Concise Communications

In conclusion, HECVs appear to be antigenically distinct from viruses of the Berne-Breda group and antigenically related to HCV OC43. The preliminary characterization of HECV polypeptides appears promising and suggests that more-extensive studies on HECV should be done to obtain further data on its biology and to further define its epidemiology and its pathological role.

Massimo Battaglia, Nilda Passarani, Angela Di Matteo, Giuseppe Gerna

Virus Laboratory, Institute of Infectious Diseases, University of Pavia, and the Istituto Ricerche e Cura a Carattere Scientifico Policlinico S. Matteo, Pavia; and the Consiglio Nazionale Ricerche, Institute of Experimental Medicine, Rome, Italy.

References

1. Garwes DJ. Coronavirus in animals. In: Tyrrell DAJ, Kapikian AZ, eds. Virus infections of the gastrointestinal tract. New York: Marcel Dekker, 1982: 315–59
2. MacNaughton MR, Davies HA. Human enteric coronaviruses: brief review. Arch Virol 1981; 70:301–13
3. Mortensen ML, Ray CG, Payne CM, Friedman AD, Minnich LL, Rousseau C. Coronavirus-like particles in human gastrointestinal disease. Am J Dis Child 1985; 139:928–34
4. Schnagl RD, Greco T, Morey F. Antibody prevalence to human enteric coronavirus-like particles and indications of antigenic differences between particles from different areas. Arch Virol 1986; 87:331–7
5. Gerna G, Passarani N, Battaglia M, Rondanelli EG. Human enteric coronaviruses: antigenic relationship to human coronavirus OC43 and possible etiologic role in viral gastroenteritis. J Infect Dis 1985; 151:796–803
6. Beards GM, Hall C, Green J, Fleweth TH, Lamouliatte F, Du Pasquier P. An enveloped virus in stools of children and adults with gastroenteritis that resembles the Breda virus of calves. Lancet 1984;1:1050–2
7. Sharpee RL, Mebus CA, Bass EP. Characterization of a calf diarrheal coronavirus. Am J Vet Res 1976;37:1031–41
8. Gerna G, Cereda PM, Revello MG, Cattaneo E, Battaglia M, Gerna MT. Antigenic and biological relationships between human coronavirus OC43 and neonatal calf diarrhea coronavirus. J Gen Virol 1981;54:91–102
9. Weiss M, Steck F, Horzinek MC. Purification and partial characterization of a new enveloped RNA virus (Berne virus). J Gen Virol 1983;64:1849–58
10. Woode GN, Reed DE, Runnels PL, Herrig MA, Hill HT. Studies with an unclassified virus isolated from diarrheic calves. Vet Microbiol 1982;7:221–40
11. Laemmli UK. Cleavage of structural proteins during the assembly of the head of bacteriophage T4. Nature 1970; 227:680–5
12. Hawkes R, Niday E, Gordon J. A dot-immunobinding assay for monoclonal and other antibodies. Anal Biochem 1982; 119:142–7
13. Laporte J, Bobulesco P. Growth of human and canine enteric coronaviruses in a highly susceptible cell line: HRT 18. In: Perspectives in virology. Pollard M, ed. New York: Arliss, 1981;11:189–93
14. Resta S, Luby JP, Rosenfeld CR, Siegel JD. Isolation and propagation of a human enteric coronavirus. Science 1985;229:978–81
15. Horzinek MC, Ederveen J, Weiss M. The nucleocapsid of Berne virus. J Gen Virol 1985;66:1287–96

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 155, NO. 1 • JANUARY 1987
© 1987 by The University of Chicago. All rights reserved. 0022-1899/87/5501-0020$01.00

Fulminant Necrotizing Fasciitis and Nonsteroidal Anti-Inflammatory Drugs

Necrotizing fasciitis is a distinct clinical entity usually caused by *Streptococcus pyogenes*. Although accurately defined by Wilson [1] in 1952, the disease is often unrecognized. It is potentially fatal, especially when it becomes fulminant. Even though the host factors and the infectious agent responsible for initiating and spreading necrotizing fasciitis have been identified, the pathogenesis of the disease is unclear. After examining all cases of necrotizing fasciitis occurring in the intensive medical care unit of this hospital between 1983 and 1985, we found that five of seven had a fulminant evolution. This fulminant evolution apparently resulted from nonsteroidal anti-inflammatory therapy.

Patients

We included only those patients who had necrotizing fasciitis that fulfilled strict criteria: a soft-tissue infection involving the superficial fascia and resulting in extensive undermining of surrounding tissues. The infection was considered fulminant when the delay between the first functional and local signs and surgery did not exceed six days (table 1).

All patients had previously been healthy, and none had a predisposing condition—previous surgery, chronic ve-
Necrotizing fasciitis is a relatively rare disease that is often difficult to diagnose during the early stages, when the skin is apparently still normal. However, the outcome of this potentially fatal disease is largely influenced by early recognition and prompt therapy based upon antibiotics and surgery [2]. Stamenkovic and Lew [3] recently suggested that rapid performance of frozen-section soft-tissue biopsy early in the evolution of a suspect lesion may provide a definitive and life-saving diagnosis. In our patients, as in many others, necrotizing fasciitis was not initially suspected; therefore, no biopsy was performed, and treatments were prescribed for conditions such as arthritis or phlebitis.

Necrotizing fasciitis usually requires both a specific organism and an underlying debilitating disease [4, 5]. Although group A β-hemolytic Streptococcus has long been recognized as the agent of this infection, recent reports [6, 7] indicated that necrotizing fasciitis can be caused by a variety of bacteria. In patient 6, the agent was the gram-negative bacillus Serratia marcescens. The hypothesis [8] that production of hemolysins, fibrinolysins, and hyal-
Activation of infection in debilitated patients treated with anti-inflammatory drugs has been reported [11]. Observing ones isa convincing argument to establish the deleterious consequences, but the shorter delays in our study than in previous reports of such drugs. The action of bacterial toxins, together with the effect of bacterial kinases, is further enhanced by the general reduction in host defense that occurs during the postoperative period, by preexisting systemic diseases such as diabetes and malnutrition, or by conditions requiring prolonged treatment with steroids [2, 8]. However, all five of our patients were previously healthy, and no underlying disease could be found. They were all treated with non-steroidal anti-inflammatory drugs just after diagnosis of the disease. A marked acceleration of the evolution was then observed in all patients, although no other drug was given during the early stages. Necrotizing fasciitis is generally considered a fulminating disease, but the delay between first signs and surgical treatment is usually more than six days. In Freeman's study [7], most patients with necrotizing fasciitis had symptoms of disease for four days to three weeks before presenting at the hospital; the most severe infections were in patients who waited 10 to 14 days before going to the hospital. Almost all the patients had an underlying disease, and none received immunodepressive drugs [7]. In Hammar's study [4], patients with necrotizing fasciitis had been ill for four to five days before admission to the hospital, and all but two developed gangrenous ulcers that appeared at least one week after the beginning of the disease. Almost all patients presented with other diseases, but none received oral steroids or other immunodepressive drugs. In Leppard's study [9], patients with necrotizing fasciitis were divided into two groups: In the first group, the eight patients did not receive any antibiotics before admission and the evolution was considered fulminating (but the time between presentation and diagnosis was not mentioned); in the second group, the five patients had been previously treated with antibiotics, and an interval of several weeks passed before the skin became necrotic. No patients in either group received anti-inflammatory drugs. In our intensive care unit, we observed that the two non-fulminating cases of necrotizing fasciitis occurred in patients who did not receive non-steroidal anti-inflammatory drugs or antibiotics. Some cases of necrotizing fasciitis have been recently reported [10] in patients given one or several steroid and non-steroidal anti-inflammatory drugs; the delay from triggering event to overt necrotizing fasciitis and referral to hospital was from four to ten days. The limited number of patients we observed does not warrant a statistical study to affirm that non-steroidal anti-inflammatory drugs were directly responsible for a fulminating evolution in necrotizing fasciitis, but the shorter delays in our study than in previous ones is a convincing argument to establish the deleterious role of such drugs.

The mechanism can be deduced from previous studies. Activation of infection in debilitated patients treated with anti-inflammatory drugs has been reported [11]. Observations that granulocyte-mediated functions—chemotaxis, phagocytosis, and bactericidal activity—are impaired in vitro by nonsteroidal drugs have been supported by decreased in vitro bactericidal activity and reduced activation of Staphylococcus aureus and group B Streptococcus by granulocytes incubated with phenylbutazone [12]. Inhibition of granulocyte adherence has been demonstrated to be secondary to the anti-inflammatory effect of aspirin [13].

In a recent case report [14], a life-threatening case of necrotizing fasciitis occurred in a 23-year-old, previously healthy woman who took six diflunisal tablets over a 24-hr period after a minor injury; lymphocyte function and lymphocyte transformation were severely depressed. The authors suggested that these troubles represented an adverse reaction to the drug that contributed to the severe sepsis that developed. This patient had nearly normal levels of serum immunoglobulins, as did three of our five patients. It appears that the possible deleterious effect of non-steroidal anti-inflammatory drugs results from deep and quick depression of cellular defense.

Our observations suggest that non-steroidal anti-inflammatory drugs should not be used for apparently benign inflammatory cutaneous lesions when infection cannot be avoided.

**Concise Communications**

**References**

1. Wilson B. Necrotizing fasciitis. Am Surg 1952;18:416-31
2. Ledingham IMcA, Tehrani MA. Diagnosis, clinical course and treatment of acute dermal gangrene. Br J Surg 1975;62:364-72
3. Stamenkovic I, Lew PD. Early recognition of potentially fatal necrotizing fasciitis: the use of frozen-section biopsy. N Engl J Med 1984;310:1689-93
4. Hammar H, Wanger L. Erysipelas and necrotizing fasciitis. Br J Dermatologica 1977;96:409-19
5. Janevicus RV, Hann SE, Batt MD. Necrotizing fasciitis. Surg Gynecol Obstet 1982;154:97-102
6. Giuliano A, Lewis F, Hadley K, Blaisdell FW. Bacteriology of necrotizing fasciitis. Am J Surg 1977;134:52-7
7. Freeman HP, Oluwole SF, Ganepola GAP, Dy E. Necrotizing fasciitis. Am J Surg 1981;142:377-83
8. Tehrani MA, Ledingham IMcA. Necrotizing fasciitis. Postgrad Med J 1977;53:237-42
9. Leppard BJ, Seal DV. The value of bacteriology and serology in the diagnosis of necrotizing fasciitis. Br J Dermatol 1983;109:37-44
10. Brun-Buisson CJL, Saada M, Trunet P, Rapin M, Roujeau JC, Revuz J. Haemolytic streptococcal gangrene and non-steroidal anti-inflammatory drugs. Br Med J [Clin Res] 1985;290:1786
The Plaque-Neutralization Test as a Measure of Prior Exposure to Measles Virus

It has been noted that antibody levels measured by HAI decline over time after either measles or measles vaccination [1]. Some persons may lose all detectable HAI antibody. The immune status of such persons has been unclear.

In the spring of 1982, a comprehensive statewide cluster-sample serosurvey of 6th, 10th, and 12th grade schoolchildren in Massachusetts was undertaken [2]. Of the 1,871 participants, 98.1% had a history of measles vaccination. Seroprevalence levels, determined by using a standard HAI technique, were 86.8% and ranged from 84.7% in 10th grade students to a high of 89.5% in 6th grade students. Students who were seronegative by HAI were retested using a sensitive plaque-neutralization test (PNT). Seroprevalence levels rose to 98.6%, with a low of 97.7% in 6th graders and a high of 99.1% in 10th graders.

These results were difficult to interpret because the clinical significance of neutralizing antibody detected by the sensitive PNT was unclear. To evaluate the meaning of plaque-neutralizing (PN) antibody in the absence of HAI antibody, we undertook a study (in the spring of 1983) to correlate the type of immune response to measles vaccination with the prior levels of PN antibody. We had the following objectives: (1) to determine whether the absence of detectable PN antibodies before vaccination was associated with a primary immune response after vaccination, as determined by the presence of detectable levels of IgM; (2) to determine whether the presence of detectable PN antibodies before vaccination would result in a secondary immune response, as determined by the absence of IgM; and (3) to determine whether the level of PN antibodies before vaccination correlated with the development of a fourfold or greater rise in titers of antibody after vaccination.

Subjects and Methods

All students who had participated in the previous serosurvey when in the 6th or 10th grade and who did not have detectable HAI antibody at a 1:5 dilution were eligible for the study. The greatest efforts were made to enroll those students with the lowest titers of PN antibodies (<20). After obtaining informed consent, students received the measles, mumps, and rubella vaccine. Serum was obtained for analysis of HAI and PN antibodies to measles virus ~2.5–3.5 weeks after vaccination. IgM antibodies were measured in sera by using both techniques on a subsample of participants chosen to include all students with prevaccination titers of PN antibodies <100.

HAI antibodies were measured, starting at a 1:5 dilution, with a standard method using Tween ether-treated antigen, sera inactivated at 56°C to remove nonspecific inhibitors, and vervet monkey erythrocytes as indicator cells [3].

PN antibodies were measured, starting at a 1:4 dilution, in Vero cell monolayer cultures by using a low-passage Edmonston strain of measles virus and the conventional method previously published by our group [4]. The titer of PN antibody was defined as the serum dilution that would reduce the number of plaques by 50%. Levels of IgM antibody to measles virus were determined by each of the above assays from the 19S serum fractions obtained by ultracentrifugation of the serum on sucrose density gra-

Received for publication 2 April 1986, and in revised form 25 July 1986.

This work was presented in part at the 25th Interscience Conference on Antimicrobial Agents and Chemotherapy, held 29 September–2 October 1985 in Minneapolis.

Informed consent was obtained from the patients or from their parents or guardians, and the guidelines for human experimentation of the U.S. Department of Health and Human Services were followed in the conduct of this research.

We thank Dr. Nicholas J. Fiumara, State Epidemiologist in Massachusetts at the time of the study; John Narkunas for coordinating the vaccination study; Mike Baltier and Dr. George Waterman for guidance and support; Anna Hall and Karen Sanderlin for performing the HAI assay and for fractionating the sera; the epidemiologists and nurses of the Massachusetts Department of Public Health for conducting the study; and Connie Keith and staff for preparing the manuscript.

Please address requests for reprints to the Technical Information Services (WAO), Center for Prevention Services, Centers for Disease Control, Atlanta, Georgia 30333.