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Hepatitis B and Delta Hepatitis

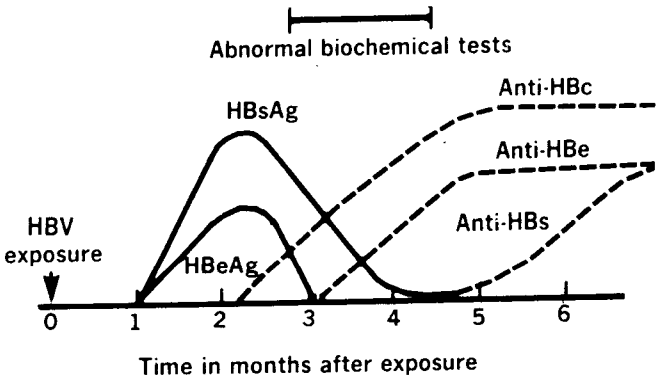
Tens of millions of persons are infected by hepatitis viruses annually, which produces a significant impact on health. Hepatitis occurs in three forms: A, B, and non-A/non-B. The Delta agent, a defective virus that requires hepatitis B virus as a helper for its replication, can aggravate hepatitis B infections, particularly when superinfection occurs.

Hepatitis B

Hepatitis B (HB) infection may lead to chronic infection and the development of long-term sequelae such as cirrhosis, chronic active hepatitis, and hepatocellular carcinoma, particularly when infection occurs early in life. There are at present an estimated 200 million persistent HB carriers worldwide. At least 250,000 cases of liver cancer occur each year, most of which are attributable to hepatitis B virus (HBV). Most HB infections occur in childhood, and it is unlikely that improvements in the environment and personal hygiene will significantly impact their transmission. HB is most effectively controlled by large-scale immunization. Several effective and safe vaccines have been developed and have been shown to provide adequate protection in both children and adults.

Hepatitis infection usually results in an acute self-limiting infection, which may be inapparent or symptomatic. The serological course of a typical uncomplicated HB infection with recovery appears in Figure 1. A proportion of infected persons, however, becomes persistent virus carriers. The development of

Figure 1. Serologic course of uncomplicated acute hepatitis B with recovery.



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the carrier state is inversely related to the age of infection, ranging from approximately 90% in newborns to 10% or less in adults. An HBV carrier is defined as one whose blood contains surface antigen (HBsAg), detected at an interval of at least six months. The occurrence of HBsAg in high titers during the acute phase of the disease, with persistence for more than six weeks, is often followed by the development of chronic hepatitis.

Likewise, presence of hepatitis B *e* (HBeAg) antigen in high titers (>1,000 in radioimmuno- or enzyme immunoassays) indicates the possible development of chronic disease, particularly if it persists for more than six to eight weeks after the acute phase. In most patients, however, HBeAg disappears early during convalescence, usually before HBsAg becomes undetectable. Presence of HBeAg in the serum indicates persisting, active viral replication, and most sera with a medium to high HBeAg titer also contain measurable HBV polymerase activity and complete Dane particles demonstrable by electron microscopy. Blood of such patients must be considered highly infectious. The disappearance of HBeAg and development of antibody to HBeAg (anti-HBe) are in general good prognostic markers, but do not guarantee complete clearance of HBV. Anti-HBs appears late, sometimes only several months to a year after the disappearance of HBsAg, and indicates immunity.

Antibody to HB core antigen (anti-HBc), especially of the IgM class, is almost without exception present in the early acute phase of the illness or even precedes the onset of symptoms. Anti-HBcIgM usually disappears within six months to two years, but may stay longer in persistent or chronic active hepatitis B. Anti-HBcIgG remains detectable for many years and perhaps for life.

Viral DNA polymerase activity in the serum indicates that viral replication in the liver is continuing. Sequential determinations of this enzymatic activity are the most sensitive measurement of a therapeutic effect during treatment of chronic hepatitis with interferon or other chemotherapeutics, but they do not add substantially to the diagnostic evaluation of the disease.

Most recently, highly specific techniques (more than 100 times that of conventional methods), have been developed to identify HBV-DNA in liver tissue and serum, which are of importance for molecular and pathogenetic studies.

The significance of HBV markers for the diagnosis of the status of HBV infection is presented on Table 1. It should be noted that the patient's history and data obtained by clinical examinations, clinical chemistry, and, when possible, liver biopsy may also be needed to arrive at an accurate diagnosis in some cases.

Epidemiology

Hepatitis B is a major public health problem in practically all parts of the world. Acute HBV infection is a notifiable disease in many countries; most reporting systems, however, are inadequate to define its epidemiology on a global basis. Deficiencies in the collection of basic information and lack of appropriate laboratory support are primary constraints. In the United States of America, for instance, some 50,000-60,000 cases of hepatitis are reported to the U.S. Centers for Disease Control each year. Approximately half of these appear to be hepatitis B; however, the real incidence may be as high as 150,000 cases per annum.

Chronic infections are now classified as "healthy" carriers, with no detectable or only minimal disease,

Table 1. Interpretation of the presence of combinations of serologic markers of the hepatitis B virus.

HBsAg[a]	HBeAg	Anti-HBe	Anti-HBc	Anti-HBs[b]	Interpretation	Infectivity of blood
+	+	–	–	–	Incubation period or early acute period during hepatitis B	high
+	+	–	+	–	Acute hepatitis B or chronic carrier[c]	high
+	–	+	+	–	Late during hepatitis B or chronic state	low
–	–	+	+	+	Convalescent from acute hepatitis B infection	none
–	–	–	+	+	Recovered from past hepatitis B infection	none
–	–	–	–	+	Immunized without infection, repeatedly exposed to HBsAg without infection, or recovered from past hepatitis B infection	none
–	–	–	+	–	Recovered from past hepatitis B infection with undetectable Anti-HBs,[a] early convalescent, or chronic infection	questionable

[a]All positive for HBsAg are acutely or chronically infected with HBV.

[b]All positive for anti-HBs are immune to hepatitis B.

[c]The titre of anti-HBc and/or the immunological class of the anti-HBc may differentiate between the convalescent phase, persistent carrier, or chronic infection.

Source: Deinhardt, F. and Gust, I. D. Viral hepatitis. *Bull WHO* 60(5):661-691, 1982. Table 4. Reprinted with permission.

persistent hepatitis with stable disease, and chronic active hepatitis with progressing disease. Most of the above-mentioned 200 million carriers of HBV in the world (Table 2) are concentrated in Asia and Africa. Figures from the Americas may actually be underestimated; there is clear evidence that in certain areas of the Region the carrier state is higher than 10%.

Table 2. Estimated number of HBV carriers in the world.

Region	Population (millions)	HBV carriers	
		%	Number (millions)
Africa	441	6.0	26.5
United States of America and Canada	338	0.5	1.8
South America	234	1.0	2.3
Asia	2,437	6.9	168.0
Europe	480	1.0	4.8
Oceania	22	2.0	0.4
Union of Soviet Socialist Republics	320	4.0	12.8

Source: Adapted from Report of a Scientific Group on Viral Hepatitis B and its related liver diseases. Nagasaki, Japan, 29 September-2 October 1982. Regional Office for the Western Pacific Region of WHO, 1982.

Extreme variations occur in the frequency of persistent infections caused by HBV. In most Anglo-Saxon populations the carrier rate is less than 1 per 1,000, while on the Pacific Island of Rapa, it is one in two. The age of infection is one of the most important risk factors for a person who becomes a long-term HBV carrier. In adults, from 5-10% of infections result in persistent infections, whereas in infants the rate may exceed 80%.

Persons with certain health problems, such as lymphoproliferative disorders, leprosy, Down's syndrome, and patients on immunosuppressive therapy, are more likely to become carriers. Carrier rates are usually higher among males than females. In chronic carriers, the titers of HBsAg usually decline with increasing age, and many of them eventually eliminate the virus from their body and develop anti-HBsAg, believed to be the protective antibody.

Patterns of Infection

A marked variation in the prevalence of HBV infection is observed in different settings: in general, it is lowest in countries or areas with high standards of living and highest in countries or areas in which the socioeconomic level is lower and where there is overcrowding. Certain population groups such as homosexuals, intravenous drug users, those in institutions for the mentally retarded, patients in hemodialysis units, and certain groups of health workers exhibit high infection rates.

Striking differences may occur in infection rates and carrier rates among different ethnic groups; for example, in New Zealand the carrier rate among the Maoris (an ethnic group of Polynesian-Melanesian origin) is 9.5%, whereas among the Anglo-Saxon population it is only 0.1%. Marked variation in carrier rates may occur even within apparently homogenous populations: among the 3,500 Micronesians who live in Nauru, for instance, the carrier rate oscillates from 5-28% in the different villages of this Pacific Island.

Worldwide patterns of HB infection may be conveniently divided into three categories (Table 3). In areas of low endemicity such as North America, Western Europe, and Australia, prevalence of HBsAg in asymptomatic carriers is 0.2-0.5%. Areas like Eastern Europe, the Mediterranean region, South-West Asia, and certain parts of South America have an intermediate prevalence (2-7%). In high prevalence areas such as China, South-East Asia, and tropical Africa rates of HBsAg may be as high as 20%.

Table 3. Hepatitis B prevalence patterns.

Low endemicity	Intermediate endemicity	High endemicity
HBsAg, 0.2-0.5%	HBsAg, 2-7%	HBsAg, 8-20%[a]
Anti-HBs, 4-6%	Anti-HBs, 20-55%	Anti-HBs, 70-95%
Childhood infection infrequent	Childhood infection frequent, neonatal infection frequent	Childhood infection highly frequent, neonatal infection highly frequent
Australia, Western Europe, North America, parts of South America	Eastern Europe, Japan, Mediterranean, South-West Asia, USSR; possibly parts of South America	Some parts of China South-East Asia, tropical Africa

[a]Prevalences up to 50% have been identified in some isolated Pacific islands.

Source: Adapted from: Deinhart, F. and Gust, I. D. Viral hepatitis. *Bull WHO* 60(5):679, 1982. Table 6.

Transmission

HBsAg is found in virtually all body secretions and excretions; however, only blood, saliva, and semen have been shown to be infectious. Transmission is often by percutaneous (intravenous, intramuscular, subcutaneous, or intradermal) inoculation of human blood, plasma, serum, thrombin, fibrinogen, and other blood products from an infected person. Immunoglobulin, heat-treated plasma, protein fractions, albumin,

and fibrinolysin are generally considered safe. Contaminated needles and syringes are important vehicles of spread, particularly among drug addicts. The infection may also be disseminated through contamination of wounds and lacerations. Exposure of mucous membranes to infective blood can also result in infection. HBV may be also transmitted by kissing or by sexual

Perinatal transmission of HBV from carrier mothers to their babies appears to be the single most important factor for the high prevalence of HBV infection in some areas. When mothers are HBsAg- and HBeAg-positive, approximately 95% of their newborn children become infected, usually in the perinatal period. Transmission during pregnancy itself is rare. In parts of Asia 30-50% of HBsAg carrier women of childbearing age are HBeAg-positive, and perinatal infections account for about half the carriers in the population. Children of non-carrier mothers can be infected by contact with other children who have been infected by their carrier mothers. Consequently, perinatal transmission appears to be the driving force in maintaining high HBsAg carrier rates in eastern Asia, for example. In contrast, perinatal transmission is uncommon in Caucasian populations, and it has an intermediate frequency in mothers of West-Asian or of Afro-Caribbean origin. In Africa the infection occurs more commonly during early childhood than in the perinatal period because HBeAg in carrier mothers is less frequent than in Asia. Infection of the baby following acute or chronic infection of the mother is usually anicteric and is recognized by the appearance of HBsAg between 60 and 120 days after birth.

It has been suggested that mosquitos and other blood-sucking insects might be important vectors of the disease in tropical areas; however, there is no convincing evidence to support this suggestion.

Prevention

Until recently, preventive measures for HB infection consisted in screening blood donors for history of hepatitis and for serologic markers of HBV infection, hygiene measures, and passive immunization. In recent years, however, active immunization has been demonstrated effective in controlling the infection.

Screening Blood Donors

Blood banks should reject as donors all individuals who have a history of viral hepatitis or jaundice. High-risk groups such as drug addicts and homosexuals should not donate blood, nor should persons who received a blood transfusion within the preceding six months. The use of paid donors should be discouraged or prohibited, and any person HBsAg-positive should not be accepted as a blood donor.

In areas where such measures have been implemented, there has been a decrease of up to 85-90% in incidence of post-transfusion hepatitis. This decline parallels the use of laboratory tests with augmented sensitivity for detecting HBsAg. Less sensitive methods such as counterimmunoelectrophoresis should be replaced by more sensitive ones like reverse passive hemagglutination, radioimmuno- or enzyme-immunoassays.

Hygienic Measures

Simple environmental precautions when dealing with persons known or presumed to be infectious, or their blood, and contaminated instruments are useful in preventing infection.

Such measures are of great importance for protecting medical and dental personnel and some hospitalized patients who are at increased risk of acquiring HB infection. In renal dialysis units where HB transmission can be very high, hygienic measures can ensure considerable reduction or prevention of transmission. This is accomplished by the careful use of instruments for individual patients and the testing and segregation of susceptible patients from infectious ones.

Disposable syringes and needles should be used. Reusable syringes and needles should be properly sterilized by boiling at 100° C for a minimum of five minutes, or preferably by autoclave at 120° C for 30 minutes. Instruments used for ear piercing or scarification should simply be heated over a flame to eliminate the unnecessary risk of transmission.

Passive Immunization

Although use of normal pooled immunoglobulin (IG) has given inconsistent results in preventing hepatitis B, special HB immunoglobulin (HBIG) rich in anti-HBs has been shown to be effective in pre-exposure and postexposure prophylaxis. Long-term use of HBIG is not practical because of its limited availability, high cost, and the potential risk of complications when frequently administered.

Until recently postexposure prophylaxis consisted in the administration of HBIG to protect babies born to carrier mothers and health personnel accidentally exposed to infectious materials during the course of work. Ideally, HBIG should be administered im-

Table 4. Hepatitis B virus postexposure recommendations.

Exposure	HBIG		Vaccine	
	Dose	Recommended timing	Dose	Recommended timing
Perinatal	0.5 ml IM	Within 12 hours of birth	0.5 ml (10 μg) IM	Within 7 days[a]; repeat at 1 and 6 months
Percutaneous	0.06 ml/kg IM or 5 ml for adults	Single dose within 24 hours	1.0 ml (20 μg) IM[b]	Within 7 days[a]; repeat at 1 and 6 months
		or[c]		
	0.06 ml/kg IM or 5 ml for adults	Within 24 hours; repeat at 1 month	—	—
Sexual	0.06 ml/kg IM or 5 ml for adults	Within 14 days of sexual contact	See footnote d	—

[a]The first dose can be given the same time as the HBIG dose but at a separate site.
[b]For persons under 10 years of age, use 0.5 ml (10 μg).
[c]For those who choose to receive HB vaccine.
[d]Vaccine is recommended for homosexually active males and for regular sexual contacts of chronic HBV carriers.
Source: Morbidity and Mortality Weekly Report 33(21), 1984.

mediately after exposure, and preferably no later than 48 hours. If feasible, a rapid test for anti-HBs should precede the decision to give HBIG. For accidental needle stick, a dose of 0.05 ml/kg of HBIG should be given intramuscularly, and repeated after one month. Infants born to HBsAg carrier mothers should receive 0.5 ml, and the same dose should be repeated one or more times 3-6 months later; the efficacy of this procedure for preventing chronic infections oscillates between 70-80%.

Concurrent administration of HBIG and vaccine has been recently recommended in the United States for postexposure prophylaxis of HBV infection (Table 4). Such procedure has a greater efficacy over the use of HBIG alone in preventing infection due to perinatal exposure of HBV.

Active Immunization

The most effective means of controlling hepatitis B is likely to be by wide-scale active immunization. Several purified subunit vaccines have been developed from HBsAg existing in the blood of chronic HBsAg carriers. Various controlled trials have shown that HB vaccines are safe and induce antibodies to HBsAg in about 95% of healthy recipients.

Immunogenicity studies have demonstrated that more than 90% of newborns develop HBsAg antibodies by six months of age in response to two doses of vaccines. These findings are unusual since the response of newborn infants to other vaccines is generally poorer than that of older infants and children. The immunization is effective even in the presence of passively acquired antibodies.

Studies have been completed or are now in progress in several countries to evaluate the efficacy of HB vaccine alone or in combination with HBIG for the prevention of perinatally transmitted HBV infections. In Japan, a protection rate against the carrier state of 90-99% was demonstrated after follow-up examinations for at least 12 months. The infants were given an intravenous or intramuscular injection of HBIG at birth followed by repeated intramuscular injections of HBIG and active immunization with vaccine on three occasions. Trials in Taiwan in which HBIG was given immediately after birth to infants of HBeAg-positive mothers, followed by three different schedules of vaccination, demonstrated that all three schedules were efficacious; the combined efficacy was 94% compared with that of HBIG alone (71%) or vaccination alone (75%). Recent trials in China, utilizing vaccine developed by the U.S. National Institutes of Health, showed that immunization of infants born to HBsAg- and HBeAg-positive mothers was 91% efficacious in preventing chronic infection.

While the response to hepatitis B vaccines has been highly satisfactory in healthy persons, this has not been the case with dialysis patients because of their immunodeficiency. In a recently reported study, however, one vaccine induced anti-HBs in 88% of hemodialysis patients; the protective efficacy rate of the vaccine was 78% against all HBV infections in the entire study and 94% against HBsAg-positive hepatitis more than three months after the initial dose of the

vaccine. More studies are needed to evaluate properly the protection conferred by hepatitis B vaccines in these patients.

Large-scale studies should be conducted to measure the effectiveness of immunization in preventing hepatocellular carcinoma before mass vaccination campaigns are carried out. Such studies ought to be undertaken in different areas of the world, because the long-term efficacy of immunization may vary with factors affecting HBV transmission. Each trial would probably involve tens of thousands of individuals and would be useful in assessing the logistic problems associated with establishing and evaluating worldwide mass immunization campaigns.

Vaccination Strategies

Strategies for vaccine use must take into consideration different HB prevalence patterns (Table 3). In areas of low prevalence, selected vaccination of groups of individuals known to be at high risk of acquiring the infection appears to be the best strategy. In intermediate and high prevalence areas, large-scale administration of the vaccine could be considered, depending on the availability of vaccine (Table 5). It is unlikely that effective control of HB can be achieved unless entire populations are immunized prior to exposure (i.e., during infancy and early childhood).

Likely candidates for vaccination in areas of low endemicity include health care workers, hospital staff, clients and personnel of institutions for the mentally retarded, hemodialysis patients, recipients of certain blood products, household and sexual contacts of HBV carriers, homosexually active males, users of illicit injectable drugs, and inmates of long-term correctional facilities.

Exposure rates differ among the various units of a hospital. Clearly, staff in liver or renal units handling HBsAg-positive patients and certain others working in a related capacity such as pathologists, dentists, and surgeons are prime candidates for vaccination. Similarly, vaccination is strongly recommended to staff members who run the risk of potential high exposure to infectious HBsAg carriers, including those in genitourinary medicine (particularly in clinics dealing with large numbers of homosexual patients), those running drug addiction clinics, and those treating hemophiliacs or working in institutions for the mentally handicapped. These individuals should be immunized prior to entering high-risk environments.

A cost-benefit evaluation of HB vaccination in a given population should include the estimated attack rate, which determines the net cost of each prevented case; it has been suggested that net cost benefits emerge when the attack rate exceeds 5% or 6% per annum.

Decisions regarding pre-immunization screening will differ from country to country, depending upon the expected immune status of given population groups and the costs and availability of both the reagents and vaccine. In general, screening followed by vaccination of non-immune persons in populations with a high prevalence of HBV markers leads to a significant reduction in medical care costs.

Table 5. Recommendations for hepatitis B vaccine profilaxis according to prevalence of HBV.

Prevalence	Pre-exposure	Postexposure
Low	High-risk groups (health personnel, dialysis patients, institutionalized patients, drug addicts, and male homosexuals)	Accidental percutaneous exposure, infants of HBsAg-positive mothers, sexual contacts of acute cases or carriers
Intermediate or high	All infants[a]	Infants of HBsAg-positive mothers

[a]Depending on availability of vaccine.

Source: Adapted from: World Health Organization. Prevention of liver cancer. Geneva: World Health Organization; 1983. (WHO Technical Report Series; 691).

Hepatitis B Vaccines

Failure to propagate HBV in the laboratory *in vitro* has made it impossible to date to prepare a vaccine from virus grown in cell cultures. The demonstration that heat inactivated HBsAg-positive human plasma confers partial protection to inoculated subjects against the disease provided a great stimulus for developing vaccines using HBsAg purified from plasma obtained from antigenaemic asymptomatic carriers.

Several human plasma-derived, inactivated, subunit HB vaccines have now been prepared. The fact that the starting material is human plasma obtained from persons infected with HB requires that extreme caution be exercised to ensure their freedom from all harmful contaminating material, including host components. Different approaches have been used for purifying HBsAg from human plasma and for inactivation. WHO has formulated the requirements for hepatitis vaccine prepared from human plasma[1], and a proposal reformulating these requirements was recently pre-

[1]World Health Organization. WHO Expert Committee on Biological Standardization. Thirty-first Report. Geneva: World Health Organization; 1981. (WHO Technical Report Series; 658).

[2]WHO/BS 83.1391 Rev.2.

pared.[2] Procedures for detecting extraneous viruses include testing in adult and suckling mice, in embryonated eggs, and in cell cultures. Testing for residual HBV infectivity in susceptible chimpanzees should also be included.

Vaccines for the Future

Although plasma-derived inactivated subunit HB vaccines have been shown to be safe and effective for preventing infection both in normal children and adults, there are important concerns regarding their costs and availability for mass vaccination programs. Such constraints are associated with several problems. For example, although there are large numbers of persistent HBsAg carriers in the world, it is currently impossible to collect and process sufficient quantities of plasma to conduct mass immunization campaigns. In addition, the production and standardization of vaccines is so expensive that the countries which need them most may not be able to afford them; moreover, availability may be limited by the current requirements for safety testing. Sources of sufficient donor plasma for producing large quantities of vaccine are disproportionately located in countries that have the least capability for efficient vaccine production for their own use. Large-scale shipping of such plasma from developing countries with intermediate-to-high HB prevalence to developed countries for vaccine processing and production may create sociopolitical problems, while the hazards associated with local vaccine manufacture under conditions of inadequate technology and poor control are of equal concern.

In view of the foregoing considerations, attention must be given to preparing vaccines from alternative sources in order to improve safety and reduce costs. Fortunately, work on developing new hepatitis vaccines is in progress at several laboratories. Three approaches are being pursued:

- *Vaccines prepared by recombinant DNA technology.* Vaccine production by molecular cloning is under way. Production of hepatitis surface antigen in different prokaryotic and eukaryotic cells has been reported by several groups. Expression of HBsAg has been obtained in yeast cells, and antigenic material from this source has been recently shown to be safe and immunogenic for man. These developments are potentially important for large-scale *in vitro* production of vaccines produced by recombinant DNA technology. Scientists were able recently to incorporate the HBV gene that directs production of surface antigen to vaccinia virus DNA. When the hybrid virus was injected into rabbits, it produced a local reaction to vaccinia virus and stimulated significant amounts of antibody to hepatitis antigen. In humans, equivalent levels of antibodies would provide protection against hepatitis B virus.

- *Synthetic hepatitis peptide vaccines.* Synthetic peptides, with the amino acid sequences of HBsAg are being tested for immunogenicity in several laboratories. Synthetic peptides may possibly be employed as vaccines in the future, although mixtures of more than one of the peptides may be required. Many questions remain unanswered; the critical ones are: will antibodies induced by synthetic immunogens be protective and will that protective immunity persist? Studies using such synthetic vaccines in susceptible chimpanzees are under way.

- *Vaccines prepared from antigen "producer" cell lines.* Secretion of HBsAg by heteroploid cells derived from primary hepatocellular carcinoma has been reported. The surface antigen obtained in this way is noninfectious and of relatively simple biochemical composition. Techniques to ensure freedom from contaminating nucleic acid and potent inactivating agents are available. Since the cell lines are transformed and show hetero-transplantability, developments in this area must proceed with caution.

Delta Hepatitis

The delta agent, discovered in 1977, is a defective virus that requires HBV as a helper for successful replication. Two models of infection have been identified: acute coinfection with HBV, and superinfection of an HBV carrier. Acute coinfection with HBV, observed experimentally in chimpanzees and directly in humans, appears to cause acute hepatitis which resolves and seldom leads to chronic disease. Superinfection may cause no disease, acute hepatitis which resolves, or chronic hepatitis; however, the latter may be the most common outcome and may have the most severe consequences. It has been estimated that 50-75% of delta superinfections may result in chronic hepatitis.

The delta agent is unique among virus-like agents: it consists of a particle 35-37 nm in diameter that resembles a large HBsAg particle and possesses the HBsAg coat of HBV. It also contains specific antigen and a very small RNA molecule, which presumably is the genome of the agent. Delta antigen can be detected in the nuclei of infected hepatocytes and in the serum during the late incubation period and early acute phase of infection. When infection with the delta agent

[2]WHO/BS 83.1391 Rev.2.

occurs, synthesis of HBV components is usually suppressed: serum HBsAg and HBeAg levels and DNA polymerase may fall to low or undetectable levels and intrahepatic markers of HBV synthesis, especially HBcAg, may become undetectable.

On the basis of limited serologic surveys, the delta agent seems to have a worldwide distribution but to be epidemiologically important primarily in southern Italy, where it appears to be highly endemic. A severe epidemic of hepatitis due to superinfection of hepatitis B chronic carriers by delta agent has recently been observed in Venezuela, with an acute case fatality rate of 20% and with 60% progression to chronic illness in survivors. Preliminary observations suggest that delta agent may also be associated with fulminant hepatitis in certain areas of the western Amazon region of Brazil and in northern Colombia. The introduction of this agent into unaffected areas of the world where the frequency of HBV carriage is high could have devastating consequences.

Delta agent is transmitted by contaminated blood and blood products. It is probable that nonpercutaneous modes of transmission also exist and that the agent can be spread by sexual contact. At least one instance of perinatal transmission of the delta agent from mother to infant has been reported.

Since delta infection has only been observed in people who are acutely or chronically infected with HBV, the increasingly widespread use of hepatitis B vaccine is likely to constitute an effective mechanism for preventing delta hepatitis.

The WHO Viral Hepatitis Control Program

For almost 30 years WHO has been actively involved in the field of viral hepatitis. Specially convened groups of experts have regularly reviewed advances in the field with particular emphasis on diagnosis and control, and have prepared pertinent publications. In addition, WHO has promoted training in laboratory techniques for the diagnosis of diseases, supported field research, and established a network of Collaborating and National Reference Centers.

In recent years safe and effective hepatitis B vaccines have been developed, and hepatitis A vaccines are currently under study. Moreover, modern technological approaches are being applied to develop new hepatitis B vaccines, which eventually may be produced large-scale at a lower cost.

In view of the magnitude of the problem and the present and upcoming technological advances toward the control of viral hepatitis, WHO is launching a Viral Hepatitis Program. In July 1983 an Advisory Group on the development of such a program met in Geneva and proposed the following overall objectives:

1) Define the natural history of viral hepatitis in all regions of the world, and in particular determine ways in which the agents are spread and the mechanisms by which they produce disease.

2) Assist in the development and evaluation of safe, effective, and inexpensive means of preventing the disease and treating its long-term sequelae, including hepatocellular carcinoma.

3) Promote and assist in the application of these methods in countries in which viral hepatitis is a public health problem.

In addition, the Group defined targets and activities. Two main targets were envisaged: strengthen diagnostic capabilities, such as epidemiological surveillance, define population groups at special risk of infection, etc.; and reinforce general sanitation and environmental procedures, immunization, treatment, and other control efforts. Six main activities were identified: surveillance and epidemiological studies; information synthesis, exchange, and dissemination; training; reagents production; development of field trials for immunization; and standardization of immunoglobulins and vaccines.

Over the years, PAHO has assisted countries of the Region in promoting some of these activities. However, now is the time to formulate and implement more vigorously such activities. As a first step to accomplishing this, PAHO plans to convene a meeting of experts to discuss the Program and draft sound recommendations and approaches for its implementation.

(*Source:* Epidemiology Program, Health Programs Development, PAHO.)

Fatal Occupational Accidents

Introduction

The indicators most usually employed to assess working conditions are occupational accidents. As a rule, they are easily identified, and their causes and effects can be clearly established. The degree of injury ranges between slight and fatal. Despite the relative ease with which such accidents are identified and recorded, there are not yet any reliable data on which to determine adequately the extent and epidemiology of the problem as it exists in the Region. Though much research and many studies are done on the epidemiology of occupational accidents, few focus specifically on those in which the worker dies.

This article draws attention to the importance of the problem in the Region, the significance of some epidemiological features that have been studied, and their implications for public health programs. It is based on three studies of fatal occupational accidents done in the State of Maryland, United States of America *(1)*; Department of Antioquia, Colombia *(2)*; and the city of Campinas, State of São Paulo, Brazil *(3)*.

Extent of the Problem

According to studies and data for the Region of the Americas, there are at least 10 million occupational accidents a year, more than 50,000 of them fatal *(4)*. The diversity of the institutions and recording procedures frustrates any possibility of detailed comparison of the absolute numbers of and mortality rates among workers at risk in different countries. Statistics frequently refer only to workers enrolled in the social security system, which in many cases does not include farm workers.

However, it has been estimated that, in the United States, for example, there are about 13,000 deaths due to occupational accidents a year, which results in losses of 245 million work days and US$25 billion in direct and indirect costs *(1)*. Between 1970 and 1982 the National Institute of Social Security (INPS) of Brazil recorded about 20 million occupational accidents, which resulted in approximately 50,000 deaths *(3)*. These data are broken down by years in Table 1.

A study done in the Department of Antioquia, Colombia, examined 505 fatal occupational injuries between 1965 and 1978. Table 2 presents the mortality rates per 100,000 workers and shows an uptrend that peaked at 28.9 in 1974 and dropped to 19.9 in 1978, the last year covered by the study. A progressive downtrend has been noted in the United States where the mortality rate has dropped from 39 to 13 per 100,000 workers over the last 25 years, and the Maryland study disclosed a rate of 7 per 100,000 workers. Table 1 indicates that in Brazil the rate has dropped steadily since 1975, reaching less than 20 in 1981 and 1982. Notable among the causes of the apparent decline are the recent registration of low-risk groups and amendments to legislation on occupational accidents.

Table 1. Occupational accidents in Brazil, from 1970 to 1982.

Year	Number of workers	Number of occupational accidents	Deaths in occupational accidents	Mortality rate per 100,000 workers
1970	7,284,022	1,220,111	2,232	30.6
1971	7,764,486	1,330,523	2,587	33.3
1972	8,148,987	1,504,723	2,805	34.4
1973	10,956,956	1,632,696	3,122	28.5
1974	11,537,024	1,796,761	3,764	32.6
1975	12,996,796	1,916,187	3,942	30.3
1976	14,945,489	1,743,825	3,900	26.1
1977	16,590,000	1,614,750	4,445	26.8
1978	18,500,000	1,564,380	4,342	23.5
1979	20,322,500	1,507,930	4,500[a]	22.1
1980	23,782,216	1,404,531	4,824	20.3
1981	24,448,118	1,215,539	4,808	19.7
1982	25,000,000[a]	1,117,832	4,496	18.0

[a]Estimate.
Source: National Institute of Social Security, Brazil.

Table 2. Fatal occupational accidents among persons covered by the Social Security Institute (ISS), Department of Antioquia, Colombia, from July 1965 to December 1978.

Year	Number of members of the ISS	Number of occupational accidents	Deaths in occupational accidents	Mortality rate per 100,000 workers
1965	120,139	8,975	3	1.7
1966	125,742	16,899	10	7.9
1967	127,498	17,508	8	6.3
1968	138,194	18,275	22	15.9
1969	151,046	20,459	19	12.6
1970	174,127	21,160	29	16.7
1971	193,566	24,786	41	21.2
1972	203,272	27,102	47	23.1
1973	219,323	28,944	30	13.7
1974	235,569	30,566	68	28.9
1975	238,949	32,192	62	25.9
1976	258,340	29,592	46	17.8
1977	283,064	35,417	60	21.2
1978	301,668	37,040	60	19.9

Source: Antioquia Health Service Fund, Colombia.

However, published data on Latin American and Caribbean countries almost never include occupational accidents in farm work since workers in this line are covered by other social security schemes and in many cases have no welfare entitlements.

Some Epidemiological Features

All three studies cited underscore that workers who die of occupational injuries are usually young males. This has far-reaching social and economic implications since the victims leave dependent wives and minor children, who in turn become burdens to society. In Colombia, the median age of death was 35 years and 65% of the workers were under 40. In the Brazilian study, 68.3% of the workers were under 40 and 9.7% under 20. In Maryland, the age ranged between 16 and 83 years; the age distribution of those dying in occupational accidents in that State is illustrated in Table 3.

Table 3. Age distribution of construction workers fatally injured in 1978 in the State of Maryland, United States of America.

Age (years)	Number of deaths	(%)	Number of workers	(%)
16-17	2	(1)	66,000	(3)
18-19	5	(4)	108,000	(6)
20-24	9	(7)	283,000	(15)
25-34	33	(25)	492,000	(25)
35-44	37	(28)	358,000	(18)
45-54 / 55-64	42	(32)	587,000	(30)
≥ 65	5	(4)	56,000	(3)
Total	133	(101)[a]	1,950,000	(100)

[a]Greater than 100 due to rounding.

Source: Adapted from the table in the *State Annual Planning Information Report*, Service Department, Human Resources, State of Maryland, United States of America.

An epidemiological procedure of fundamental importance is to determine the occupations in which fatal injuries most frequently occur. Construction work accounted for about 30% of all deaths recorded in the Campinas study and for 11.5% of those in the Department of Antioquia. Construction work involves a variety of operations (earth-moving, laying foundations, working at great depths and heights, specialized operations, etc.) involving a wide range of risks. Compared with other occupations, the duration of employment in this one is very short, which makes for little interest in the implementation of prevention programs and hampers proper supervision. Moreover, the labor force is usually unskilled and the work is done under precarious health, housing, and nutritional conditions. An additional factor is that different firms frequently operate at the same work site, which reduces the responsibility for accident prevention. Construction such as dams, highways, and other public works must often be carried out in extremely adverse geographic and climatic conditions on sites that are not covered by the traditional occupational safety programs promoted by the health sector. For these and other reasons, safety in construction work poses a difficult public health problem.

A close relationship between fatal occupational injuries and traffic accidents is a common denominator in all three studies which clearly emphasizes that the problem needs attention. In Maryland, traffic accidents account for 25% of all occupational fatalities, though accidents involving other vehicles (vessels and small civilian aircraft) raise the proportion to 41%. In Antioquia, 155 (30.7%) of the 505 deaths, were caused by motor vehicles. In Campinas, traffic accidents accounted for about 50% of all fatal injuries during the period considered. As is to be expected, in some occupational categories—drivers of commercial vehicles, for example—the proportion of traffic accidents is even higher.

An interesting epidemiological aspect that stands out in the Maryland and Antioquia studies is the high proportion of occupational homicides. In Antioquia, 135 (26.7%) of the 505 deaths were caused by firearms, knives, blunt instruments, and strangulation. The occupational group at greatest risk of homicide was building watchmen. In Maryland, 11% of the fatal injuries resulted from homicides. The authors identify the following groups of workers as particularly exposed to the risk of assault by virtue of their occupation: taxi drivers, policemen, and retail shop salespersons. Data on occupational accidents caused by homicides are of a highly particular nature; discrepancies result when comparisons are made among different countries, owing to frequent differences in classification criteria and no one single legal interpretation.

Some Implications for Public Health

Because most of their victims are young men and are entirely avoidable, occupational fatalities pose a major challenge that demands the attention of the public health authorities in a system-wide and intersectoral context. Together, the three studies cited point to the following recommendations:

• Occupational risk prevention programs should be revised in view of the findings of epidemiological studies on fatal occupational accidents. The Maryland study on deaths among truck drivers, for example, emphasizes that most occupational safety programs virtually ignore commercial vehicles, which account for close to 40% of all fatal occupational accidents. Even in the manufacturing industry, more workers' deaths are caused by freight vehicles than by fixed machinery. In framing policies for the prevention of occupational accidents, and especially serious and fatal ones, it is important to regard occupational and traffic accidents as inseparable when they occur in occupational situations (commercial drivers, transportation of workers, running over workers in the vicinity of the work site, etc.). In addition to the legal implications, the employer's responsibility in relation to his participation in prevention measures should be clearly spelled out.

• Epidemiological research of fatal occupational accidents shows without exception that some as yet unknown aspects should undergo epidemiological analysis. In Latin American and Caribbean countries, for example, there is not yet any understanding of the true extent of the problem, chiefly because of the limited social security coverage of large groups of workers, including, among others, those employed in agriculture.

• Occupational accidents should be included with a systematic and coordinated focus in the sphere of action of public health programs. In some countries this area is the jurisdiction of institutions and programs not properly coordinated with the health sector, and hence the problem is rarely addressed as a public health issue.

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(Source: Worker's Health Program, Health Programs Development, PAHO.)

WHO Collaborating Centers for Tropical Diseases in the Americas

One of the purposes of the *Epidemiological Bulletin* is to provide information on national and international health institutions which are technical resources available to PAHO member countries in the Americas. The WHO Collaborating Centers—national institutions that function as reference centers for service, research, and training in the health field—are included in this group of institutions.

The *Epidemiological Bulletin* (Vol. 4, No. 3, 1983) published the list of WHO Collaborating Centers for Viral Diseases in the Americas. Table 1 below lists the WHO Collaborating Centers for Tropical Diseases.

Table 1. WHO Collaborating Centers for Tropical Diseases in the Americas.

Area of activity	Institution	Location
Diagnosis and research on Chagas' disease	Instituto Fatala Chaben	Avenida Paseo Colón 568 Buenos Aires 1063 Argentina
Research and training in the immunology of parasitic diseases	Oswaldo Cruz Foundation	Avenida Brasil 4365 Manguinhos, CEP 21040 Rio de Janeiro Brazil

Table 1. WHO Collaborating Centers for Tropical Diseases in the Americas *(Cont.)*.

Area of activity	Institution	Location
Pesticide toxicology	Seção de Toxicologia e Higiene Comparada Instituto Biológico	Avenida Cons. Rodrígues Alves 1252, C.P. 7119 São Paulo 01000 Brazil
Serology of Chagas' disease, leishmaniasis, and toxoplasmosis	Laboratorio de Inmunología Instituto de Medicina Tropical de São Paulo	Avenida Dr. Enéas de Carvalho Aguiar 470 São Paulo 05403 Brazil
Cryopreservation of strains of American *Trypanosoma*	Centro de Pesquisas René Rachou FIOCRUZ	Avenida Augusto de Lima 1715 Belo Horizonte, Minas Gerais Brazil
Training of personnel in the control of leprosy, mainly for Portuguese-speaking countries	Hospital Lauro de Souza Lima	Rodovia Comandante João Ribeiro de Barros Km. 115, Caixa Postal 62 Bauru 17100, São Paulo Brazil
Pesticide application testing and development	Dirección de Campañas Directas Sección *Aedes*-Vacunación	Avenida Caracas 1-91 Sur Bogotá Colombia
Onchocerciasis	Centro de Investigaciones Ecológicas del Sureste (CIES)	Carretera Panamericana y Periférico Sur Código Postal 29290 San Cristóbal de las Casas, Chiapas Mexico
Work on insecticide resistance	Department of Entomology Division of Toxicology and Physiology University of California	P.O. Box 112 Riverside, California 92521 USA
Evaluation and testing of new insecticides	Insects Affecting Man and Animals Research Laboratory Agricultural Research (Southern Region) U.S. Department of Agriculture	1600 S.W. Twenty-third Drive, P.O.Box 14565 Gainesville, Florida 32604 USA
Reference and research on *Mycobacterium leprae*	Virology Division Bureau of Laboratories Centers for Disease Control	Atlanta, Georgia 30333 USA
Studies on *Mycobacterium leprae*	National Hansen's Disease Center Laboratory Research Branch U.S. Public Health Service Hospital	Carville, Louisiana 70721 USA
Parasites of insect vectors and the impact of biological control agents on nontarget species	Gulf Coast Mosquito Research Laboratory U.S. Department of Agriculture Agricultural Research Service	P.O. Drawer 16923 Lake Charles, Lousiana 70616 USA
Biological control of vectors of human diseases	Department of Entomology College of Biological Sciences Botany and Zoology Building, Room 185 The Ohio State University	1735 Neil Avenue Columbus, Ohio 43210 USA
Evaluation and testing of new insecticides	Division of Parasitic Diseases Control Technology Branch Centers for Disease Control	Atlanta, Georgia 30333 USA
Histopathology of filarial diseases in man	Department of Infectious and Parasitic Diseases Pathology Armed Forces Institute of Pathology	6825 Sixteenth Street, N.W. Washington, D.C. 20306 USA
Research on the chemotherapy of parasitic diseases	Division of Experimental Therapeutics Walter Reed Army Institute of Research	Washington, D.C. 20307 USA
Host and parasite studies on malaria	Malaria Branch Parasitic Diseases Division Center for Infectious Diseases Centers for Disease Control	Atlanta, Georgia 30333 USA
Applied medical malacology	School Public Health and Tropical Medicine Tulane University	Tulane Avenue New Orleans, Louisiana 70112 USA
Reference and research on histological identification and classification of leprosy	Instituto Nacional de Dermatología Universidad Central de Venezuela	Apartado Postal 4043 Caracas 1010 Venezuela

(Source: Epidemiology Program, Health Programs Development, PAHO.)

Contemporary Epidemiology: Perspectives and Uses[1]

Background

Epidemiology is concerned with the study of health, disease, and health services in groups of people or populations in contrast to the study of other aspects of these phenomena in individuals, cells, and molecules. Translated literally, epidemiology means "that which is upon the people." Its intellectual siblings are demography, economics, statistics, and sociology, all of which had the same origins in the XVIIth century. Epidemiology is an essential tool for measuring the burden of illness and suffering in the population being served by the entire health care enterprise, for assessing the relative costs, risks, and benefits of a wide variety of interventions designed to improve health, for evaluating the impact of health services and practice on the populations' health status, and for developing clues to the web of causality which influences diseases of all types.

The term "epidemiology" was first given wide currency by the clinicians who founded the London Epidemiological Society in 1850 *(1)*. Over the years, however, epidemiology's clinical origins have been forgotten, and until recently most contemporary clinicians have had no exposure to the population-based perspective. Their views are usually grounded in educational experiences that have been confined largely to tertiary care hospitals and that concentrate on molecular and cellular processes. Many, if not most clinicians (mainly those in academic clinical departments) have had little, if any, exposure to the concepts, methods, and applications of epidemiology. It is these academic clinicians, especially professors of medicine and surgery, who treat politicians and administrators the world over, give advice, and exert a powerful influence based on what they know and experience in university teaching hospitals. They are unfamiliar with the great bulk of the population's health problems which exist outside hospital walls where people live, work, suffer, and die. These distortions of viewpoint and experience have resulted in gross imbalances in the organization of health services, in the training of health manpower, and in the setting of priorities. The net effect is the absurd misallocation of resources, intolerable inequities in access to care, and escalating health care costs which threaten to bankrupt societies.

Much of this isolation from the population-based perspective is attributable to an earlier decision of the Rockefeller Foundation to support the establishment of schools of public health administratively and, unfortunately to a growing degree, intellectually and scientifically separate from schools of medicine. The problems are recounted in Professor John Evans' recent report written for the Foundation *(2)*. The disparity between the population's burden of illness and the health care establishment's priorities for education, research, and services has serious consequences for developed countries, yet in the developing world, these consequences are often disastrous. The Foundation's current hypothesis, held also by other agencies and by leaders in both developed and developing countries, is that one way to restore to medical science and education a population-based perspective and eventually influence the setting of priorities and allocation of resources at institutional and national levels, is to train established young clinical faculty members in epidemiology and to do so in settings where credible clinicians both care for patients and conduct epidemiological studies. Although the fellows the Foundation supports receive a Master of Science degree (or in some instances a Ph.D.) and are equipped to undertake independent research on their return home, the main concern is the change of attitudes, practices, and priorities. It is too early in the course of the planned evaluation to judge, but solid evidence now exists in Brazil, the People's Republic of China, and Thailand, for example, of substantial changes in attitudes and interests associated with the return of these promising young leaders to their home universities and the establishment of clinical epidemiology units within the medical schools.

Epidemiology is the one science that can shift the balance in the health care establishment's priorities from a predominant preoccupation with individual transactions between doctors and their patients to a broader collective concern on the part of all health professionals for the care of entire populations. At the very least, epidemiology should help sensitize medicine to society's health needs and prepare for demands which will inevitably find expression through the political process. In this global arena, the simple definition of epidemiology as "the study of that which is upon the people" will suffice; more restrictive definitions that refer to "distributions of diseases" or to the "causes of epidemics" seem outmoded and unhelpful in the broader context in which contemporary health problems are now being viewed.

The epidemiologists' opportunities to contribute

[1]Presented by Dr. Kerr L. White, former Deputy Director for Health Sciences, The Rockefeller Foundation (New York, USA), at the Seminar on Uses and Perspectives of Epidemiology, Buenos Aires, Argentina, 7-10 November 1983.

have been restricted not only by their fragmentation into camps concerned with communicable diseases, noncommunicable diseases, environmental problems, population dynamics, or health services, for example, but also by the arbitrary limitations each camp places on the applicability of a rather simple set of ideas and methods to an ever-broadening array of contemporary health problems. The history of epidemiology is replete with tales of the strong views expressed by the communicable disease epidemiologists with respect to the legitimate application of "their" methods to noncommunicable diseases and by both these groups with respect to the use of epidemiological principles in studying population trends and evaluating health services. Even now, questions are raised about the appropriate use of epidemiological methods in the study of such contemporary problems as delinquency, social deviance, emotional deprivation, drug abuse, attempted suicide, and loneliness or even in the study of doctors' prescribing patterns or patient's attitudes toward keeping appointments or complying with treatment regimes. There is a definite need for a theoretical framework that does not require all noxious agents to be physical, chemical, or biological and that leaves room for such complex deleterious influences on health as noise pollution, jet fatigue, occupational stress, domestic violence, inadequate parenting, and sexual strife.

Of all the disciplines that constitute the scientific basis for health care, epidemiology should be the last to resort to defensive postures and restrictive practices. The fact that laboratory sciences have concentrated on cellular activities, hospital medicine on the more florid manifestations of acute diseases, general practice on symptomatic treatment of individuals, and traditional public health on limited services for categorical health problems is no justification for epidemiology to limit its view of the origins and distribution of health, disability, and distress in populations. Each of these components has a legitimate role in any contemporary health services system that employs epidemiology directly or indirectly for at least part of its scientific underpinning. It is epidemiology that relates the individual to the population and epidemiology that can help balance personal and public needs, burdens, risks, and benefits. One cannot over-emphasize the power of the epidemiological viewpoint in redirecting the priorities of most health care establishments. While there are those who would argue that this is a form of market research more compatible with the activities of a commercial enterprise than of a learned profession, others contend that this approach redresses the overemphasis on what has been called "half-way technology" in medicine.

The intellectual tools provided by epidemiology enable all clinicians to examine not only the history of disorders presented by their patients but also the natural history of medical care and its outcomes. Both the hospital-based specialist or consultant and the generalist or family physician can undertake epidemiological and operational studies, or at least learn to use and interpret the kinds of clinical and management information that is increasingly available to them. Indeed, it can be argued that the medical practice of the future in most industrialized countries will find groups of general and specialized doctors with their related hospitals and facilities taking responsibility for the care of entire populations, not just of those who present themselves as patients. Their concern and efforts will focus on detecting health problems at the earliest possible stage and, when feasible, preventing their occurrence in high-risk groups. To better manage their patients' health care, general or primary care physicians and specialists and consultants will use clinical and epidemiological information about them in conjunction with data on the populations from which they come. Similarly, health services administrators and the statisticians and epidemiologists with whom the clinical physicians work will be responsible for developing health information systems to serve multiple purposes. These will include the clinical management of patients as well as the management of medical practices, health centers, hospitals, and related resources that serve defined populations. The health problems and care provided will need to be monitored both within medical practices and institutions and for local, regional, and national populations. It is one of the tasks of epidemiologists to design these health information systems so that clinical and administrative decision-making can be based on a reliable flow of useful information.

Future Challenges

What follows is a brief consideration of the range of tasks contemporary epidemiology could undertake more aggressively. In all these areas of concentration, it has been assumed that, because the studies aspire to being scientific in form and content, some attempt has been made to measure the phenomena observed. This is as it should be, but it must be remembered that the precision of most measurement instruments varies with duration of use and is most likely to be improved with experience derived from repeated applications. All science starts with observing and describing; epidemiology is no exception. Many observations can at least be ranked or scaled, and while not denying the role of observer error and observer variation, "soft" data

about important problems, when objectively collected, may be more informative and useful in improving health than "hard" data about unimportant problems. Examples of the former are data on such variables as attitudes, disability days, presence of subjective symptoms or pain, use of drugs, or measures of perceived morbidity, in contrast to physiological or anthropometric data or that derived from ECGs or X-rays. The issue is not whether error is present, but rather whether its nature and amount in relationship to the observed variance of the phenomenon studied can be specified so that important differences can be distinguished with confidence.

There are six areas in which epidemiology can be a powerful force in helping society cope with its contemporary health problems; each lends itself to descriptive, analytical, or experimental studies.

Etiology

The traditional search for causal agents or configurations of risk factors should be pursued vigorously but should perhaps be approached from an ecological perspective with respect to the nature of disease and its genesis. Nevertheless, the detection of each new agent or factor found to be necessary, if not sufficient, for the development of any recognizable ailment places us closer to ultimate prevention or cure. Epidemiology is likely to play an increasingly important role in this regard as new sources of data emerge with the development of contemporary health information systems.

Efficacy

This is concerned with objectively establishing that a new form of preventive, diagnostic, curative, or restorative intervention is more useful and beneficial than it is harmful or useless vis-à-vis the purposes for which it is advocated, or that it is more efficacious than the type of intervention it is designed to replace or, in fact, that it is better than doing nothing. This is the arena of the randomized clinical trial (RCT). Although there may be other experimental or observational designs that provide for the control of selective bias and the placebo and Hawthorne effects, the predominant means is the RCT. It should be noted that the methods for assessing the efficacy of clinical measures are also applicable to the study of administrative practices.

Effectiveness

Effectiveness is concerned with measuring the extent to which an efficacious form of intervention can be shown to have been made available or applied to all those in a defined population who could benefit from it. Effectiveness studies focus as much on those who do not use health services or receive efficacious forms of intervention as on those who do.

Efficiency

This measures the extent to which a stated level of effectiveness can be achieved with the lowest expenditure of personnel, resources, and money. One part of the equation involves monetary units or equivalents but the other requires measures of disability levels, health status, or disease prevalence expressed in units familiar to epidemiologists who themselves are essential participants in designing and conducting such studies.

Evaluation

This generic term can be applied to studies of efficacy, effectiveness, and efficiency. It requires establishing a "valued" goal, objective, or standard and assessing the extent to which that goal is achieved as a result of some form of intervention or provision of services. This approach to the problems of health and health care is especially suited to epidemiologists.

Education

Education offers the challenge of preparing new generations of epidemiologists and the equally great opportunity (if not obligation) to sensitize and perhaps indoctrinate clinicians, administrators, and policy makers with the epidemiological viewpoint and perspective. These members of the health sector can be made aware of the need for help from epidemiologists in any arrangement of health services that seeks to balance equity of access to care, fair shares in the distribution of resources, and responsible moderation of costs. Both clinicians and administrators will have to consider the needs of populations as well as those of individual patients. Inculcation of statistical compassion in administrators and policy makers may be as important as encouraging personal compassion in clinicians.

There is a broad range of uses for the epidemiological viewpoint and epidemiological method. Epidemiology should assume a posture and declare its value as one of the fundamental sciences that underpins medicine and the other "caring" services. The contemporary concern in all countries with the provision of health services requires the epidemiologist's skills. Epidemiologists themselves should adopt a broader stance and take a more aggressive position. If medicine is being viewed increasingly by society as a social service, then epidemiology should accept the fact that it is a social as well as a biological science, and, like all social enterprises, it should serve society. Epidemiology can be the vehicle for broadening the use of the

scientific method in medicine and for putting life, meaning, and relevance into what could be sterile statistics. Greenwood undoubtedly had this in mind when he remarked that "health statistics record births, deaths, marriages and divorces; people with the tears wiped off" *(3)*. Many sources of tears, anguish, distress, and failure to cope and thrive challenge medicine, as do the opportunities for improving the prospects for attaining man's full potential.

Latin America has an unusual obligation, if not an urgent need, to accept the challenge to broaden the base of epidemiological understanding and the range of epidemiological applications in the entire health care enterprise. Several countries have already shown substantial initiatives and PAHO is fostering these. The Rockefeller Foundation offers fellowships for training young clinical faculty members and additional financial support will undoubtedly be forthcoming from national, bilateral, and international agencies. The opportunity for epidemiology to serve as society's ombudsman of health has never been greater. Latin America can show the way.

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Diseases Subject to the International Health Regulations

Cholera, yellow fever, and plague cases and deaths reported in the Region of the Americas up to 30 June 1984.

Country and administrative subdivision	Cholera Cases	Yellow Fever		Plague Cases
		Cases	Deaths	
BOLIVIA	–	*2*	*2*	–
La Paz	–	2	2	–
BRAZIL	–	*37*	*22*	*8*
Amazonas	–	9	8	–
Bahia	–	–	–	2
Ceará	–	–	–	4
Minas Gerais	–	–	–	2
Pará	–	27	13	–
Rondônia	–	1	1	–
COLOMBIA	–	*3*	*3*	–
Cesar	–	1	1	–
Cundinamarca	–	1	1	–
Santander	–	1	1	–
ECUADOR	–	–	–	6
Chimborazo	–	–	–	6
PERU	–	*17*	*13*	*78*
Cajamarca	–	–	–	62
Huanuco	–	12	8	–
Junín	–	3	3	–
Madre de Dios	–	1	1	–
San Martín	–	1	1	–
Piura	–	–	–	16
UNITED STATES	–	–	–	*11*
Arizona	–	–	–	1
California	–	–	–	3
New Mexico	–	–	–	4
Texas	–	–	–	1
Utah	–	–	–	1
Washington	–	–	–	1

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