Hepatitis E in the Royal Nepal Army and the Kathmandu Valley

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Introduction:

Acute viral hepatitis is a disease due to virus infection that causes inflammation of the liver. Though other viruses can cause hepatitis, customarily acute viral hepatitis is restricted to infection by hepatitis viruses A-E. The name also excludes other causes of hepatitis, e.g., bacterial and parasitic infection, drugs, etc.

Hepatitis E virus (HEV) infection is enterically transmitted and resembles hepatitis A (HA) infection in mode of transmission and clinical presentation as an acute self-limiting illness without sequele. The virus was not differentiated until 1980, when serological tests for the diagnosis of hepatitis A and hepatitis B were applied to stored clinical samples collected during a viral hepatitis epidemic in New Delhi in 1955 and 1956. In this epidemic more than 29,000 acute jaundice cases occurred and the source of infection was traced to the contamination of a major water treatment plant with raw sewage. This was originally cited as a classical example of water borne hepatitis A epidemic, but as stored sera from this epidemic did not demonstrate the markers for A, the epidemic was later attributed to enterically transmitted non-A non-B hepatitis virus, in short 'ET- NANB hepatitis'[1]. Similarly a 1973 epidemic of hepatitis in the Kathmandu valley, initially reported as hepatitis A[2], was also designated as ET- NANB hepatitis. Several water borne epidemics of ET-NANB hepatitis from different countries have been recorded. Table 1.

Table 1 Outbreaks of ET – NANB hepatitis

Site	Date	Number of cases	Source of infection
Indian subcontinent			
India (New Delhi)	1955 - 56	29,000	Contaminated water
India (Ahmedadbad)	1975 – 76	2,572	Contaminated water
India (Kathmandu Val.)	1973	10,000	Not determined
Nepal (Kathmandu Val.)	1981 – 82	6,000	Not determined
Pakistan (Karachi)	1985	several cases	Not determined
Southeast Asia			
Myanmar (Yengon)	1982 – 83	399	Contaminated water
Indonesia (Borneo)	1987 – 88	2,000	(?) Contaminated water
Central Asia			
USSR (Kirgiz Republic)	1955 – 56	10,812	Not determined
China (Xinjiang Region)	1986 – 88	2,000	Contaminated water
*Africa**			
Algeria	1980-81	788	Contaminated water
Ivory Coast (Tortiya)	1983-84	623	Not known
Chad	1983 – 84	38	(?) Contaminated water
Sudan (Eastern)	1985	2,012	Contaminated water
Somalia (Refugee camps)	1985 – 86	2,000	Contaminated water
North America			
Mexico (Huitzililla)	1986	94	Contaminated water
Mexico (Telixtac)	1986	129	Contaminated water

* Outbreaks in Gambia and Nigeria were also reported

The viral etiology and fecal route of ET-NANB was confirmed in 1983. An intrepid Russian investigator while investigating an outbreak of ET-NANB hepatitis in Tashkent, deliberately ingested a pool of stool filtrates from a patient. He described his resultant hepatitis, demonstrated fecal shedding of virus like particles and subsequently transmitted the hepatitis to cynomolgus monkeys. It also demonstrated an incubation period of 36 days. Ultimately this agent was characterized as hepatitis E virus that was found to be the cause of ET-NANB epidemics from New Delhi and many other countries.

Hepatitis E is sometimes described as a new disease; however, it is likely that hepatitis E was a disease of antiquity. Hepatitis, most likely HE, is mentioned in an Ayurvedic treatise called 'Charak Samhita' written some 2500 years ago. During the Middle Ages enterically transmitted diseases were constantly present. There are records from the 11th to the 13th centuries that several outbreaks of jaundice occurred amongst crusaders during their marches to the Middle East. At the turn of the 18th century many soldiers and officers of Napoleon's army in Egypt and Syria were affected with this disease. Epidemics of 'catarrhal jaundice" were common in Europe before the turn of the 18th century which were also probably caused by HEV[5]. Hence, industrialized and developed countries have in the past suffered from endemic HE. Now, however, it is mainly a disease of tropical and semitropical countries with poor hygienic conditions viz. Indian subcontinent, Northeast Asia, Central Asia, Africa and Nepal where it poses a major public health problem.

HEV Hepatitis: HE, as in HA, is transmitted through the fecal-oral route and has an incubation period of 30 – 40 days. It presents with jaundice, usually accompanied by malaise, anorexia, abdominal discomfort and liver enlargement. It is usually preceded for a few days by a prodromal phase characterized by fever and nausea. Clinical signs and symptoms of the acute icteric phase last about 14 days. Bilirubin and aminotransferase levels are elevated. The highest incidence occurs in young adults, 15 to 40 years old with a higher incidence in males than females, shown in figure 1, a feature different from enterically transmitted HAV infection. Overall the severity of illness increases with age and case–fatality rates range from 1– 3 % in males and non-pregnant females. A conspicuous feature of HEV hepatitis is the high mortality in pregnant females, 20 – 30 % especially in those in the third trimester of pregnancy[6]

Presentation of HEV Hepatitis: HE presents in Nepal in two forms: endemic with superimposed epidemics and focally in outbreaks.

Endemic with superimposed epidemics: The Kathmandu valley has experienced HE with superimposed annual epidemics for at least the past three decades. Three hepatitis epidemics are recorded in the Nepal medical literature. The first occurred in 1973 from January to October, with a peak incidence in June, July and August. In this epidemic a total of more than 10,000 jaundice admissions were estimated for different hospitals in the valley. The highest incidence was in young males of the age group 16 to 35. Royal Nepal Army troops stationed in Kathmandu valley witnessed a similar surge in the number of hospital admissions for hepatitis in 1973. They had to be accommodated in a specially vacated hall above the X-ray and Pathology departments and in erected tents on the premises of old T.C. Military Hospital Mahankalsthan. All RNA admissions were male adults and there was no mortality.

A second epidemic was reported in 1981 and 1982 with more than 12,000 cases. It started in May 198 and continued through September 1982 with peak period in June to August of both years. This epidem was due to ET- NANB virus[7]. The epidemiological features were similar to those of the1973 epidem There was again a corresponding rise in number of cases in the Royal Nepal Army in the valley, figure Temporary wards in tents had to be set up in the open grounds of an infantry battalion in Chhauni. accommodate the cases.

A third epidemic occurred in 1987 with 7405 cases with similar epidemiological features.

Jaundice or acute viral hepatitis is present in the valley through out the year. However there is alway seasonal pattern with an increased incidence in the months of June to September. The RNA Milit Hospital shows the same trends of hepatitis admission as in other hospitals in the Katmandu Vall figure3.

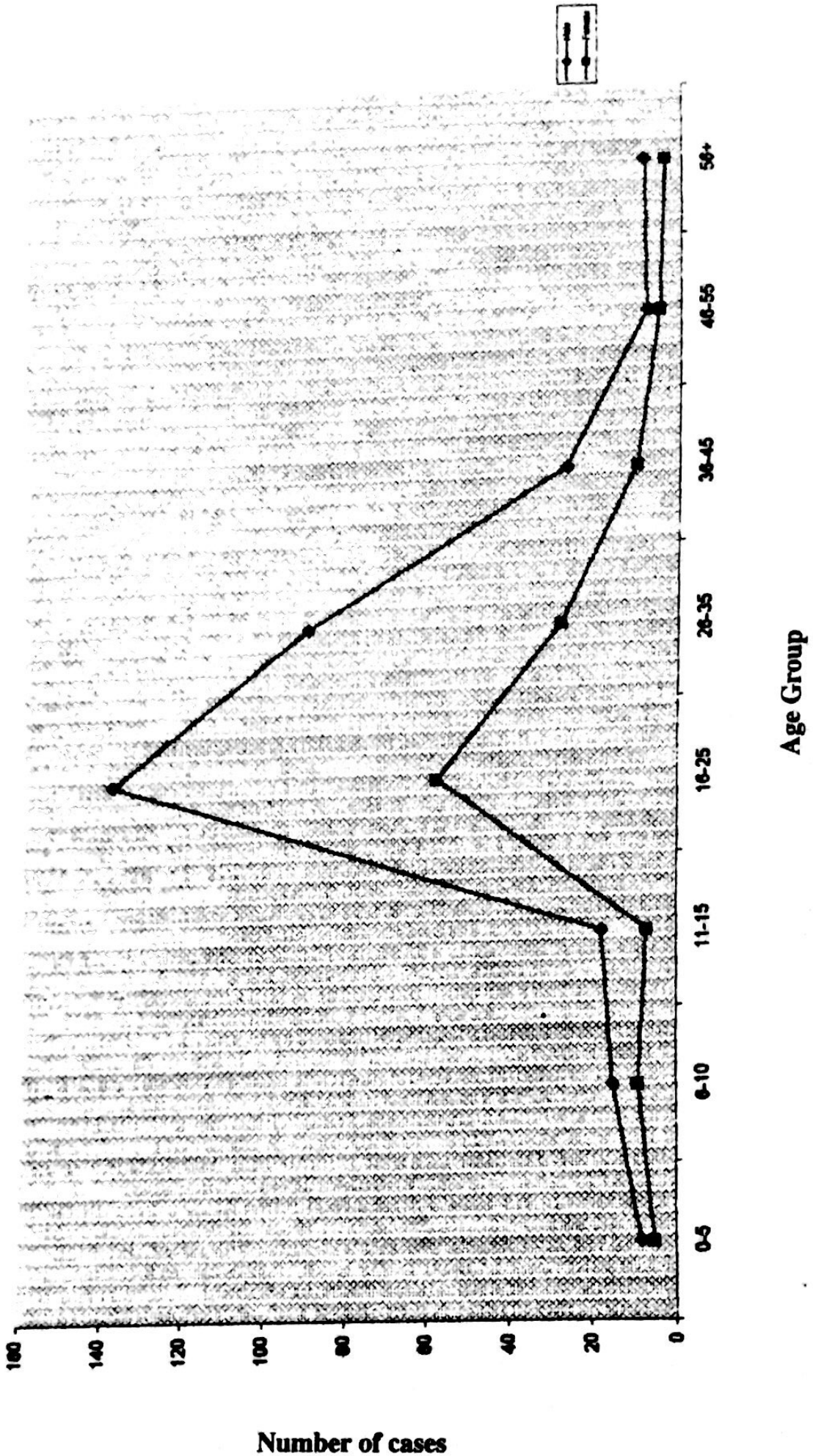

Fig. 1 Out-patient cases with jaundice by age at the Ayurveda Hospital in Kathmandu, 1987

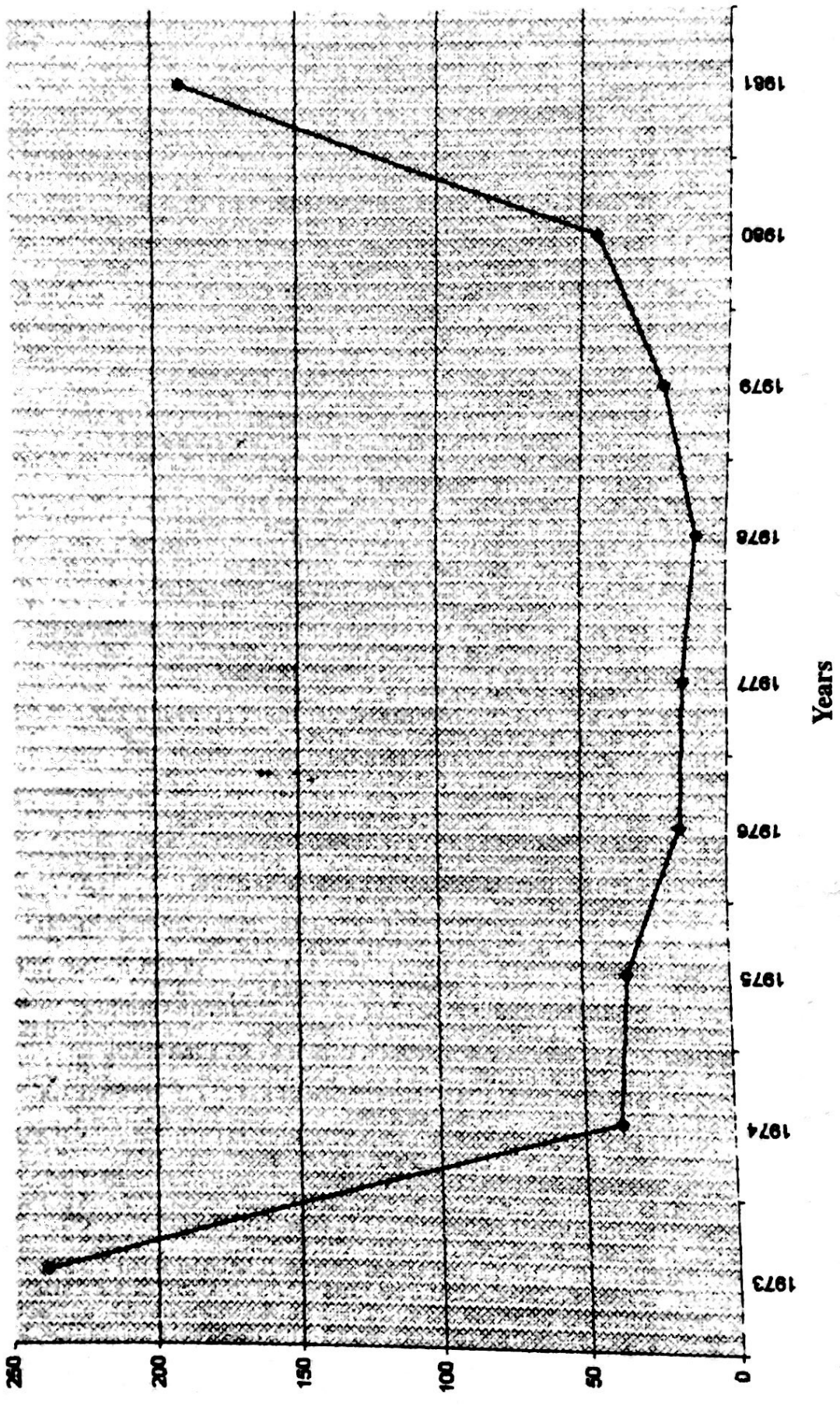

Fig. 2 Inpatient discharges for hepatitis from teh Birendra Military Hospital (1973-1981)

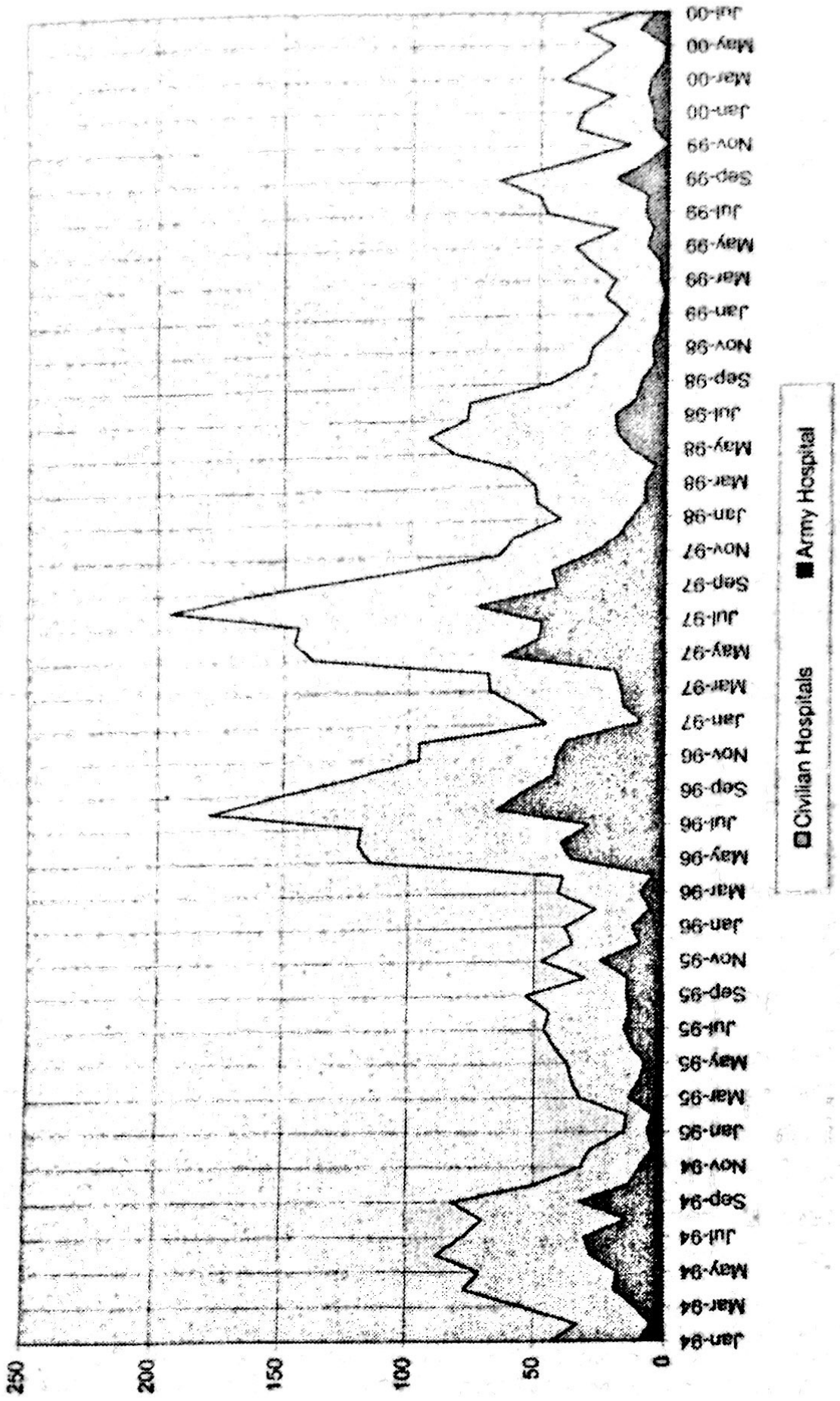

Fig. 3 Jaundice Admission To Kathmandu Valley Hospitals

During Oct 1982 to Dec 1986 149 army personnel with jaundice were admitted to the Bir Hospital Jaundice ward and 81 % were diagnosed as ET-NANB hepatitis[8]; almost all of these cases which were tested proved to be due to HEV.

Focally in outbreaks: As the name suggests focal outbreaks are characterized by increased number of hepatitis cases within certain limited areas, often covered by a common water source. Focal outbreaks have been recorded in various parts of the Kathmandu valley from time to time. There were outbreaks in the Bhramhatole and Gofaltole area during December 1985 and January 1986. At the same time an outbreak occurred at the Police Training Centre, Maharajganj, affecting 150 (15%) of 1000 recruits. The source of infection here was traced to a heavily polluted well. In November 1986, 40 cases of hepatitis (27 acute clinical disease and 13 with markedly raised SGOT only) occurred among inmates of the Central Jail, Kathmandu. Of these, 39 (97.5%) were diagnosed as ET-NANB hepatitis in absence of serological markers of acute hepatitis A & B. The piped water supply of the jail was heavily contaminated with coliform bacteria and was incriminated. Alapot village near Sundarijal and Jitpur village near Nagarkot experienced outbreaks of HE in Sept – Oct 1997[9].

Royal Nepal army units stationed in the Kathmandu valley have had their share of hepatitis outbreaks. In 1986 there was a sharp rise in number of hepatitis cases in the T.C. Military Hospital, Mahankalsthan which coincided with the opening and maintenance of a blocked sewage pipe which ran beside a feeder water pipe near the reservoir tank.

Another outbreak occurred in Royal Nepal Army U. N. Peace Keeping Force Training Centre, Panchkhal an isolated camp about 25 km east of Kathmandu from 29 January to 15 March 1995[10]. This proved a unique opportunity to study the epidemiology of HE. The outbreak was apprehended early and immediate investigations were initiated to determine it's cause and to curb it's spread. Thirty-two cases of acute clinical hepatitis from a total of 692 army personnel, all male, occurred approximately 8 weeks after arrival at the camp, figure 4.

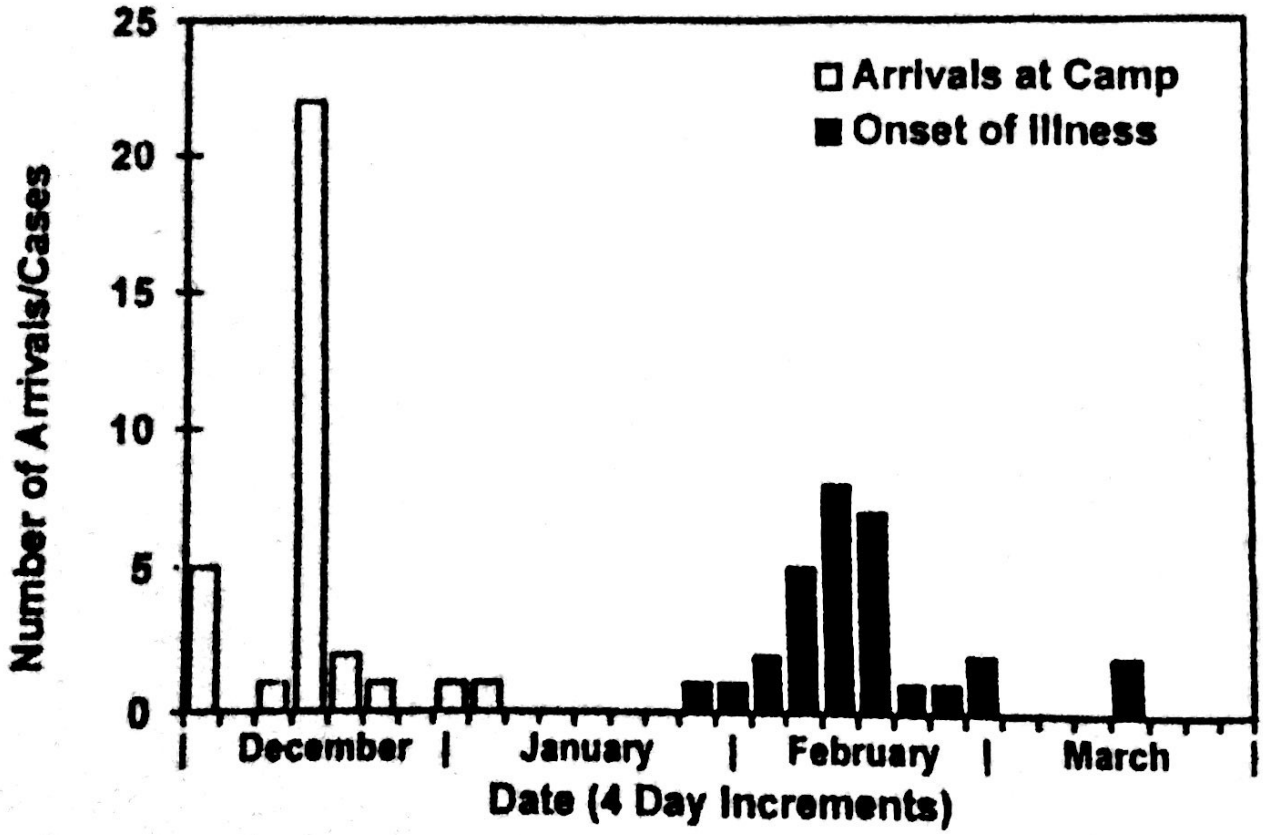

Fig. 4 Distribution of arrivals and onset of illness among 32 hepatits cases at a military training camp Nepal. Nepalese soldiers arrived at hte camp to form and train a new unit for deployment. Approximat 8 weeks after arrival, 32 soldiers became ill with hepatitis. Shown are the distributions and dates arrival of the 32 patients (white bars) as well as the epidemic curve of the outbreak (black bars).

Sera from all 32 cases were examined for evidence of infection with hepatitis A, B, C and E. Evidence of recent infection with HEV was found in 30 of the 32, and none had evidence of recent infection with hepatitis A or B or C viruses. Hence the outbreak was attributed to HEV. To further determine if inapparent HEV infections occurred in those without clinical evidence, sera from the remaining troop were examined for the markers of HEV infection. Evidence of recent infection was found in 83 and evidence of past infection in 204. Antibody was present in 115 i.e. 30 % of the 488 susceptibles. The disease and infection rates obtained during the outbreak were 7 % and 24 % respectively and case to infection ratio was 1: 3.5.

The source of infection could not be pinpointed, but contaminated drinking water was suspected. Water sources for the camp consisted of springs and creeks that were accessible to animals and local people and so potentially contaminated. The camp was located nearby and down hill from inadequately maintained public latrines. Orders were issued not to use water from the springs or creeks. Potable drinking water was provided regularly from a nearby town and no further hepatitis cases were observed during the remainder of the 6 months stay in the camp.

Epidemiology: The Kathmandu Valley is an endemic area for HEV infection. An epidemiological survey in the Kathmandu valley, in March 1992 examined 4486 Nepalese volunteers from campuses, schools, the Nepal Police Force and the RNA (1200). The average age was 18 years with 2168 (48.3 %) in the12 to16 age group. No subjects were under 7 and only 23 were older than 41. The overall sero-prevalence was 10.2 %. The prevalence appeared to increase with age[11]. A serum sample obtained from a 757 susceptible Nepal Police Force & RNA volunteers, one and a half years later identified a 2% annual attack rate[12].

Following identification of 4 cases of acute hepatitis in Bangladeshi soldiers among peace keepers from the United Nations Mission in Haiti a serological survey was conducted to determine the prevalence of HEV infection in UN peace keeping forces from different countries (Bangladesh, Djibouti, Haiti, Honduras, Guatemala, India, Nepal, Pakistan and USA HEV) antibody was found in 42 out of 114 (37 %) Nepalese volunteers.

Hepatitis virus has been isolated from different mammals (pigs, rats and dogs) and birds (chicken and ducks) in the Kathmandu valley. Hepatitis E virus may be a zoonotic virus with animals as its natural hosts[14]

Socioeconomic impact of HEV Hepatitis: HEV hepatitis causes substantial morbidity due to its acute presentation and prolonged convalescent period. Using a modified health status index to quantify healthy days lost, structured interviews were conducted on recovered cases of HE during June 1988. This estimated the impact on individual health across three dimensions viz. morbidity (or mortality), real and perceived disability and direct and indirect expenditures. Hepatitis E disease rates in the Kathmandu valley were estimated to be 20/1000 person-years. From the 134 HEV hepatitis respondents the estimated total burden of HE in the Kathmandu valley for one year was estimated to be more than NRs 89 million with 32 healthy days lost for each of the estimated 24,000 individual with HE, totaling 768,000 days[15].

The economic impact of hepatitis E was also estimated for the Royal Nepal Army. From July 1997 to June 1998 155 army personnel were admitted to Birendra Military Hospital with HEV hepatitis. The average hospital stay was 15 days (1 – 92 days). The cost estimated at NRs 1000/ patient hospital day was NRs 15,000 per patient and for 155 patients NRs 2,325,000. Due to further convalescent leave the duty days lost per patient was on average 6.8 weeks (2 – 14 weeks). For 155 patients the total days lost from duty was 7250. If a day's duty is valued at NRs 200, the total amount of NRs lost for the155 patients was NRs 1,475,600 and the total cost of HEV disease to the Royal Nepal Army for that year was NRs 3,800,600.

Hepatitis E Studies by the Royal Nepal Army: During the past eight years Shree Birendra Military Hospital in collaboration with Walter Reed Army Institution of Research, Washington D.C. (WRAIR), Armed Forces Research Institution of Medical Sciences, Bangkok (AFRIMS) and Walter Reed/AFRIMS

Research Unit, Nepal (WARUN) conducted a series of studies on HEV Hepatitis in RNA troops in Kathmandu valley.

1. From March 1992 to Sept 1993 a serosurvey was conducted in RNA troops located at different areas in the valley. Sera from 591 troops were examined for HEV antibodies and 147, almost a quarter of them were positive, indicating past HEV infection. Of the remaining 444 susceptible to HEV infection 43 developed HEV antibody and 14 of those reported jaundice over the subsequent 18 months[12].
2. In June 1996, a 50 months follow-up study was done in 539 RNA personnel. HEV seroconversion was found to be 8.7% (2.0% per year) amongst those susceptible, indicating that transmission is reasonably stable in Kathmandu valley, especially in the army units.
3. From 1997 to Feb 1999, a hepatitis surveillance study identified 183 jaundiced soldiers, of which 182 were diagnose as HE. This indicated the HE is almost the only cause of hepatitis in the RNA.
4. From September 1997 to Feb 1999, an observational cohort study of 1289 RNA troops detected HEV seroconversion in 3.1 %.
5. Study of an outbreak in the RNA U. N. Peace Keeping Force Training Centre, Panchkhal, from 2 January to 15 March 1995 was mentioned above.

Treatment and Prevention:

There is no specific treatment for hepatitis E and there are no specific preventative measures now available. Immune serum globulin is not protective. As the infection is transmitted through the fecal oral route, the only way to prevent the transmission lies in improvement of socio-economic conditions, improvement of hygienic standards and general sanitation, provision of proper sewage disposal and supply of potable drinking water. In their absence, the use of boiled water for drinking, avoiding unprotected and unhygienic foods, personal hygiene and use of proper latrine should be rigorously practiced.

Like in many other virus infections, e.g., hepatitis A and B, an effective vaccine could be used to prevent disease, however, a vaccine for HEV is not yet available. A candidate recombinant HEV vaccine has been developed and has successfully completed safety and immunogenecity trials under national and international scientific and ethical norms. These successful trials include challenge trials in monkeys which showed that the candidate vaccine prevented disease in these animals. Human safety and immunogenecity trail preformed in 88 informed American volunteers followed by 44 informed Nepalese showed the candidate vaccine to be very safe and immunogenic. The final trial necessary for the ultimate manufacture and use of the HEV vaccine in health programs is a placebo controlled, double blind study in 3000 informed susceptible volunteers. This trial remains to be performed.

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