outcome? Were there any electing expectant management who had deterioration before 30 weeks' gestation and altered their treatment?

We also follow our at-risk fetuses carefully by means of ultrasound before, during, and after transfusion if they require it. Occasionally, we have noted the development of a thin rim of ascites when ΔOD 450 measurements were not yet in Liley Zone III, with rapid progression to full-blown hydrops in a matter of three or four days, despite intrauterine transfusion. Have the authors had any similar experiences, and if so how often?

Although the authors state that all 11 infants were discharged in good condition, several — because of their prematurity and severe erythroblastosis — are at considerable risk. What is the developmental follow-up of these 11 infants to date? Are all developing normally?

In the past 76 months, we have carried out 202 intraperitoneal transfusions and 9 intravascular transfusions in 78 fetuses, with a traumatic fatality rate of 3 percent per procedure. With the exception of the authors' Patient 6, who had a Zone III ΔOD 450 reading at 23 weeks' gestation, the other fetuses with Zone III values between 28.5 and 29.5 weeks' gestation could have been carried to 34 to 35 weeks' gestation, with two intraperitoneal transfusions at a risk of 6 percent per fetus. The infants would have been two to four weeks more mature at delivery, and their hematocrit and hemoglobin levels would have been at least 10 g per deciliter and 0.30, respectively — levels present without intrauterine transfusions in only two of the six fetuses.

Another question: Was the Zone III amniotic fluid the initial fluid in each case? Were serial amniotic-fluid measurements made? How many readings remained in Zone III, and how many fell into Zone II? In our experience, a single value in Zone III is not as accurate a prediction of Rh disease as serial values showing a rise toward Zone III or a drop toward Zone I.

The authors comment on fetal blood sampling, a direct measurement of fetal red-cell hemoglobin levels, and indicate that fetal blood sampling, combined with ultrasonography and surveillance of fetal well-being, may be the safest and most accurate approach to Rh-affected fetuses. We concur but would advocate direct intravascular transfusion at the time of fetal blood sampling, to obviate the need for a second venipuncture, if the subsequently determined fetal red-cell hemoglobin level is low, indicating the need for fetal blood transfusion.

We again caution that if serial ΔOD 450 measurements indicate increasing severity of disease before 30 weeks' gestation, delaying treatment may be associated with very rapid deterioration and full-blown hydrops fetalis.

Dr. J.M. Bowman
Dr. F.A. Manning
Dr. C. Harman
Faculty of Medicine
Winnipeg, MB R3E OL8, Canada University of Manitoba

The above letters were referred to the authors of the article in question, who offer the following reply:

To the Editor: We would like to thank Dr. Reiss and her colleagues for providing data on three more cases that support our hypothesis. We would argue only with their contention that few people would have advocated intrauterine transfusion for the patients in our series. In fact, the values for the optical density at 450 nm for every one of our patients should have indicated transfusion according to the very reference that Reiss et al. cite.* That source recommends intrauterine transfusion for any fetus whose serial spectrophotometric determinations rise into the upper 70 to 80 percent of Zone II before 30 weeks of gestation or into Zone III between 30 and 34 weeks of gestation. Thus, each of our patients would have been given transfusions by many, according to this standard recommendation. It is precisely the point of our paper that this standard recommendation must be reevaluated, and care for these patients individualized, as Dr. Reiss and her colleagues have stated; we commend them.

Dr. Bowman and his colleagues raise points that are well taken. We regret that we do not have systematic long-term follow-up data on the development of all our babies. We do not underestimate the potential morbidity of premature delivery and the lengthy nursery stays of many of our newborns. Several of the patients seen for consultation because of Rh sensitization during this period were considered for conservative treatment but underwent transfusion because their optical-density values either were very high at the start or tended to rise very sharply early in gestation. This report does not address those patients.

At no point does our protocol suggest that a solitary spectrophotometric value be used as a guide for or against intrauterine transfusion. Space limitations did not permit us to report all the spectrophotometric data on every patient. For the 11 patients, a total of 51 serial spectrophotometric determinations were present in Zone III. The values listed in Table 1 of our article are the last values in Zone II before the patients passed into Zone III, or are the first values in Zone III. In some cases, these were the first values obtained for a patient. In no case were these the last values obtained. All serial determinations following the listed values were in Zone III in each case, with the exception of transient falls noted in association with steroid administration.

We do not suggest that intrauterine transfusion should be reserved for infants with hydrops. We believe that a combination of fetal cord-blood sampling and surveillance of fetal well-being will become accepted as the safest and most accurate approach. Fetal cord-blood sampling and intravascular transfusion have been added to our own diagnostic and therapeutic armamentarium.

Fredric D. Frigoletto, Jr., M.D., Michael F. Greene, M.D., Beryl R. Benacerraf, M.D., Vanessa Barss, M.D., and Daniel H. Saltzman, M.D.
Harvard Medical School
Boston, MA 02115 Brigham and Women's Hospital

*Bowman JM. Maternal blood group immunization. In: Creasy RK, Resnik R, eds. Maternal-fetal medicine: principles and practice. Philadelphia: WB Saunders, 1984:581.

HIGH FREQUENCY OF HERPES ZOSTER IN YOUNG HEMOPHILIACS

To the Editor: Herpes zoster usually occurs in elderly or immunocompromised patients. More recently, it has been reported in homosexuals and patients at risk for the acquired immunodeficiency syndrome (AIDS), with and without biologic evidence of immune deficiency.[1-6] We wish to report the recent occurrence of a high frequency of herpes zoster infection in a population of 259 patients with hemophilia who were followed regularly. Using blood samples stored during the past 10 years for various protocols, we were able to relate this observation to the development of antibodies specific for human immunodeficiency virus (HIV).

In the past five years herpes zoster was observed in 12 patients (4.6 percent of the total population), whereas no case had been noted during the five preceding years. Our first case was diagnosed in 1982 in a patient who had antibodies to HIV early in 1980, when 95 percent of the patients were still seronegative for HIV. The 11 other patients have been observed since 1984. During the same period, the incidence of antibodies to HIV rose sharply, reaching 66 percent in 1985. One patient had severe hemophilia B, and two had moderate and nine severe hemophilia A, including one with inhibitor. In the year before herpes zoster appeared, none of the patients had been receiving long-term steroids or long-term prophylaxis. All patients had had chickenpox, and the herpes zoster was not clinically unusual except for its occurrence in young patients from 4 to 27 years of age. Oral or local antiviral agents were prescribed only in the last two cases. Hemorrhagic complications were observed in the single case of ophthalmic zoster with subsequent scarring. None of the patients had disseminated zoster, and although two children were living in a boarding school for hemophiliacs, there was no outbreak of shingles.

At the time of zoster, 11 of 12 patients had antibodies to HIV. One was seronegative for HIV and remains so 28 months later. All patients had normal T4-cell counts (over 0.4×10^9 per liter), and 11

Table 1. T4/T8 Ratios in Relation to the Appearance of Herpes Zoster in 11 Patients with Hemophilia.

	Age	Months after Seroconversion	T4/T8 Ratio		
			before zoster (2–20 mo)	after zoster (1–6 mo)	after zoster (7–23 mo)
Mean	14	21	1.17	1.35	1.66
Range	4–27	9–47	0.77–1.6	0.43–2.1	0.64–2.3

had normal T4/T8 ratios at the time of viral infection and during the follow-up period (Table 1). In one patient, the T4/T8 ratio was low 7 months before and immediately after zoster, but became normal 18 months later. Delayed cutaneous hypersensitivity was detectable for at least four of seven antigens used in five of six patients tested. At present, neither AIDS nor AIDS-related complex has developed in any of these patients.

In conclusion, these observations show that herpes zoster infection may occur frequently in patients with hemophilia, as previously reported in other populations at risk for AIDS.[1-3,5,6] In our experience it was diagnosed in the months following seroconversion, when clinical and biologic symptoms of immune deficiency are not apparent, and did not herald the occurrence of AIDS.

F. Verroust, M.D.
D. Lemay, M.D.
Centre de Traitement de l'Hémophilie
78940 La Queue lez Yvelines, France Croix Rouge Française

Y. Laurian, M.D.
Centre de Traitement
94275 Kremlin Bicetre, France de l'Hémophilie

1. Rowland Payne CME, Farthing C, Byrom N, Staughton RCD. Shingles in seven homosexuals. Lancet 1984; 1:103-4.
2. Cone LA, Schiffman MA. Herpes zoster and the acquired immunodeficiency syndrome. Ann Intern Med 1984; 100:462.
3. Pinching AJ, McManus TJ, Jeffries DJ, et al. Studies of cellular immunity in male homosexuals in London. Lancet 1983; 2:126-30.
4. Daly HM, Scott GL. Fatal AIDS in a haemophiliac in the UK. Lancet 1983; 2:1190.
5. Murray HW, Hillman JK, Rubin BY, et al. Patients at risk for AIDS-related opportunistic infections: clinical manifestations and impaired gamma interferon production. N Engl J Med 1985; 313:1504-10.
6. Sandor E, Croxson TS, Millman A, Mildvan D. Herpes zoster ophthalmicus in patients at risk for AIDS. N Engl J Med 1984; 310:1118-9.

INDOMETHACIN AND ATRIAL NATRIURETIC PEPTIDE IN PSEUDO-BARTTER'S SYNDROME

To the Editor: Gordon et al.[1] (Aug. 14 issue) reported the effects of indomethacin on excessive secretion of plasma atrial natriuretic peptide (ANP) in Bartter's syndrome. We measured plasma ANP concentrations in a 27-year-old woman with pseudo-Bartter's syndrome due to furosemide abuse and a 38-year-old man with "true" Bartter's syndrome, in the control state and during treatment with indomethacin.

The woman had various symptoms of Bartter's syndrome, including hypokalemic hypochloremic alkalosis (potassium, 2.2 mmol per liter; chloride, 81 mmol per liter; pH 7.54), hyperactivity of the renin–angiotensin–aldosterone system (plasma renin activity, 24 ng per milliliter per hour [normal, 0.3 to 2.9]; plasma aldosterone concentration, 23.9 ng per deciliter [normal, 3.5 to 17.5] by radioimmunoassay), normotension (blood pressure, 96/65 mm Hg), pressor insensitivity of angiotensin II, and increased urinary levels of prostaglandin E (396.3 ng per day; normal mean ±SD, 317±22). A renal biopsy revealed juxtaglomerular hyperplasia. Although the patient repeatedly denied ingestion of diuretics, screening of urine samples by high-performance liquid chromatography gave consistently positive results for furosemide (37.5±7.5 mg per day). A final diagnosis of pseudo-Bartter's syndrome due to furosemide abuse was made. Plasma ANP was measured by direct radioimmunoassay, with use of rabbit anti-α-human ANP antibodies.[2] The plasma ANP level in this patient was above the normal range (316 and 338 mg per milliliter; normal mean ±SD, 188±16.3) and declined to 201 and 193 pg per milliliter on the 7th and 12th days of treatment with indomethacin (125 mg per day). After the cessation of indomethacin therapy, the plasma ANP levels increased to 436 pg per milliliter.

The values for plasma ANP in a man with Bartter's syndrome[3] were also above the normal range (291 and 221 pg per milliliter) two weeks after the cessation of treatment and decreased to 184 and 116 pg per milliliter on the 6th and 14th days of treatment with indomethacin (150 mg per day). At that time, indomethacin led to a significant reduction in the activity of the renin–angiotensin–aldosterone system and the urinary excretion of prostaglandin E.

We found high levels of plasma ANP in the control state and suppression during indomethacin treatment not only in patients with "true" Bartter's syndrome but also in those with pseudo-Bartter's syndrome. A volume-contracted state in these patients[4] would not explain the high ANP levels. Although the specific factor involved in this phenomenon is unknown, an increased sympathetic tone in Bartter's syndrome[5] may lead to release of ANP.[6] The long-term ingestion of furosemide may induce release of ANP; however, an excessive production of ANP in patients with Bartter's syndrome may be a secondary rather than a primary phenomenon.

Haruka Sasaki, M.D.
Makoto Okumura, M.D.
Fukuoka University
Fukuoka 814-01, Japan School of Medicine

Terukazu Kawasaki, M.D.
Kyushu University Institute
Fukuoka 816, Japan of Health Science

Kenji Kangawa, Ph.D.
Hisayuki Matsuo, Ph.D.
Miyazaki 889-16, Japan Miyazaki Medical College

1. Gordon RD, Tunny TJ, Klemm SA. Indomethacin and atrial natriuretic peptide in Bartter's syndrome. N Engl J Med 1986; 315:459.
2. Miyata A, Kangawa K, Toshimori T, Hatoh T, Matsuo H. Molecular forms of atrial natriuretic polypeptides in mammalian tissues and plasma. Biochem Biophys Res Commun 1985; 129:248-55.
3. Sasaki H, Kawasaki T, Okumura M, Asano T, Abe K, Arakawa K. Bartter's syndrome: effect of indomethacin on prostaglandins, urinary kallikrein, renin-angiotensin-aldosterone system, and the response to angiotensin II antagonist. Endocrinol Jpn 1980; 27:417-29.
4. Boer P, Koomans HA, Hené RJ, et al. Blood to interstitial fluid volume ratio in chronic hypokalaemic states. Eur J Clin Invest 1985; 15:276-80.
5. Güllner H-G, Gill JR Jr, Bartter FC, Lake CR, Lakatua DJ. Correction of increased sympathoadrenal activity in Bartter's syndrome by inhibition of prostaglandin synthesis. J Clin Endocrinol Metab 1980; 50:857-61.
6. Sonnenberg H, Veress AT. Cellular mechanism of release of atrial natriuretic factor. Biochem Biophys Res Commun 1984; 124:443-9.

HISTORY OF ELECTROCARDIOGRAPHY

To the Editor: In regard to Dr. Cooper's Occasional Note on the history of electrocardiography (Aug. 14 issue),* although his reference to Ader as originator of the string galvanometer is correct (Einthoven himself quoted Ader), I am not quite in agreement with Dr. Cooper's summing up of Einthoven's major contributions. The "application of existing techniques" and the "modification of instrument design" hardly describe the physical and technical innovations that produced an instrument of an unheard of (for that time) sensitivity and frequency response, fit to record without distortion the electrical activity of the heart. With some exaggeration, Einthoven's contribution may be compared with James Watt's invention of the steam engine, which was anticipated, both in principle and application, by Heron of Alexandria. I also must take exception to

*Cooper JK. Electrocardiography 100 years ago: origins, pioneers, and contributors. N Engl J Med 1986; 315:461-4.