Mary Hospital
Hong Kong, China

FOR THE HONG KONG–GUANGZHOU NEPHROLOGY STUDY GROUP

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Exercise-Induced Premature Ventricular Depolarizations

To the Editor: Jouven et al. report on the long-term outcome in asymptomatic men with exercise-induced premature ventricular depolarizations (Sept. 21 issue).[1] In 1977, a colleague and I reported the results of a similar study involving 6500 patients, although most of them had chest pain as an indication for exercise testing.[2] We also found that premature ventricular depolarizations (contractions) were predictive of coronary events, especially when combined with ST-segment depression. The risk of death in a five-year follow-up study increased from 8 percent when premature ventricular depolarizations were induced by exercise to 22 percent when ST-segment depression was also present. In an editorial accompanying the report by Jouven et al., Dr. Calkins states that this is the first report on the risk associated with exercise-induced premature ventricular depolarizations.[3] For the record, many others reported on this issue before we did.[2]

The low incidence of premature ventricular depolarizations is of interest. Although we counted premature ventricular depolarizations before, during, and after exercise, 20 percent of our patients had this abnormality. Froelicher et al. reported that 35 percent of 1390 active-duty airmen had premature ventricular depolarizations.[4] According to several reports,[5] in the absence of evidence of ischemia, premature ventricular depolarizations have almost no power to predict coronary disease, a finding that seems to conflict with that reported by Jouven et al. The much longer follow-up period in the study by Jouven et al. may explain this discrepancy. Over the years, most cardiologists have largely ignored premature ventricular depolarizations during exercise testing, a practice that should probably change.

A final comment may be of interest. A colleague and I recently correlated ST-segment depression in premature ventricular depolarizations with abnormalities on coronary angiograms.[6] If this finding can be confirmed, the predictive value of these arrhythmias, which are usually overlooked, may be more robust than heretofore believed.

M.H. ELLESTAD, M.D.
L.B. Memorial Heart Institute
Long Beach, CA 90801

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The authors reply:

To the Editor: Although the opposite has been described by many authors, premature ventricular depolarizations were found to be predictive of coronary events and of coronary lesions in patients with known or suspected cardiovascular disease in many studies that we cited and others that we did not cite.

However, the new information provided by our study was that frequent premature ventricular depolarizations during exercise were associated with an increased rate of mortality from cardiovascular causes in middle-aged men who were free of known cardiovascular disease, and as Dr. Ellestad pointed out, this finding is at variance with the results of previous studies. Moreover, the design of our study probably explains the relatively low proportion of subjects with premature ventricular depolarizations or ST-segment depression, or both, during exercise.

As Dr. Ellestad mentioned, an analysis of ST-segment depression in relation to premature ventricular depolarizations might provide additional information about coronary disease. However, in our study, very few subjects with frequent premature ventricular depolarizations also had signs of ischemia during exercise, and the subjects with an exercise test that was positive for ischemia and those who had frequent premature ventricular depolarizations during exercise apparently did not have the same pattern of risk factors.

Finally, we agree with Dr. Ellestad and with Dr. Calkins that physicians should probably be more concerned than before about frequent premature ventricular depolarizations during exercise.

XAVIER JOUVEN, M.D., PH.D.
Hôpital Européen Georges Pompidou
75015 Paris, France

PIERRE DUCIMETIÈRE, PH.D.
Hôpital Paul Brousse
Villejuif, France

The editorialist replies:

To the Editor: Ellestad's letter calls attention to the study in which he and a colleague evaluated the predictive implications of premature ventricular depolarizations associated with stress testing in patients referred for a clinically indicated stress test.[1] The follow-up period ranged from 6 to 60 months. The incidence of a cardiac event was 1.7 percent among patients without premature ventricular depolarizations or ischemia, 6.4 percent among patients with premature ventricular depolarizations but without ischemia, and 11.4 percent among those with both premature ventricular depolarizations and ischemia. Patients in whom premature ventricular depolarizations increased during exercise were more likely to have a cardiac event during follow-up than those in whom premature ventricular depolarizations decreased with exercise.

Although Ellestad claims that the study by Jouven et al. was similar to the previous study that he reported with a colleague, this does not appear to be the case. Whereas in the study by Udall and Ellestad stress tests were performed for clinical indications in patients with known or suspected cardiac disease, the study by Jouven et al. involved subjects without known or suspected cardiovascular disease. Udall and Ellestad reported that they followed most patients for 2 years or less, as compared with a 23-year follow-up period in the study by Jouven et al. It is because of this difference in follow-up that I concluded that the study by Jouven et al. was the first to evaluate the long-term prognostic implications of premature ventricular depolarizations that occur during exercise stress testing.

Before the study by Jouven et al., it was generally accepted that premature ventricular depolarizations during stress testing do not have prognostic importance in apparently healthy persons.[1-3] Therefore, the finding that frequent premature ventricular depolarizations during exercise in apparently healthy persons are associated with a 2.6-fold increase in long-term mortality from cardiovascular causes is new.

HUGH CALKINS, M.D.
Johns Hopkins University School of Medicine
Baltimore, MD 21287-0409

1. Udall JA, Ellestad MH. Predictive implications of ventricular premature contractions associated with treadmill stress testing. Circulation 1977;56:985-9.
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Treatment of Ectopic Pregnancy

To the Editor: Lipscomb et al. (Nov. 2 issue)[1] describe medical treatment for ectopic pregnancy almost as a standalone approach, which may leave nongynecologists with the wrong impression. For balanced decision making, several factors should be considered.

If the serum human chorionic gonadotropin level exceeds 4000 mIU per milliliter, the ectopic pregnancy should be treated laparoscopically, as should an ectopic pregnancy with a mass larger than 3.5 to 4.0 cm in diameter.[2] At the other extreme, if the human chorionic gonadotropin level is below 2000 mIU per milliliter, the ectopic pregnancy may regress spontaneously.[3] Medical treatment may thus erroneously be deemed very effective, which explains in part the difference in efficacy between parenteral and direct intratubal injection.[4] Although ultrasonography is highly accurate in diagnosing ectopic pregnancy,[2] there remains the possibility of a regressing intrauterine pregnancy.

Hajenius et al. concluded on the basis of the Cochrane Database[5] that systemic treatment with methotrexate administered as a single intramuscular injection is less effective than laparoscopic salpingostomy, whereas multiple intramuscular doses have a similar efficacy but are associated with a greater impairment of the health-related quality of life. Systemic methotrexate therapy is also more expensive because of surgical interventions for tubal rupture, prolonged hospitalization, and loss of productivity. Only with a low

initial level of human chorionic gonadotropin does systemic methotrexate therapy lead to cost savings, as compared with laparoscopic salpingostomy. There is also evidence that salpingectomy does not impair future fertility, as compared with salpingostomy, and eliminates the possibility of residual products of conception after surgery. We suggest that the choice between surgery and medical treatment should be left to the patient and should be based on her preferences and her perception of the risks associated with each of the options.

ELIEZER SHALEV, M.D.
IZHAR BEN-SHLOMO, M.D.
Haemek Medical Center
Afula 18101, Israel

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Dr. Lipscomb replies:

To the Editor: Since the focus of our review was the nonsurgical management of ectopic pregnancy, we did not attempt to discuss all other appropriate treatment methods. The available data do not conclusively favor any particular approach, either surgical or medical, and we certainly concur with Shalev and Ben-Shlomo that surgical options should be considered and discussed with the patient. The choice of treatment for a particular patient must reflect not only the patient's desires and the characteristics of the disorder but also the physician's level of comfort, surgical ability, and experience with each of these approaches.

GARY H. LIPSCOMB, M.D.
University of Tennessee
Memphis, TN 38163

Repair of Large Bone Defects with the Use of Autologous Bone Marrow Stromal Cells

To the Editor: The reconstruction of large bone segments is an important clinical problem, and none of the approaches proposed thus far have proved very effective. In animals, repair and functional recovery of segmental bone defects have been reported with the use of marrow-derived osteoprogenitor cells grown on scaffolds of macroporous hydroxyapatite.[1-3]

We report the use of this cell-based tissue-engineering approach to treat three patients with large bone defects. Patient 1 was a 41-year-old woman with loss of a 4.0-cm segment of the mid-diaphysis of the right tibia as the result

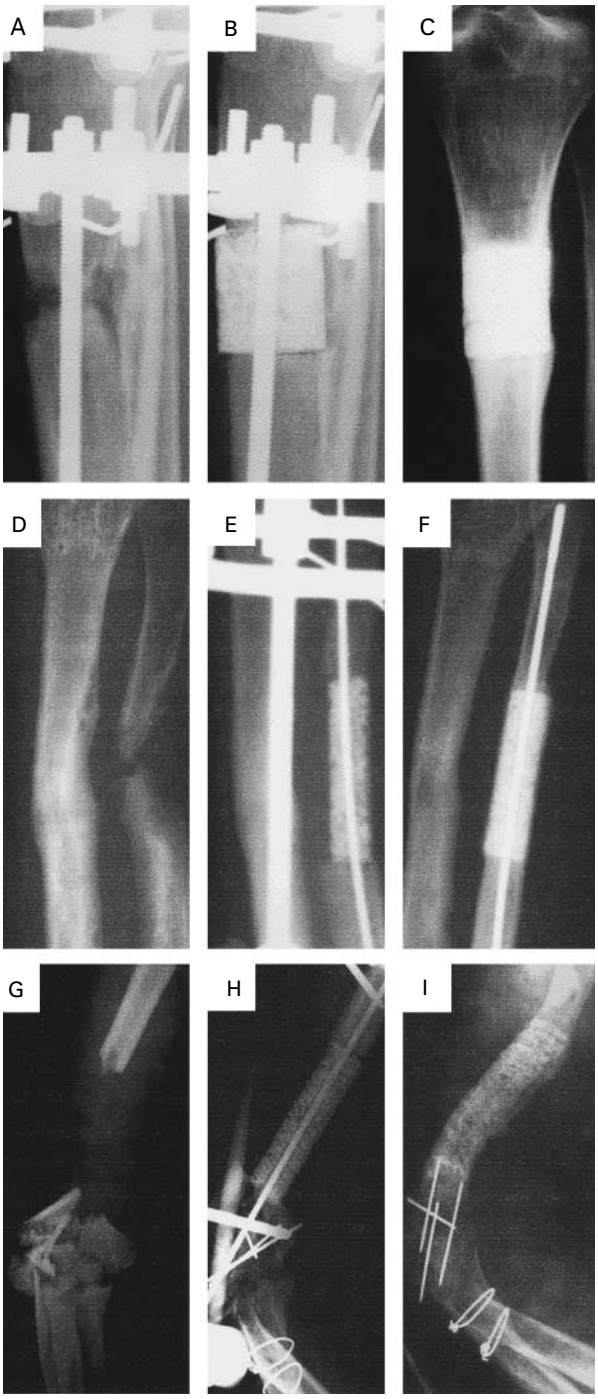

Figure 1. Radiographs Obtained before and after the Repair of Large Bone Defects in Three Patients.

Panels A, B, and C show films obtained from Patient 1 before, immediately after, and 18 months after surgery, respectively. Panels D, E, and F show films from Patient 2 before, immediately after, and eight months after surgery, respectively. Panels G, H, and I show films from Patient 3 before, immediately after, and 15 months after surgery, respectively.

of an unsuccessful attempt at bone lengthening. Patient 2 was a 16-year-old girl with traumatic loss of a 4.0-cm segment of the distal diaphysis of the right ulna. Patient 3 was a 22-year-old man with loss of a 7.0-cm segment of the right humerus as a result of a plurifragmental fracture. The study protocol was approved by the ethics committees of the centers where the patients were treated, and all the patients gave written informed consent.

For each patient, osteoprogenitor cells were isolated from bone marrow and expanded ex vivo.[4] These cells were placed on macroporous hydroxyapatite scaffolds, the size and shape of which reflected the particular bone defect in each patient, and implanted at the lesion sites. External fixation was provided initially for mechanical stability and was subsequently removed (6.5 months after surgery in Patient 1, 6 months after surgery in Patient 2, and 13 months after surgery in Patient 3). All patients recovered limb function. As of this writing, 27, 16, and 15 months, respectively, after surgery, the patients have reported no problems with the implants.

In all three patients, radiographs and computed tomographic scans revealed abundant callus formation along the implants and good integration at the interfaces with the host bones by the second month after surgery. Representative radiographs are shown in Figure 1. With the use of a traditional bone-graft approach, recovery would have required 12 to 18 months, under the most favorable conditions and in the absence of complications.[5]

We believe that the use of culture-expanded osteoprogenitor cells grown on porous bioceramic scaffolds will result in substantial improvement in our ability to repair large defects in long bones.

RODOLFO QUARTO, M.D.
MADDALENA MASTROGIACOMO, PH.D.
RANIERI CANCEDDA, M.D.
Istituto Nazionale per la Ricerca sul Cancro
Genoa 16132, Italy

SERGEI M. KUTEPOV, M.D.
VLADIMIR MUKHACHEV, M.D.
ALEXANDER LAVROUKOV, M.D.
Ural Scientific Research Institute of Traumatology and Orthopedics
Ekaterinburg 620014, Russia

ELIZAVETA KON, M.D.
MAURILIO MARCACCI, M.D.
Istituti Ortopedici Rizzoli
Bologna 40136, Italy

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Transmission of Glomerular Permeability Factor from a Mother to Her Child

To the Editor: In the idiopathic nephrotic syndrome, including focal segmental glomerulosclerosis, a glomerular permeability factor may be responsible for the development of proteinuria and the recurrence of disease after renal transplantation.[1,2] Plasma from patients with active focal segmental glomerulosclerosis can cause proteinuria in rats.[3] The effect of a glomerular permeability factor after transmission from one person to another is not known. We report the transfer of an unknown glomerular permeability factor from a mother with focal segmental glomerulosclerosis to her child.

The nephrotic syndrome developed in a 35-year-old woman (gravida 5, para 3) in the 13th week of gestation during her fifth pregnancy. Laboratory studies showed proteinuria (26 g of protein per day), a serum albumin level of 1.6 g per deciliter, and a serum creatinine level of 1.2 mg per deciliter. Renal biopsy showed focal segmental glomerulosclerosis without evidence of tubulointerstitial fibrosis. The patient was treated with prednisone (90 mg per day) for eight weeks without an effect on the proteinuria. Because of the development of severe hypertension and erosive gastritis, the prednisone was tapered and finally discontinued before delivery.

At 33 weeks' gestation, a cesarean section was performed because of preeclampsia and fetal dystrophy. A girl was delivered without complications; the birth weight was 1030 g, the length 38 cm, and the head circumference 28 cm (all below the 3rd percentile). The child's blood pressure was 51/28 mm Hg. Laboratory studies showed a serum creatinine level of 0.3 mg per deciliter and a serum albumin level of 2.7 g per deciliter, with normal values for triglyc-

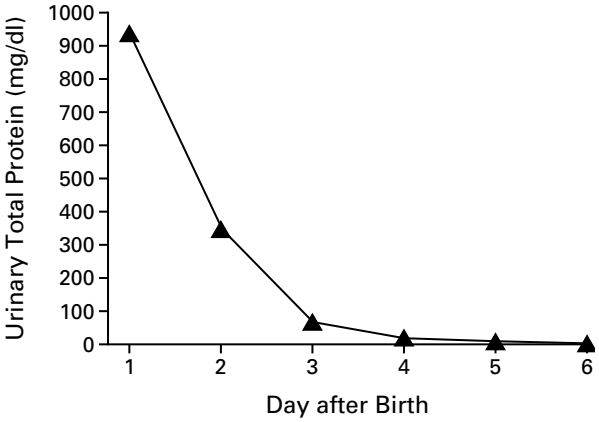

Figure 1. Course of Proteinuria after Birth in the Infant of a Woman with Focal Segmental Glomerulosclerosis.

erides and cholesterol. On day 1, proteinuria (935 mg per deciliter) was present. The proteinuria was highly selective (76 percent albumin, 5 percent transferrin, and 1.5 percent $alpha_1$-microglobulin, with no IgG). It diminished during the next several days (Fig. 1). The serum albumin level increased to 3.4 g per deciliter on day 5. The child had no overt edema. Immunosuppressive therapy with cyclosporine was initiated in the mother two weeks after delivery. Proteinuria was subsequently reduced to about 10 g of protein per day, and the serum albumin level increased to 2.8 g per deciliter.

Our observations provide evidence that a glomerular permeability factor can be transferred through the placenta and that it loses its proteinuric effect within a few days. In this case, in utero exposure did not cause chronic glomerular disease in the neonate. This finding suggests that the molecular size of the factor was smaller than that of IgG, which would persist in the infant's circulation for many months. A group of investigators has recently reported a glomerular permeability factor with a molecular size of 30 to 50 kd.[3] The biochemical structure and properties of glomerular permeability factors require further study.

MARKUS J. KEMPER, M.D.
University Children's Hospital
CH-8032 Zurich, Switzerland

GUNTER WOLF, M.D.
DIRK E. MÜLLER-WIEFEL, M.D.
University Hospital Eppendorf
D-20246 Hamburg, Germany

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