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ACUTE HEMORRHAGIC CONJUNCTIVITIS EPIDEMIC IN COLON, REPUBLIC OF PANAMA

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Acute hemorrhagic conjunctivitis has caused numerous outbreaks throughout Africa and Asia since it was first recognized in 1969 but did not involve the New World until 1981. This unprecedented outbreak reached Colon, Panama during August 1981 and by October 8,401 cases had been reported (14% of Colon's population). In October the Gorgas Memorial Laboratory and Ministry of Health conducted a survey in Colon to collect descriptive data on household living units, epidemiologic and clinical data from residents, and venous blood from all residents one year or older. The survey sampled 127 households and interviewed 608 people (1% of Colon's homes and 1% of the population). Overall 336 (55%) study subjects recalled having conjunctivitis. Disease rates differed according to residence; poor sectors of the city had 67% attack rates, lower class 52%, middle class 34%, and upper class 13%. Within each sector adults were more likely than children to be index cases, and communal bathrooms and household crowding were the most important risk factors for acute hemorrhagic conjunctivitis. Between 4–20% of people denying acute conjunctivitis had antibody to enterovirus 70 and may represent asymptomatic cases.

conjunctivitis; disease outbreaks; enterovirus infections; eye diseases; serology

Acute hemorrhagic conjunctivitis is a highly contagious ocular infection with a short incubation period (24–48 hours) and rapid evolution to involve both eyes; it is characterized by ocular pain and itching, palpebral edema and conjunctival hemorrhage (1). The disease is usually self-limited and resolves within a week. Kono (2) has written an excellent review of acute hemorrhagic conjunctivitis epidemiology before 1975. Epidemic acute hemorrhagic conjunctivitis first occurred during June 1969 in a suburb of Accra, Ghana. It spread northward and westward throughout West Africa

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and reached North Africa by December 1970. Small outbreaks also began in Djakarta, Bali, and Vietnam in mid-1969 and reached major proportions by 1970. By 1971, acute hemorrhagic conjunctivitis involved all South East Asia and extended to India where more than a million cases were estimated from Bombay and Calcutta. Japan experienced acute hemorrhagic conjunctivitis between 1971–1972; at this same time cases were reported from the Middle East (Bahrein and Saudi Arabia), and small nosocomially related outbreaks occurred throughout Europe (London, Rotterdam, Moscow, Yugoslavia). Major acute hemorrhagic conjunctivitis epidemics involved Singapore, Taiwan, Thailand, and India during 1974 and 1975.

Acute hemorrhagic conjunctivitis was a new clinical entity caused by a previously unknown virus, enterovirus 70 (3, 4). Enterovirus 70 appeared to be the major etiologic agent during the African and Asian acute hemorrhagic conjunctivitis outbreaks but adeno 11 and coxsackie A-24 viruses were also isolated from patients during epidemics (5). A post-acute hemorrhagic conjunctivitis radiculomyelitis syndrome has been described (6) and enterovirus 70 is neurovirulent for monkeys, under experimental conditions (7).

Millions of enterovirus 70 conjunctivitis cases occurred throughout the world for more than 10 years but remarkably the pandemic did not spread to the Americas. Between January and June 1981, extensive acute hemorrhagic conjunctivitis epidemics involved Nigeria, Pakistan, and India. In February 1981, acute hemorrhagic conjunctivitis was finally documented from the New World. The first cases occurred in Macapa, Brazil; the epidemic rapidly involved the entire Caribbean Basin including Belem, Manaus, Surinam, Guyana, Trinidad-Tobago, Columbia, Panama, Costa Rica, Honduras, Belize, and Cuba (8). By September 1981 the acute hemorrhagic conjunctivitis pandemic reached Florida (9). Enterovirus 70 was identified as the etiologic agent; patients from Brazil and Honduras seroconverted to enterovirus 70 and it was isolated from a patient in Key West, Florida (10).

In the Republic of Panama, acute hemorrhagic conjunctivitis began in Colon, Panama's second largest city and the Panama Canal's Atlantic terminus. The first officially reported acute hemorrhagic conjunctivitis case occurred the first week of August 1981 and by October 8,401 cases had been reported from Colon. The outbreak spread across the isthmus to Panama City and then continued westward to the Costa Rican border. By December 1981, 30,000 cases (primarily in adults) had occurred throughout Panama (8). We did not isolate enterovirus 70 during the Panama epidemic even though many specimens were tested but, in a tube neutralization assay, several acute hemorrhagic conjunctivitis patients seroconverted to enterovirus 70.

Although acute hemorrhagic conjunctivitis involved all Panama's major population centers, the epidemic was most extensive in Colon where 9,614 reported cases between August and December 1981 represented an overall 14 per cent attack rate. To ascertain information on acute hemorrhagic conjunctivitis introduction and spread within families, measure utilization of public health services, determine and compare clinical attack rates with enterovirus 70 infection rates, we conducted a detailed seroepidemiologic study in Colon City on October 3 and 4, 1981.

Materials and methods

Study population

Colon City occupies a Peninsula in Limon Bay, the Caribbean anchorage for the Panama Canal. It is politically divided by 9th Street into Barrio Norte and Barrio Sur. The 1980 census enumerated almost 60,000 inhabitants, just over half lived in Barrio Norte which is largely residential and the remainder in Barrio Sur which contains an extensive commercial area.

Our seroepidemiologic study was intended to provide a representative sample

of residential Colon; it encompassed all Barrio Norte and the poorest areas of Barrio Sur. We conducted the survey over a single weekend to insure that most people would be at home. In order to maximize recruitment, major radio stations announced the survey throughout the preceding Thursday and Friday. Three study teams of five people each conducted the survey; a team was responsible for a two-block-wide transect of Colon. Because of time and logistic limitations, the study population was not selected in a formal randomized fashion; rather, study teams selected and surveyed one or two representative dwellings per block (figure 1).

Two interviewers worked at each selected dwelling. If a residence was unoccupied, the head of household could not be found, or the family refused to participate the next closest household was selected. If a responsible adult was not present the team attempted to ascertain his (her) whereabouts and to locate him (her); verbal informed consent was obtained. Fewer than 1 per cent of subjects refused to participate. Information describing each dwelling was collected and transcribed to standard forms. Epidemiologic and clinical data from each household resident were obtained by interview and entered onto standardized forms. After the interview the study team collected a 10-ml venous blood specimen from all subjects older than one year, upon consent of the adult participants for themselves and their children. Interviewers arranged to return, interview and bleed family members who were not at home. If a resident could not be directly interviewed we interviewed a responsible surrogate.

Survey data

Information to describe each dwelling included address, the type of house, individual or communal toilet facilities, number of rooms, number of inhabitants, number of persons sleeping per room, and monthly family income.

Epidemiologic data concerning household residents included age, sex, race, occupation, whether they had had acute hemorrhagic conjunctivitis and if so the date of onset, symptoms and their duration, days absent from work or school, and type of treatment. An acute hemorrhagic conjunctivitis case was defined as having one major symptom or two minor symptoms lasting at least 24 hours. Major symptoms were: tearing or mucoserous discharge, ocular hyperemia, ocular hemorrhage, and palpebral edema; minor symptoms included ocular pain, itching, foreign body sensation, and photophobia. All information was recorded on standardized forms and maintained on interactive computer files using the CCSS data processing system (11).

Laboratory methods

All blood specimens were collected into vacutainers which were held on wet ice; sera were separated the next day, aliquoted, and stored at −20 C until tested. Antibody to enterovirus 70 was determined using a tube neutralization assay; approximately 100 tissue culture infective doses of enterovirus 70 were mixed with diluted serum, incubated two hours at 34 C and then transferred to fetal tonsil fibroblast cultures. Tube cultures were read at seven days after inoculation and the readers were unaware of subjects' clinical classification. The highest serum dilution which completely prevented cytopathic effects was considered endpoint. Prototype enterovirus 70 (J670/71) was kindly provided by the Centers for Disease Control.

Pre-epidemic serologic survey

In June 1978 the Ministry of Health and Gorgas Memorial Laboratory conducted a random serologic survey of the Republic of Panama; the purpose was to assess immunity to vaccinable diseases such as polio, measles, diphtheria, tetanus, and pertussis. The survey sample from metropolitan Colon was picked using standard methods (12) to randomly select census tracts in Barrio Norte and Barrio Sur and then randomly select households within the chosen census tracts so that by surveying all household

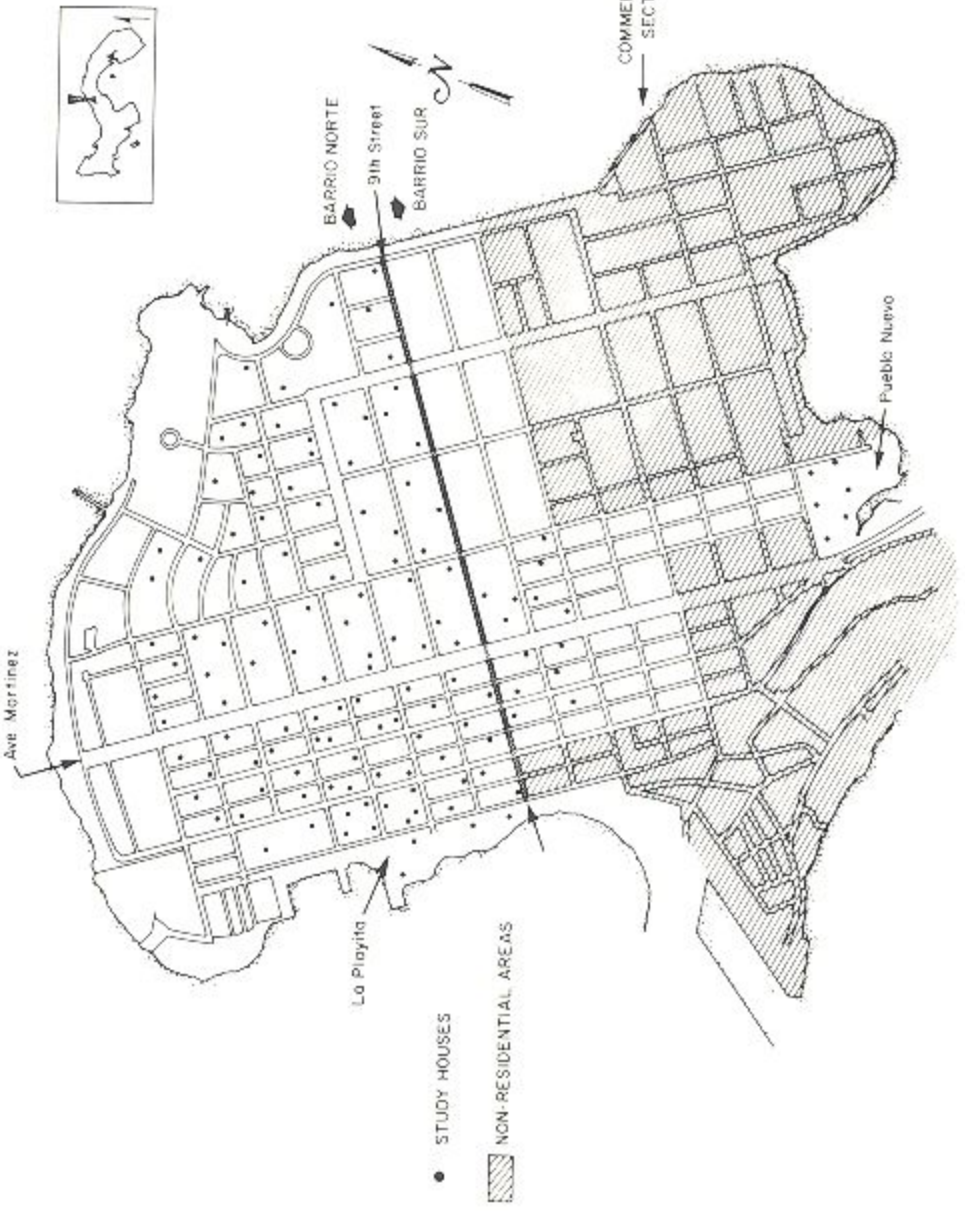

FIGURE 1. Study houses, acute hemorrhagic conjunctivitis epidemic, Colon, 1981.

members approximately 1 per cent of the total population would be included. The survey obtained 277 sera or 0.6 per cent of the estimated 1978 Colon population and these were assayed for antibody to enterovirus 70 using the methods described above.

RESULTS

Overall we sampled 127 Colon households (figure 1), or 1.2 per cent of known residences, and obtained epidemiologic data concerning 608 inhabitants, 1.6 per cent of the 1980 census population. The study population's age and sex composition was similar to that enumerated during the 1980 census, but since the sample was determined geographically we undersampled the lower socioeconomic population concentrated to the west of Avenida Martinez.

Overall 336 of 608 (55 per cent) interviewed people had acute hemorrhagic conjunctivitis and the epidemic curve was similar to that estimated by the Ministry of Health (figure 2). Six per cent of the study population had consulted a government clinic because of acute hemorrhagic conjunctivitis. The earliest case occurred June 14, but all the remainder dated from August 2 and the epidemic peaked in mid-September. Twenty four cases occurred within five days of interview. Overall male and female attack rates were similar, 54 per cent and 57 per cent, respectively; age-specific attack rates showed that school-age children between five and 14 years of age had the highest risk for developing disease while people older than 50 were less frequently ill (table 1).

A significant geographic gradient existed with respect to acute hemorrhagic conjunctivitis occurrence, with the greatest incidence in the western sectors (figure 3). This reflected a similar socioeconomic gradient; 46 per cent of the families from the poor and low class sectors had average monthly household incomes less than $200 and none had incomes over $1,000; no family in the middle and upper class sectors earned less than $200 per month and 28 per cent had monthly incomes greater than $1,000; other

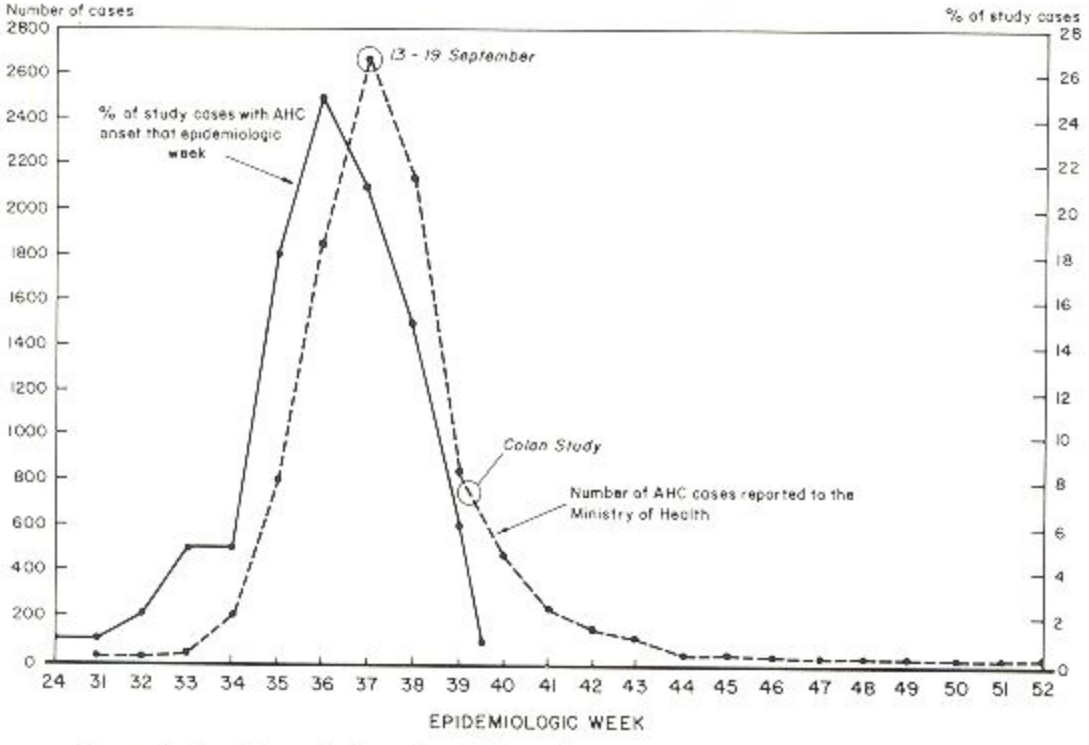

FIGURE 2. Acute hemorrhagic conjunctivitis (AHC) cases by week of occurrence, Colon, 1981.

TABLE 1

Age- and sex-specific acute hemorrhagic conjunctivitis attack rates, Colon, 1981

	Age in years*							
	0–4	5–9	10–14	15–19	20–29	30–39	40–49	50+
Male†	14/26	21/34	31/40	18/35	28/53	17/33	7/16	13/41
	54%	62%	78%	51%	53%	52%	44%	32%
Female†	11/27	30/45	32/43	21/38	35/60	22/32	15/28	16/48
	44%	67%	74%	55%	58%	69%	54%	33%

* Age was unknown for nine people.

† Number of cases/number of people queried; per cent of age group reporting acute hemorrhagic conjunctivitis.

TABLE 2

Acute hemorrhagic conjunctivitis attack rates by average monthly income and sector of residence, Colon, 1981

Income*	Sector								χ^2	df	*p* value
	Poor		Low class		Middle class		Upper class				
	No.†	%‡	No.	%	No.	%	No.	%			
<$75	25/29	86	0/2	0	0		0				
$75–200	95/135	70	15/27	56	0/7	0	0		15.8	2	<0.001
$201–1,000	130/212	61	17/32	53	25/82	30	5/27	19	34.2	3	<0.001
>$1,000	0		0		15/32	47	0/13	0	9.1	1	<0.05
χ^2	8.5				6.5						
df	2				2						
p value	<0.025				<0.05						

* Average monthly household income was unknown for 15 people.

† Number of cases/number of people queried.

‡ Per cent of queried population with clinical disease.

factors such as age or condition of houses and housing density also differed markedly between sectors.

Since many factors varied with sector of residence we controlled for this in risk factor analysis. For example, acute hemorrhagic conjunctivitis was more common overall among blacks and mestizos, with 61 per cent having had the disease, than among whites with a 24 per cent attack rate or Orientals with a 5 per cent attack rate, but race-specific attack rates did not differ when controlled by residence. Average monthly household income had an inverse relation to disease risk and risk varied significantly by sector of residence (table 2).

Crowding was the most important risk factor for acute hemorrhagic conjunctivitis and the effects of crowding were influenced by type of residence. We quantified crowding by ascertaining the number of people sleeping per room and whether the family had a private bathroom or shared communal sanitary facilities with other families. All households in the middle and upper class sectors used private bathrooms and attack rates in people with private bathrooms were similar (30–36 per cent) in poor, low and middle class sectors. Within the poor and low class sectors, people using communal bathrooms had significantly greater acute hemorrhagic conjunctivitis attack rates than those with private bathrooms, and within these sectors incidence also increased significantly with increasing numbers of people per sleeping room (table 3).

We also collected data to describe intrafamily transmission. We defined an index case as the first person with acute hemorrhagic conjunctivitis in a family. Essentially all family members were at equal risk

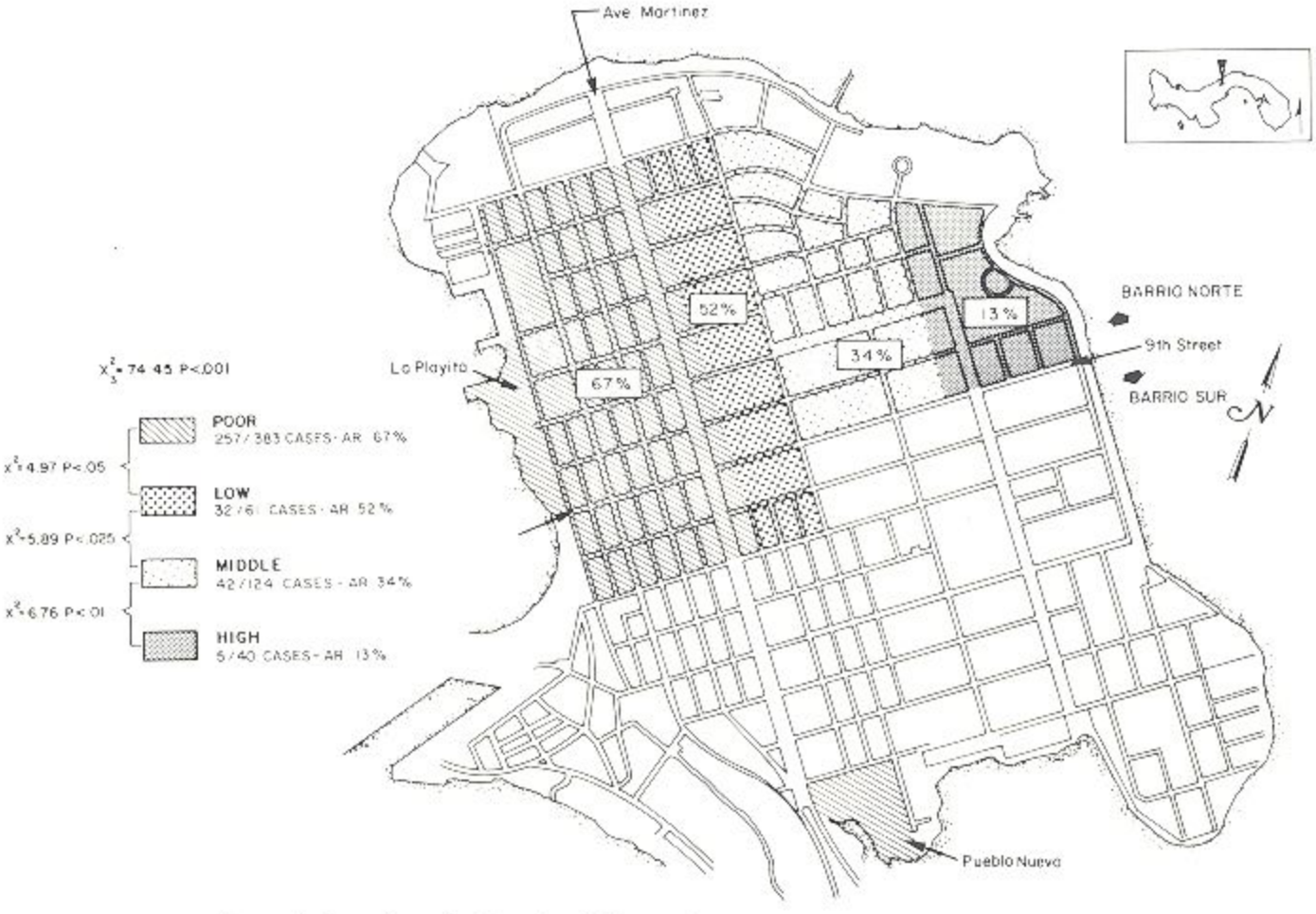

FIGURE 3. Acute hemorrhagic conjunctivitis attack rates (AR) by sector of residence, Colon, 1981.

TABLE 3

Acute hemorrhagic conjunctivitis attack rates according to communal or individual bathroom and household crowding for residents of poor and low sectors, Colon, 1981

No. sleeping	Type of bathroom: Communal No.	%	Individual No.	%	χ^2	df	*p* value
≤2 per room	20/35	57	12/37	32	4.5	1	<0.05
3–5 per room	66/99	67	15/43	35	12.4	1	<0.001
>5 per room	165/201	82	11/26	42	20.9	1	<0.001
χ^2	15.0						
df	2						
p value	<0.001						

of being the index case and once conjunctivitis occurred in a family everyone was at essentially equal risk for becoming a secondary case.

The ocular symptom complex was typical of other acute hemorrhagic conjunctivitis epidemics. Eighty per cent of cases reported tearing, itching and mucoserous discharge; 76 per cent had foreign body sensation; 86 per cent of cases described conjunctival injection but only 27 per cent had ocular hemorrhages. Fever, headache, or gastrointestinal problems were reported in 15–20 per cent of cases and 8 per cent described mild transient musculoskeletal dysfunctions.

Acute hemorrhagic conjunctivitis was a mild disease of short duration and minimal short-term sequelae. We ascertained duration of ocular symptoms from 274 of 336 cases (82 per cent) and 174 (64 per cent) said they were ill for five or fewer days; however, duration of disease varied significantly with age (table 4). Thirty per cent of children younger than five years had symptoms for just one day and the remaining 70 per cent for less than five days, no subjects 30 years or older had symptoms for less than 24 hours and 60 per cent of people age 50 or older were sick more than five days. Cases were treated by many modalities including governmental health centers, private physicians, pharmacists and assorted folk medicines. Type of treatment was not related to disease duration.

Sera were collected from 352 of the study population (58 per cent) and 183 (52 per cent) had neutralizing antibody to enterovirus 70. Refusal to give a blood sample was influenced by: 1) sector of residence—63 per cent of upper class sector participants refused to give blood as did 51 per cent of middle class sector residents, 34 per cent of low class sector residents, and 41 per cent of people from poor sectors; 2) by sex—50 per cent of males and 35 per cent of females refused; 3) occupation—77 per cent refusal for preschool children, 50 per cent for employed adults, 35 per cent for students, and 26 per cent for housewives. Refusal to give blood was not influenced by whether the individual had had acute hemorrhagic conjunctivitis, or by race, sanitary facilities or household crowding. Overall, 144 of 183 cases (79 per cent) with onset of disease at least one week before the survey (the minimum time required for a measurable anti-

TABLE 4

Duration of ocular symptoms in acute hemorrhagic conjunctivitis cases by age, Colon, 1981

Duration	Age in years: 1–4 No.	%	5–14 No.	%	15–29 No.	%	30–39 No.	%	40–49 No.	%	50+ No.	%
1 day	6	30	3	3	4	5	0		0		0	
2–5 days	14	70	86	86	54	67	17	50	9	45	8	40
>5 days	0		11	11	22	28	17	50	11	55	12	60
	20		100		80		34		20		20	
χ^2	77.1											
df	10											
p value	<0.001											

body response) and 29 of 148 people denying acute conjunctivitis (20 per cent) had detectable antibody (table 5). Age- and sex-specific antibody rates paralleled attack rates as did antibody rates when controlled for sector, crowding, income, and sanitary facilities. To verify that enterovirus 70 had not been present in the population before the epidemic, we tested all 277 sera collected from Colon during the 1978 random serologic survey. Only four sera had neutralizing antibody to enterovirus 70 and the maximum titers were 1:4.

Discussion

Colon, a crowded tropical coastal city at the peak of the rainy season represented a model setting for acute hemorrhagic conjunctivitis (13, 14). The Epidemiology Section, Ministry of Health, Colon detected the epidemic at its inception, compiled excellent morbidity statistics (8) and instituted a control program. Rapid recognition of the epidemic allowed a detailed population survey to be conducted immediately after the epidemic peak, which helped to minimize recall bias. Our data constitute the first detailed epidemiologic description of enterovirus 70 infection on mainland Latin America.

Previous reports of acute hemorrhagic conjunctivitis indicated that it mainly involves adults and that males are more frequently affected than females (2, 13); the Panamanian Ministry of Health data supported this and also indicated that approximately 14 per cent of Colon's population had been ill. In contrast, our study ascertained that 55 per cent of the study population reported having had acute hemorrhagic conjunctivitis; but only 6 per cent had consulted government health centers because of acute hemorrhagic conjunctivitis (health centers were the sources of reported cases). Adults may be more likely to seek formal medical care because they require a medical certificate to document absence from work and because symptoms persisted for a longer time period than in children. Acute hemorrhagic conjunctivitis attack rates exceeded 40 per cent in all age groups younger than 50 years; five- to 14-year-old children had the highest attack rates and women caring for children had the next highest. Other recent population-based studies (14, 15) reported age-specific attack rates similar to those we documented. Both our study and a study in Florida (15) found low attack rates in people older than 50. Enterovirus 70 infection rates, reflected by serum neutralizing antibody, paralleled clinical attack rates. Only 15 of 54 (28 per cent) people older than 50 years had detectable antibody as contrasted to 167 of 298 (56 per cent) people younger than 50. It is possible that older age groups are more likely to live alone or have less intimate contact with children and thus are less often exposed to enterovirus 70.

A variety of risk factors were associated with acute hemorrhagic conjunctivitis. Locality within Colon and average monthly household income were independently associated with conjunctivitis incidence. However, crowding was the most important determinant and the type of bathroom, communal vs. private, constituted the single most important risk factor. People using communal bathrooms were twice as likely to develop acute ocular disease as people with private bathrooms, and this excess risk was independent of the number of people per sleeping room. However, people who lived in houses where more than five people shared sleeping quarters also had a significantly elevated acute hemorrhagic conjunctivitis incidence which was even more marked in families using communal bath-

Table 5

*Enterovirus 70 neutralizing antibody titers according to clinical history, Colon, 1981**

Titer	Clinical status				Total
	Case		Not case		
	No.	%	No.	%	
<1:4	39	21	119	80	158
1:4	32	18	23	16	55
1:8	32	18	3	2	35
1:16	37	20	3	2	40
1:32	43	23	0		43

* Four cases and one noncase were not titrated to endpoint.

rooms. Enterovirus 70 is more likely to be introduced into families which use communal bathrooms and the probability of intrafamilial transmission is greater in excessively crowded households, for example with many people sleeping together. Other studies (3, 15) have reached similar conclusions regarding the importance of personal hygiene and crowding as risk factors but none have calculated specific risks while controlling for cofactors.

Interpretation of these risk factors should take into account some methodological compromises which were necessary in order to accomplish the survey. The most important compromise was our failure to survey a randomly selected population. The fact that field work had to be accomplished within two days by a limited number of people rendered this impossible. We sought to limit systematic biases by assigning three separate teams parallel transects across the same socioeconomic gradient and by assigning responsibility for selection of sample living units to a trained, experienced epidemiologist who headed each team. To help select representative living units each team drove or walked around the block, prior to sampling, to assess its general character. As noted previously, since the sample was determined geographically (by block) the more densely populated lower socioeconomic areas were undersampled. We could not identify major sampling bias which would affect the defined risk factors. Another important methodological factor involves our clinical case definition which is highly sensitive but not a priori specific for enterovirus 70 acute hemorrhagic conjunctivitis. Obviously, all conjunctivitis reported was classified as acute hemorrhagic conjunctivitis; we presume that the majority of cases should have been due to enterovirus 70 and that any not enterovirus 70 conjunctivitis cases would not exert a major effect on risk factor analysis. Indeed, of 183 cases tested, 79 per cent had antibody to enterovirus 70.

The Colon epidemic study also offered the opportunity to conduct serologic surveys in an area where enterovirus 70 had not occurred (13). The four positive sera collected from Colon residents in 1978 had titers of only 1:4 and probably represented cross-reactive antibody (13, 16–18). Because enterovirus 70-associated acute hemorrhagic conjunctivitis had not occurred previously in Colon, the incidence of asymtomatic infection could be estimated by measuring antibody prevalence. The 29 antibody-positive subjects denying ocular disease probably represented a mixture of false positives and asymptomatic infection; for example 22 (76 per cent) had maximum antibody titers of only 1:4 and a proportion of these undoubtly represent cross-reacting antibody; however, individuals with neutralizing antibody titers more than 1:8 are likely to represent true enterovirus 70 infections. It is reasonable to conclude that between 4 and 20 per cent of infections are asymptomatic. This is similar to estimates from recent studies in Florida (15) and Puerto Rico (19). Seventy nine per cent of cases detected by the household survey had enterovirus 70 antibodies, which is similar to findings from other studies (16); antibody-negative cases may not have seroconverted at the time sera were obtained or may represent conjunctivitis due to other agents (5). During clinical studies of the outbreak we inoculated 82 eye swab specimens from acutely ill patients onto Vero and fetal tonsil fibroblast cell lines (30 were also inoculated into suckling mice) and 40 throat swab specimens from these patients were inoculated onto the same two cell lines. We isolated adenovirus 37 from one acute hemorrhagic conjunctivitis case and also documented seroconversion to adenovirus 37 in the same individual. Enterovirus 70 was not isolated.

Another important reason for conducting detailed population studies of acute hemorrhagic conjunctivitis was to determine the risk of neurologic complications following disease (6, 20). Panama offered an excellent setting to measure this since no cases of polio have been diagnosed since 1970. No one interviewed during the Colon

study reported symptoms of radiculomyelitis. Approximately 30,000 acute hemorrhagic conjunctivitis cases were reported to the Panamanian Ministry of Health during the epidemic. Post-acute hemorrhagic conjunctivitis neurologic complications may occur in 1:10,000 to 1:15,000 cases (6, 21). Increased surveillance at major hospitals detected two cases resembling radiculomyelitis. One patient developed a facial nerve palsy shortly after the onset of acute hemorrhagic conjunctivitis but serologic studies were not done (22); Bell's palsy was reported as complicating acute hemorrhagic conjunctivitis in Florida (15) and Puerto Rico (19) and has been described in India (23). Saenz et al. (22) have described detailed studies of the remaining case compatible with post-enterovirus 70 neurologic disease. This was a 28-year-old female school teacher who developed radiculomyelitis following acute hemorrhagic conjunctivitis. A battery of viral cultures and serologic determinations were negative for agents such as polio and other enteroviruses and antibody to enterovirus 70 titers were 1:16 in serum and cerebrospinal fluid.

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