SOME USES AND MISUSES OF EPIDEMIOLOGY

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When one uses the term "epidemiology" in this audience, and indeed for many involved with studies of disease in populations of humans and lower animals, the name of Calvin Schwabe is often invoked. Of the numerous professional experiences Cal and I have shared, I will mention only one, apart from his classic book *Veterinary Medicine and Human Health,* that illustrates his unusual abilities: his contributions and masterful chairing of the WHO Expert Committee on Veterinary Public Health held in Geneva in 1975 (ref.1). In my view the report of that meeting is the best overview of a much-argued and often overdefined subject, and Cal steered the talented though somewhat contentious group safely to shore with an excellent report. We are now some 20 years later, and I believe that the principles and precepts contained in that report will continue to exert their influence for an indefinite future.

When considering epidemiology as a science we should keep in mind the contributions of the philosopher, Karl Popper, whose views were strongly endorsed by the Nobel scientist, Peter Medawar. Popper maintains that in seeking the truth or falsity of a scientific statement it must be stated as a proposition that can be proven false, for example, Einstein's relativity formulations which were confirmed in the solar eclipse of 1919. This can be both easy and difficult for the claims of some epidemiologists. I shall revert to this point when discussing selected diseases later.

In the examples discussed later I apply the term epidemiology in its wide sense. By that I mean that any information used to examine a disease problem in population groups should meet tests for validity, which are often statistical in nature. This applies as well to the design and results of laboratory experiments, and to declarations and descriptions of such procedures as, for example, oral polls, written interviews, or the use of shoe leather to gather data.

In stating some rather strong opinions, as epidemiologists often do, I hope I am constrained by Ambrose Bierce's observations to the effect that we often call "absurd" a statement or belief manifestly inconsistant with our own opinion; that we use the term "bigot" for someone who is obstinately attached to an opinion that we do not entertain; and we call a "bore" a person who talks when you wish them to listen. I shall try to avoid these pitfalls.

We all recognize that from shoemakers to theoretical mathematicians, a good technical knowledge of the discipline employed is essential for any degree of success. My emphasis here will be on qualitative rather than quantitative aspects of epidemiology, and I will give only short attention to technical details of the subject, for example statistics. Instead I shall discuss a few diseases to illustrate the points I wish to make, namely, that studies of diseases in populations, i.e., epidemiology, have uses as well as misuses. The diseases I will discuss, time permitting, are rabies, brucellosis, anthrax, influenza, and bovine spongiform enchephalitis.

In a spirited account of who and what to believe in science and the world around us, the distinguished biologist, Richard Lewontin, recently expounded on shoddy thinking in reputable scientific circles as well as among believers in Scientology (ref. The New York Review of Books, 9 January 1997, pp. 28-32). He notes that even Lewis Thomas, the great populizer and proponent of modern scientific medicine, is not blameless in regard to loose speculation in epidemiology. He points out that Thomas, in praising modern medicine for conquering disease, he sometimes does so excessively. Lewontin cites as an example that Thomas overlooks the fact "... the unchallenged statistical compilations on mortality show that in Europe and North America infectious diseases, including tuberculosis and diphtheria, had ceased to be a major cause of mortality by the first decades of the twentieth century, and that at age 70 the expected further lifetime for a white male ...[despite vaunted claims in medicine]... has gone up only two years since 1950".

This illustrates to some degree both the use and misuse of epidemiology and its major tool, statistics. It brings to mind the observations of an English economist in the last century that the use of statistics resembles that of a drunk leaning against a lamp post -- more for support than for illumination.

Rabies

I will begin with a discussion of an aspect of rabies that may be unfamiliar to you, i.e. WHO's attempt in 1953 to clarify whether or not rabies antiserum would be effective in improving results obtained with vaccine alone in the prevention of human rabies.

Studies on vaccine treatment of humans exposed to rabies have been notoriously untrustworthy. McKendrew's {QUERY: MK to verify name} laborious analysis for the League of Nations of experience in India up to the 1940s indicated that no conclusions could be drawn about the value of vaccine from the vast number of recorded histories of its use in India. WHO's own similar appraisal of this situation in 1950 at the first meeting of the WHO Expert Committee on Rabies led to the setting up of a trial in Iran. I will first describe the background of how and why the trial was conducted, its results, and then the reasons for the decision taken by the Expert Committee.

There were some indications -- reinforced by laboratory research in animals by Hilary Koprowski and Karl Habel (WHO Bulletin 1955 - PK: Get reference) -- that rabies antiserum may have value in post-exposure treatment in humans. The Expert Committee designed a careful experiment and entrusted it to our colleagues at the Pasteur Institute in Iran, where patients who were severely exposed to the bites of rabid wolves were often admitted. The plan was to divide a large group of patients bitten by the same proven rabid wolf (a not uncommon occurrence) into two groups, one group to receive the usual course of potent vaccine (21 . inoculations) prepared at the Iran Institute, and the other to be given the vaccine course plus one inoculation of Lederle's high-titre antiserum prepared in horses. After several false alarms, the important day arrived in 1954. Twenty-nine patients were brought to Teheran from a distant mountain village where they had been bitten by a rabid wolf on a rampage some 30 hours previously. The results were clearcut: survivals in the group who were treated with antiserum were greater than amongst the control group that had received vaccine alone. (Fig. 1 and 2 and 3 and 4 (rabies figures 1-3, figure 4: wolf bite (PR GET PICTURE

FROM BALTAZARD), Reference: Baltazard and Ghodssi, WHO Bulletin 1955)

There was one small hitch, however. On seeing the savage wounds inflicted by the wolf, Carlton Gajdusek, who happened to be at the Iran Institute during one of his trips to the Pacific, advised that the small group receiving the serum be split into two parts, one to receive a single inoculation of serum, and the other two inoculations of serum several days apart (see rabies figure 3). No amount of statistical juggling could furnish significant. differences between these two groups. Thus, we were in a quandry about whether to recommend one or two inoculations of serum. The fact that the equine origin of the serum resulted in a high incidence of serum sickness led us to opt for the single dose. The anathema we invoked on Gajdusek for fouling up our experiment protocol was lifted only after he had won the Nobel Prize for his work on kuru.

Obviously, a statistically significant result could not be derived from that experiment on the efficacy between one or two inoculations of serum, and the problem remained of what to do about the unquestionably high mortality of severe exposures to rabies shown by Iran's experience over the years, as well as in this experiment, and the poor evidence available that vaccine treatment alone was effective.

The Expert Committee made a Solomon-like decision. Evidence of the effectiveness of serum use in rabies prevention in laboratory animals was clear. The Committee therefore decided to recommend the use of serum with vaccine on the basis of the Iran trial. But should one or two doses of serum be recommended? The Committee chose one dose because of the frequency and degree of serum reactions from the use of animal serum for treatment, the only source of antibodies available at that time. The combination of serum-vaccine for humans remains the standard treatment today, that was originally based on the Iran results. Much additional work on animals, of course, has been done since

then that indicates the value of serum, so we need not feel too guilty about making the early decision on such slim evidence.

But the question remains: is this an example of the use or misuse of epidemiology?

Brucellosis

According to numerous WHO publications, brucellosis is the most important zoonosis in Asia, Africa and Latin America in terms of human illness and economic losses in animals. Diagnostic testing and elimination of positive reactors in dairy livestock are costly procedures in North America and Western Europe adding to the worldwide economic toll this single disease exacts, despite the existence of effective vaccines against animal brucellosis since the 1930s. The malady in humans is usually long drawn out and debilitating, and chemotherapy is expensive and often unsuccessful. Further research is therefore desirable in both human and animal brucellosis. Epidemiological factors enter into efforts at research in these areas, and therefore will be considered briefly.

Vaccines are of proved efficacy in cattle in the developed world, but in developing countries brucellosis takes its greatest toll in humans and goats and sheep.

Therefore, efforts have continued to improve the situation in those cases. Brucella melitensis causes the greatest harm in both humans and animals and, consequently, efforts have focussed on effective chemotherapy for humans and vaccines for animals to combat such infections.

Animal brucellosis

There has been much controversy about the effectiveness of different vaccines to combat melitensis infection of sheep and goats. An authoritative review of this question has recently been made by Professor Sanford Elberg of the University of California in Berkeley (Veterinary Bulletin, 6 (12):1193-1200). The vaccine Rev.l has been shown in this review and elsewhere to be the most effective vaccine in sheep and goats, but the S-2 vaccine recently developed in China was claimed to have the extraordinary advantage of being effective if given in drinking water or by drench, as well as by parenteral or conjunctival inoculation. In the Early 1990s pressure was brought to bear on WHO to recommend the S-2 vaccine. A large field experiment had been carried out in Libya sponsored by the Food and Agricultural Organization (FAO). No controls of unvaccinated sheep were included in the trial, and presumably favorable results were reported, and the S-2 strain, which had shown some indications of positive results in laboratory animals, received a great boost.

WHO then sponsored carefully controlled experiments in France and Spain comparing Rev.1 and S-2 vaccine in sheep. Results showed unequivocally that Rev.1 had an excellent protective action, while 5-2 vaccines had no protective effect. (cited by Elberg and published by WHO). The results of these WHO sponsored experiments have been influential in dissuading wide indiscriminate use of S-2 vaccine in many countries that might have credited the favorable but faulty epidemiological observations reported for S-2 vaccine - observations that were a misuse of epidemiology.

Human Brucellosis

Effective chemotherapy of human brucellosis has been claimed for several chemicals. An attempt is underway, sponsored by the WHO Centre in Athens on Mediterranean zoonoses, to make a comparative study of three different combinations of chemotherapeutic agents. Preliminary statistical analysis has indicated that at least 500 proven cases of human brucellosis would be required to obtain borderline statistically significant results. Hospitals in three different countries would be involved in the experiment. Experience has shown that the stringent experimental conditions required under the circumstances to obtain credible evidence to answer the question proposed would in all likelihood not be fulfilled. This, I believe, is an example of the questionable use of epidemiology.

Anthrax

In the spring of 1979 an anthrax outbreak occurred in humans and livestock in Sverdlovsk, USSR. Articles in Soviet publications attributed the outbreak to contaminated meat from animals that had died of anthrax. Some claims in the Western press, however, asserted that the outbreak resulted from activities prohibited by the Biological Weapons Convention of 1972, which the USSR had signed. This was a serious accusation that stirred embers in the Cold War that was in full spate at that time.

As Secretary-General of the Pugwash Conferences on Science and World Affairs, I became interested and involved in the international debate which had erupted. I took steps in the 1980s to determine whether a Pugwash group could visit Sverdlovsk to investigate the incident, and to report on it. This included taking up the matter privately with the Deputy Foreign Minister of the USSR, Vladimir Petrovsky. I was accompanied at that meeting by Professor Matthew Meselson of Harvard University and Academician Vitalii Gondanskii, a distinguished Soviet scientist who headed the Soviet Pugwash group, and who was a friend of Petrovsky. When intervention by Petrovsky failed to obtain the necessary permission, Goldanskii went to high KGB authorities but could get no satisfactory help from them. Meselson persisted in trying to obtain permission to visit Sverdlovsk with an international group of independent experts, and finally succeeded. The history and results of the above were published in *Science,* Vol. 266, 18 November 1994, pp.1202-1208.

I shall mention here only the steps taken by Meselson and his team to obtain the epidemiological information required to arrive at their conclusion. Slides 1 - 4 indicate the care and thoroughness of their investigations.

Their sources of information were the following:

administrative lists giving names, birth years and residence addresses of 68 people who died; household interviews with relatives and friends of 43 people and 9 survivors or relatives, or both, designed to identify workplaces and other whereabouts of patients before illness; grave markers of victims in a cemetery sector set aside for anthrax victims; and pathologists' notes of 42 autopsies.

Table 1 presents information on patients who died

Fig. 2 - probable locations of patients who died

{QUERY: MK TO CHECK "Died" vs "exposed"

Fig. 3 - villages where anthrax occurred in animals

Fig. 4 - wind directions and speeds reported by the city airport for the period 2 to 4 April 1979.

I believe that the investigations and conclusions reported by Meselson et *al* should be included in the highest ranks of epidemiology literature. Their investigation showed without a doubt that the airborne anthrax epidemic originated in a military laboratory in Sverdlovsk, although it could not be determined whether work on anthrax in that laboratory was for permissible defensive studies or for treaty-breaking offensive purposes. It also pinpointed the event for Monday, 2 April 1979, using epidemiological techniques ranging through shoe leather, wind currents and sophisticated mathematics.

Influenza

The epidemiology of influenza is one of the most fascinating histories in tales of infectious diseases. The story began to unfold in the early 1930s with the isolation of human and swine influenza viruses and continues today.

WHO's first involvement in identifying the importance and possible relation of influenza in animals to human influenza occurred during the 1957 Asian influenza pandemic which witnessed the emergence of a new strain of influenza H2N2 (Ref. Kaplan, M.M. Phil. Trans. R. Soc. Lond. B288, 417-421 (1980). Since then epidemiological animal-human influenza relationships have been pursued energetically, and at present Robert Webster and his group at St. Jude Children's Hospital in Memphis, Tennessee is a leader in this endeavor. In my view, the scope of the combination of field and laboratory studies for influenza to clarify the epidemiology of a communicable disease is unparalleled, and can be considered as a paradigm of epidemiological investigation.

The findings of some of these investigations are illustrated in the following figures:

Fig. 1 - The anatomy of the influenza virus

Fig. 2 - Reassortment of human and animal influenza strains.

Fig. 3 - Flyways of wild avian carriers of the influenza virus.

Fig. 4 - Genealogical tree constructed on the basis of nucleotide changes (Fig. 1 of Webster and Kawaoka).

Fig. 5 - Chart of antigenic changes in human virus and possible contributors from animal species

The story remains open-ended. The goal is to be able to predict possible new strains that may emerge, any one of which may become the killer-type strain of the 1917-1918 pandemic. With modern technology it is quite possible that vaccines could be constructed and produced in advance or quickly enough to blunt the possible catastrophe by using vaccine combined with chemoprophylactic preparations.

I have used influenza as one example of how a monster virus may theoretically be constructed for biological warfare purposes, which may then spread with catastrophic effects. Figures 6 and 7 {PK: can be cut if necessary, as can brucellosis if necessary} will illustrate this point.

Bovine Spongioform Encephalitis (BSE)

The popular name for BSE is "mad cow disease", and from the uproar it has caused overseas it might well be called "mad European disease," whose echoes have reached these shores. Here, I give a background sketch before we consider the theme of this paper. A memorandum of two meetings covered by WHO in April and May of last year, which I attended, covers most of the relevant points about this extraordinary disease (Bull. World Health Organization 74(5): 453-470, 1996.) I and many others believe it is caused by the so-called prion protein rather than by a classical microbe containing RNA or DNA.

Briefly, WHO received official word from its collaborating center on neurological disease in Edinburgh in March 1[0]96, one day before its release to the press and public, that BSE had apparently caused disease and death in humans. In WHO the VPH-zoonoses unit was designated to be responsible for organizing the two meetings mentioned above. The delay in releasing information to the scientific community and to the general public has been characteristic of British policy on this disease until fairly recently. It was a serious error on their part to follow such a policy, as it was a major cause of public fear, distrust and the string of economic sanctions on the UK cattle industry by the European Community.

In August 1996 an analysis and comments on the transmission dynamics and epidemiology of BSE in British cattle was published in Nature (Anderson et al, Skegg, volume 382, pp. 765-766 and 779-788). My remarks on BSE epidemiology will be confined to those articles. The lack of time precludes a detailed account which would best be dealt with in a seminar or a series of meetings. Since I do not have expertise on the mathematical techniques used I depend on my first reference given above for assurance that the mathematical modelling of the dynamics of BSE and alternatives for its elimination is of the highest order. I will confine my remarks to the conclusions of the article which are reproduced in the accompanying slide {PK see bse fig

They raise the following questions which merit thorough examination and discussion:

1. Do the conclusions provide an adequate guide for government policy decisions?

2. Can the recommendations be readily refuted, or their validity challenged by the criterion as falsifiable as noted in my previous reference to Karl Popper?

3. What further research should be recommended in light of the analysis made by the authors?

A thorough examination of this subject will have to await another time and place. I will only state here my brief judgement that the analysis may well prove to be by events as they unfold a good example of both the use and misuse of epidemiology.

The history of medicine is replete with examples of violations of Hippocrates to "do no harm". The sins of misuse of epidemiology are minor compared to the benefits obtained from the proper use of this discipline, as Cal Schwabe has shown in his outstanding book on veterinary medicine and human health. The wide use of epidemiology is manifested by the voluminous literature-- good and bad-- which continues to pour out on the subject. I therefore look forward to further discussions here this week in trying to separate the wheat from the chaff.