Epidemic Hemorrhagic Fever in Argentina

D. J. GREENWAY, H. R. RUGIERO, A. S. PARODI, M. FRIGERIO, E. RIVERO, J. M. de la BARRERA, F. GARZON, M. BOXACA, N. METTLER, L. B. de GUERRERO, and N. NOTA

A DISEASE of unknown etiology appeared a few years ago in the northwestern part of the Province of Buenos Aires. The clinical aspects were first described by Arribalzaga (*1*) and later by Duva (*2*), who suggested that it may be of leptospiral origin. The disease appeared again in 1958, and in May of that year we went to the city of Junín to study its clinical and etiological features. This study was the first to provide evidence of the virological nature of the causative agent (*3*). Later, Margni and co-workers, on the basis of little evidence, presented the opinion that poisoning by dieldrin, aldrin, or other products, might be an auxiliary factor (*4*).

At a special meeting held in the University of Buenos Aires on December 19, 1958, we presented a full report of our work with the disease, defining it as new in Argentina and giving additional evidence of its virus etiology (*5,6*). This work has since been confirmed by other investigators (*7*).

The clinical descriptions, which we had previously published, were recently confirmed by studies of the disease produced by inoculation of human volunteers. This research was conducted by two groups, working independently, and their reports appeared at about the same time (*7,8*).

Clinical Characteristics

Argentine epidemic hemorrhagic fever is an infectious disease, attacking principally male rural laborers with a characteristic symptom complex—renal, nervous, cardiovascular, and hematic. The disease lasts from 10 to 15 days and may end in recovery without sequellae or in the patient's death (*9,10*).

The onset of the disease is usually gradual, the symptoms making their appearance insidiously. There is general discomfort, asthenia, cephalea, myalgia, anorexia, saburral tongue, vomiting, alternations in movements, especially in gait, and sometimes slight strabismus. Some cases show palatal enanthema, but exanthema is not seen. The pulse is rapid or normal, the blood pressure tends to be low, and the fever may be moderate or high (40° C.).

Three to five days after onset the symptoms become accentuated. There is marked dehydration, exanthema, and discrete congestion involving the thorax and flanks which may later show petechiae. In some cases there is epistaxis, hematemesis, melena, hematuria, and gingival hemorrhages. The Rumpel-Leede phenomenon is usually positive.

Respiratory symptoms are rare and X-rays are negative. There may be a cough and moist stertorous breathing. The hypotension becomes quite marked, sometimes to the point of collapse.

Abdominal palpation reveals epigastric sensitivity and sometimes a slightly enlarged liver. In some cases there is icterus. Oliguria or anuria is sometimes seen. Nervous symptoms include cutaneous hyperesthesia, muscular spasms, and spasms of the glottis. The patient may become stuporous or delirious.

In cases with favorable evolution, the fever drops rapidly; there is progressive disappearance of the urinary symptoms; and the general condition gradually improves. The patient

The authors are in the department of microbiology and parasitology of the medical school of the University of Buenos Aires, except Dr. Rugiero, who is in the school's department of infectious diseases.

commences to urinate abundantly but continues to eliminate a large amount of albumen.

In the very severe cases, the patients go into coma of the uremic or encephalopathic type, and die in collapse.

Laboratory Findings

According to findings in the laboratory, the blood picture is characterized by leukopenia, sometimes quite accentuated (400 leukocytes per milliliter), with preservation of normal percentages in the differential count except for the absence of eosinophiles (*9,11*). There is a marked reduction in platelets, which may reach 20,000 to 30,000 per milliliter. The red cell of the bone marrow reveals hypofunction during convalescence.

Blood chemical findings (glucose, creatinine, bilirubin) are generally normal. Liver function tests, thymol and Hanger, also give normal results. The urea usually increases to 0.60 and to 1.00 precent (urease test). Sodium and calcium levels are low within normal range. Total lipids, cholesterol, and esters decrease, especially in acute cases. Proteins keep within normal values, with slight hypoalbuminemia.

There is moderate albuminuria with marked quantities of cellular and granular casts, and characteristically vacuolated epithelial cells. In many cases with favorable progress, we have observed intense and brief albuminuria for 1 or 2 days toward the end of the clinical phase of the disease.

Postmortem Findings

The pathology of the disease is characterized by injury to the vascular system which is demonstrated by interstitial edema and degeneration of organs, especially the kidneys and liver.

Epithelial cells of the kidney show an indefinite border and granulous cytoplasm, with alteration of the nucleus. Hyaline and blood casts are seen in the tubular lumen. Intratubular hemorrhages are noted. In the epithelial cells of the convoluted tubules, a granular hyaline appearance is observed. The capillaries of the glomeruli are completely filled with blood.

Liver pathology consists of a granular degeneration of the cytoplasm in the hepatic cells. The central vein is dilated, and sinusoids contain a deposit of bile pigment. Edema is observed in the connective tissue surrounding the dilated central vein, as well as lymphocytic infiltration in some of the Kierman spaces.

In the brain there is congestion with marked meningial edema with some mononuclear infiltration (*13*).

Microbiological Findings

The search for the causative agent included two different microbiological approaches (*3,8,12*). In one field of research, bacteria and fungi were considered, while in the other, viruses and rickettsiae were investigated. Negative findings proved this disease not to be of bacterial (including leptospiral) or fungal origin (*12*). Infectious material was inoculated in mice, rats, guinea pigs, hamsters, pigs, monkeys, embryonated eggs, and tissue culture of monkey kidney, HeLa, and KB cells. Only guinea pigs were infected, as evidenced by illness and death within 15–20 days after inoculation. Necropsy showed the following pathological picture: petechial hemorrhages in the subcutaneous tissue, hemorrhagic abdominal lymph glands, intestines empty with small hemorrhages in the mucosa, hemorrhagic adrenal gland, and general congestion of internal organs. These animals were invariably negative for bacteria and fungi.

A suspension of organs from the infected guinea pigs was inoculated intracerebrally into white suckling mice 24 to 48 hours old. Consistently on the ninth day, disturbance in locomotion, muscular contractions, and, occasionally, paralysis were noted.

Further investigative work proved that the same symptoms could be produced in suckling mice by direct inoculation of original source material. Guinea pigs were susceptible by subcutaneous intraperitoneal and intracerebral routes, but suckling mice by the intracerebral and subcutaneous only. Suckling rats were found susceptible to intracerebral inoculation with brain from infected suckling mice.

As a result of this work, we have now three virus isolates, each from a different patient.

The first from blood; the second from a suspension of viscera: brain, liver, spleen, and kidney; and the third from urine containing large amounts of blood.

Tissue culture did not propagate viral growth. The hemagglutination test was negative at different pH adjustments using chicken red blood cells from day-old chicks and adults. The virus is inactivated at 56° C., for 30 minutes, and also by ether and by trypsin.

The relation of the isolated virus with the disease was demonstrated by rise in antibody titer (complement fixation and neutralization tests). This relation was also demonstrated by the inoculation of a human volunteer with infected material, thus reproducing the disease, with subsequent isolation of the virus from his blood in the acute stage of the disease. Serologic tests were confirmatory in this case.

Epidemiology

Most of the patients are rural laborers, employed in the corn (maize) harvest beginning in April and ending in July or August. Some patients have not been engaged in such activity, but have had some contact with the cornfields. The occupations of 73 patients seen by us during the 1958 epidemic are the following:

Occupation	*Number*
Corn harvester	37
Rural worker (general)	11
Housewife (rural)	5
Housewife (urban)	1
Dairy-farm worker	5
Farm supervisor	3
Cattle driver	2
Rural mechanic	2
Tractor driver	2
Public road worker	1
Veterinarian	1
Entomologist	1
Rat exterminator	1
Hobo (tramp)	1
Total	73

The sex and age of the same group of patients are presented in the table. There is no evidence of interhuman transmission of the infection. The case-fatality rate in that group was 23.28 percent (*9*).

The field where the patients worked contained large numbers of field mice (*Hesperomys laucha laucha*), which are heavily parasitized with blood-sucking mites. The nests of these rodents are also heavily infested with the mites. It is interesting to note, however, that no unusual morbidity or mortality in either wild or domestic animals was observed in the district during the course of the epidemic. There is one report (*14*) of recovery of the virus from arthropods from the epidemic district, but this work awaits confirmation.

Sex and age distribution of 73 patients with Argentine epidemic hemorrhagic fever, 1958

Age group (years)	Recovered cases		Fatal cases		Total
	Male	Female	Male	Female	
10–20	10	3	1	0	14
21–30	13	1	6	0	20
31–40	10	3	3	0	16
41–50	7	2	4	0	13
51–60	4	2	1	0	7
61–70	1	0	2	0	3
Total	45	11	17	0	73

Subsequent to the submission of this paper for publication two others appeared with further information on the subject. In one, the authors announced the isolation of the virus from field rodents: several times from *Mus musculus*, once from *Hesperomys laucha*, and once from *Akodon arenicola*. Tests with *Oryzomys flavescens* and *Rattus* sp. were negative (Parodi and others, Prensa Med. Arg. 46: 555, 1959). In the other paper, the authors demonstrated the neutralization in vivo of the virus with the immune serum of Russian spring-summer encephalitis (Parodi and others, Rev. Soc. Arg. Biol. In press).

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