The achievements of epidemiology over animal methods

It is a medical cliché that prevention of disease is better than cure. But first, doctors must discover the causes so that people know how to avoid illness. This is the primary role of epidemiology - the study of disease in human populations. Researchers monitor different groups of people to discover the true origins of disease. By providing the evidence on which to base disease prevention campaigns, epidemiology becomes the most important method available to medical science.

Some idea of the contribution of epidemiology comes from just two examples. During the 19th century, population studies revealed that people who lived and worked in dirty, overcrowded and unsanitary conditions with little food or clean water, were much more likely to die of infectious disease. Social reformers such as Edwin Chadwick in Britain and Lemuel Shattuck in the United States used these epidemiological findings to influence sanitary reform and the resulting improvements in public health were chiefly responsible for the increase in life expectancy over the following 100 years. Drugs and vaccines had only a comparatively small effect. The same measures would transform health in Third World countries today where the pressing need is for food, clean water, sanitation and improved living and working conditions. And it is careful detective work by modern day epidemiologists that has identified the main causes of heart disease, cancer, strokes and AIDS, showing how major killers in the West can be prevented.

Epidemiology - The Method

Epidemiology is based on comparisons: researchers obtain
clues by comparing disease rates in groups with differing levels of exposure to the factor under investigation. For instance, studies of a rubella outbreak in Australia during 1941 revealed more cases of congenital cataract in infants whose mothers had been exposed to the virus during pregnancy. This was the first evidence that rubella causes birth defects.²

Some population studies, where one community is compared to another, involve huge numbers of people. A recent survey of eating habits in China, referred to as the “Grand Prix” of epidemiology, compared people from 65 counties. The findings indict fat and meat as major causes of chronic disease and point to a vegetarian diet as most likely to promote health.³ ⁴

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On the other hand, vital clues also come from tiny “clusters” of very unusual disease. One of the first reports of radiation-induced cancer came from an epidemiological study in New Jersey where young women were employed to paint the luminous faces on wrist watches with radium. The survey found more cases of the normally rare cancer, osteosarcoma, than would have been expected among the general population. The victims had all been swallowing the substance when moistening the paint brushes between their lips.⁵

►Epidemiological studies in China have shown the simple, traditional, largely vegetarian diet to be healthiest.
The Australian obstetrician William McBride was first alerted to the dangers of thalidomide after seeing just three babies born with birth defects. However, the deformities were so unusual that McBride strongly suspected the drug. Unfortunately, his warnings to the medical profession were delayed because he tried to “confirm” his observations in mice and guinea pigs, both of whom proved resistant to the drug. And it was the dramatic increase in a virtually unknown form of vaginal cancer that warned doctors of the carcinogenic effects of diethylstilbestrol. The cancer appeared in young women whose mothers had taken the drug during pregnancy to prevent miscarriage.

Initial population studies often provide only circumstantial evidence of the causes of disease but epidemiologists have developed a wide range of techniques to strengthen and verify their conclusions. One of the most ingenious is the study of immigrants. For instance, by observing people who move from Japan, where there is a strikingly low death rate from heart disease, to the United States with its much higher mortality, researchers can decide whether the illness is largely preventable or linked to hereditary factors. It transpires that the Japanese owe their low rates not to their genes but to their way of life, because immigrants quickly acquire America’s higher death rates.

Another powerful technique is the discovery of a “dose-response” relationship where the risk of illness rises with increasing exposure to the suspected agent. The link between smoking and lung cancer was confirmed when population studies showed that the chances of becoming ill increased with the number of cigarettes smoked. Proof that 2-naphthylamine caused bladder cancer in the aniline dye industry, came with the discovery that risks depended on the time spent distilling the chemical, so much so that workers exposed for five years were nearly 100% certain to develop cancer!
Doll and Hill used epidemiology to prove that deaths from smoking increase with the amount consumed.

Epidemiological studies proved that fluoride helps reduce tooth decay.

Hypotheses can also be tested by experimental trials in which different groups of people are exposed to differing amounts of the test substance. A classic example is the use of fluoride to reduce dental caries. A practicing dentist noticed that children with mottled teeth, caused by a high concentration of fluoride in the water supply, seemed to have less tooth decay than usual. This prompted the Public Health Service to initiate epidemiological surveys of children from cities where the fluoride concentration varied considerably. The results indicated that dental caries decreased with increasing content of fluoride in the water. But final proof was only obtained through an epidemiological experiment in which fluoride was added to the water supply of one community and the subsequent dental experience of school children compared with another town with little or no fluoride in the water.

An early epidemiological experiment is said to have ended the fashionable practice of bleeding as a medical treatment.
1835, Pierre Louis studied the outcome of pneumonia in patients hospitalized in Paris and discovered that bleeding increased the death rate. Until then, millions of leeches were imported into Paris every year.

Experimental epidemiology provided compelling proof of the link between oxygen treatment and retrolental fibroplasia, a condition where fibrous tissue proliferates behind the lens of the eye causing blindness. It was noticed that the disease occurred much more commonly in premature babies who had continuous oxygen therapy during the first few days of life. The observation led to trials with reduced amounts of oxygen, when the disease completely disappeared.¹²

More recently, US researchers led by Dr Dean Ornish at the University of California, have carried out experiments to see whether lifestyle changes normally suggested as preventive measures can also be effective in treating people with heart disease. They found that if patients with advanced heart disease adopt a low fat vegetarian diet, stop smoking, take moderate exercise and use relaxation techniques, the plaques in their arteries actually start to disappear, the changes occurring in only a year and without the use of drugs.¹³

Although epidemiologists prefer planned experiments, this is not always possible. Nevertheless a great deal can be learned from critical analysis of unplanned “experiments” such as natural or man-made disasters. For example, much of our knowledge concerning methylmercury toxicity comes from the notorious outbreaks of poisoning at Minimata Bay in the 1950s and in Iraq during 1971-72. In what came to be known as “Minimata disease”, a total of 121 people living in villages around Minimata Bay were poisoned by eating contaminated fish: 46 died. The poisonings were traced to release of methylmercury compounds from plastics industries into the waters of Minimata Bay.¹⁴ According to Dr Dewar of the Shell Center in London,¹⁵ such studies have given “infinitely more relevant knowledge than
even the most careful and elegant animal tests.”

The Atomic Bomb Casualty Commission has monitored the long-term effects of radiation following the Hiroshima and Nagasaki explosions and, as Gilbert Beebe of the National Cancer Institute explains, 16 “we have learned more about the human effects of ionizing radiation from the experience of the A-bomb survivors than any other source.”

Epidemiological studies of soldiers exposed to atom bomb tests in 1957, and of workers at the federal government’s nuclear site at Hanford in Washington State, have revealed the hazards of low-level radiation.

► **Atomic bomb explosions, World War II:** Survivors were closely monitored and radiation effects studied. Despite the colossal amount of human data, animals continue to be subjected to radiation injury.
Historically, some of the most famous medical breakthroughs have featured epidemiology. An early success was James Lind’s dramatic treatment of scurvy. Lind had been familiar with the disease during his service as a naval surgeon and by comparing seamen who developed scurvy with those who remained healthy, he deduced that it was a deficiency disease caused by lack of fruit and vegetables. In 1747, aboard HMS Salisbury, Lind put his theory to the test and treated some patients with oranges and lemons while others received non-dietary remedies. The experiment worked beautifully but it was not until 1795 that the Admiralty finally accepted his conclusions and included limes or lime juice in the diet of seamen. As a result, British seamen became known as “limeys.”

In 1846 Ignaz Philipp Semmelweiss joined the obstetric staff at Vienna’s General Hospital and within months showed how the appalling mortality from puerperal, or childbed, fever could be cut and the disease banished. By the time Semmelweiss arrived, the first ward in the hospital had acquired such a bad reputation on account of its high mortality rate that expectant mothers begged not to be placed in it. Semmelweiss carried out a meticulous epidemiological study, comparing the first ward with the second which had a much lower mortality. The key difference, he soon discovered, was that students entered the first ward for their instruction in obstetrics, straight from the dissecting room, whereas in the second ward, the work was done by midwives who had nothing to do with the dissecting and post-mortem rooms. The final clue came when a colleague fell victim to blood poisoning caused by a wound inflicted during a post-mortem examination: the symptoms, Semmelweiss observed, were similar to those of women who had died of puerperal fever. Convinced now that childbed fever was due to an infection carried from the dissecting room on the hands of doctors and students, he issued strict orders that their hands be thoroughly washed between each case they attended. As a
result, the death rate promptly dropped from one in eight confinements to one in a hundred.

Sadly, it was not enough for the professors who responded with such hostility that Semmelweiss was forced to leave. The American researcher and humanitarian Oliver Wendell Holmes had reached the same conclusions in 1843 and had been similarly vilified.\footnote{}

Another famous case is the conquest of cholera. Based on his theory that cholera is spread by contaminated water, John Snow, an early English anaesthetist, cut short an epidemic in the Soho district of London by removing the handle of the Broad Street pump.\footnote{The outbreak had killed 500 people within ten days and Snow found that only households receiving water from the Broad Street pump were severely affected.} Snow’s theory derived from epidemiological studies of the two London outbreaks of 1848-9 and 1853-4. By carefully charting the course of the disease among affected households, he deduced that the cholera agent enters the body via the mouth through contaminated food, water or the human hand: it is unhygienic conditions, he concluded, that create and perpetuate the chain of cholera victims. He then confirmed the role of contaminated water by showing that deaths were highest in households receiving the most contaminated water.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{public_pump.png}
\caption{Public Pump, England, 1855: \footnotetext{John Snow’s careful detective work showed how water-borne cholera could be prevented and paved the way for public health legislation.}}
\end{figure}

Snow’s epidemiological studies not only dispelled current
theories of cholera based on animal experiments but also formed the basis of successful anticholera campaigns and led to legislation mandating all the London water companies to filter their water by 1857. This was still 26 years before Koch first isolated the guilty microbe from cholera patients.

Similar detective work gave doctors the knowledge to control malaria. During 1898 Grassi painstakingly documented cases of the disease in the malaria region of Italy and noted the kind of mosquitoes prevailing in houses where outbreaks occurred. It had already been suggested many years before that mosquitoes could be the origin of the disease and parasites had been found in the blood of patients in 1880. Grassi was able to discount most types of mosquito and was left with the Anopheles as the only possible vector of the human disease. He obtained final proof by allowing Anopheles to bite a human volunteer who subsequently developed malaria.

While Grassi carried out his epidemiological studies, Ross proved that mosquitoes were involved in the transmission of malaria in birds but provided no evidence that such was the case in people, nor that Anopheles was definitely the correct vector. Nevertheless, it was Ross and not Grassi who received the Nobel Prize. As epidemiologist Dr Sigmund Peller explains, this

“proves only that, in the medical world and with the Nobel Committee, microscopical and experimental studies on animals have carried more weight than the epidemiological method, although the latter, and it alone, had led to the human experiment, the final indisputable truth.”

Epidemiology and Chronic Disease

Epidemiology had played the dominant role in controlling the destructive epidemics but for a long time little attention was given to the non-infectious disorders: before 1950 practically nothing was known about the causes and prevention of major
illnesses such as heart disease, lung cancer and chronic bronchitis. Many believed epidemiology was only concerned with infectious disease but that wasn’t the only reason for its neglect. A preference for laboratory research and animal experiments diverted attention from epidemiology and with it a true understanding of major diseases like cancer.

Before the first World War, population studies had identified several causes of cancer: it was found, for instance, that pipe smokers were prone to lip cancer; that workers in the aniline dye industry contracted bladder cancer; and that radiologists often developed skin cancer. It was also known that combustion products of coal (soot and tar) could cause the disease, an observation dating back to 1775 when the English surgeon Potts identified soot as a carcinogen in chimney sweeps. Attempts to reproduce Pott’s findings by experimenting on animals repeatedly failed but finally, in 1918, Japanese researchers produced cancer on a rabbit’s ear by repeatedly painting it with tar, a discovery that captured the imagination of the scientific world and changed the course of cancer research. According to British epidemiologist Sir Richard Doll, human observational data was now commonly dismissed because it was confidently assumed that laboratory experiments held the key to success. Crucial epidemiological studies like those of Percy Stocks at London University, who reported in 1933 that people consuming large amounts of fruit and vegetables were less likely to develop cancer, received little attention. Today we know that Stocks was right: recent epidemiological research has shown that a vegetarian diet, or at least one low in meat and rich in fruit and vegetables, can substantially reduce the risk of cancer.
The absence of epidemiological data allowed mistaken theories based on animal research to flourish. It also misdirected vast resources into areas irrelevant to most human cancers. Although we now know that only about 5% of US cancers are associated with viral infection,\textsuperscript{23} scientists once confidently believed that most, if not all, cases were caused by viruses, a view derived from experiments on animals where it is easy to transmit the disease in this way.\textsuperscript{24} It was even argued that because breast cancer in mice can be produced by a virus, women should not nurse their babies in case a corresponding infection is transmitted in the mother’s milk.\textsuperscript{25} With the origin of breast cancer differing even between rats and mice, it is hard to see how such views could ever be taken seriously.

\textsuperscript{Epidemiological studies of the notorious London Smog of 1952, connecting ill-health with pollution, led to the Clean Air Act of 1956.}

Fortunately, following the second World War, interest in the epidemiology of non-infectious disease was re-awakened. The most striking discovery connected smoking with lung cancer. By 1954, when Richard Doll and Bradford Hill published their famous investigation into the smoking habits of British doctors,\textsuperscript{6} there were already more than a dozen population studies linking cigarettes and the disease. In 1951 Doll and Hill had sent questionnaires to 59,600 physicians on the British medical
register requesting information about their smoking habits. The 40,000 doctors who responded were divided into non-smokers and three groups of smokers, depending on the number of cigarettes consumed. The causes of any deaths were then recorded over the ensuing 29 months. The study revealed an all-important dose-response relationship with the chances of developing lung cancer increasing with the number of cigarettes smoked. Later studies by the same researchers found that doctors giving up the habit substantially reduced their risks of becoming ill. Further population studies subsequently linked many other types of cancer to cigarettes so that today, smoking is held responsible for 150,000 US cancer deaths a year.

Perhaps the most important study in the history of heart research began during 1948 in the small Massachusetts town of Framingham. Inhabitants received medical examinations and supplied information about their diet and lifestyle with doctors monitoring their health over the ensuing years. The aim was to determine “factors influencing the development of heart disease,” and the results demonstrated clearly, and for the first time, that smoking, high blood pressure and too much cholesterol are major risk factors.

The Framingham project, together with further population studies showing that coronary illness is more common in people who seldom take exercise, demonstrated how heart disease could be prevented. Since the 1960s, when the United States had one of the highest death rates from coronary disease in the world, mortality has fallen sharply, declining by 25% within a decade. The improvements are in line with changes in diet and lifestyle with specific medical measures such as bypass operations and coronary care units having only a small impact, at best.
By comparing bus drivers with their more active counterparts, bus conductors, epidemiology first identified lack of exercise as an important factor in heart disease.

Epidemiological studies have shown that communities such as the Alaskan eskimos, who consume very little salt, do not suffer from high blood pressure. Substantial reductions in salt consumption would cut Western stroke and heart disease deaths by 39% and 30% respectively.

The message soon spread to the North Kariela region of Finland where, in 1971, the death rate from coronary disease was the highest in the world. The people set up a community action program with everyone advised to stop smoking, eat less fat and more vegetables, avoid obesity and have their blood pressure checked. By 1979, death rates had fallen by 24% in men and 51% in women.

The Framingham project stimulated further epidemiological research and, in all, over 20 population studies in 14 countries have confirmed the link between heart disease and high blood pressure, smoking and levels of cholesterol in the blood. The recent Chinese study of diet and disease found that, as a result of the largely vegetarian, almost vegan diet in rural China, cholesterol levels are by Western standards extremely low, with heart disease rarely recorded as a cause of death. According to Richard Peto, a co-author of the study, “The Chinese experience shows us that most of Western coronary heart disease is unnecessary.”

Today the Framingham project is devoted to stroke and ageing, together with follow-up studies of children of the original participants.
Epidemiology versus Animal Experiments

The revival of interest in epidemiology has been especially important for cancer research. Doctors now know much more about the causes and 80-90% of cases are considered potentially preventable. Population studies have proved so valuable that an editorial in the medical journal *Clinical Oncology* described the epidemiologist as the most important member of the cancer research team. Epidemiology has shown that differences in cancer between communities and between people are associated with differences in the local environment or the behavior or genetic constitution of individuals. According to Richard Doll,

“The knowledge gained in this way has led, directly or indirectly, to nearly all the steps that have been taken to reduce the incidence of cancer in practice.”

The great majority of cancer-causing agents were first discovered from their effects on people following widespread use rather than by experiments on animals. It is also revealing that the 1980 United States Congress Office of Technology Assessment Report into the causes of cancer, relied far more on epidemiology than laboratory tests because, its authors argued, these “cannot provide reliable risk assessments.” Nevertheless, animal experiments have consistently been allowed to undermine epidemiological findings, often with disastrous results.

The failure to induce lung cancer in animals by forcing them to breathe tobacco smoke, cast doubt on the results of human studies, delaying health warnings for years and costing thousands of lives. Summing up nearly two years of experiments, the British Empire Cancer Campaign reported that mice, rabbits and other animals who were exposed to tobacco derivatives by direct inhalation, feeding, injection into the lungs and skin painting developed no signs of cancer. And a year later, in 1957, American pathologist Eric Northrup concluded in
his book *Science Looks at Smoking* that “(the) inability to induce experimental cancers, except in a handful of cases, during 50 years of trying, casts serious doubt on the validity of the cigarette-lung cancer theory.”

Northrup described how “it is reassuring ... that public health agencies have rejected the demand for a mass lay educational program against the alleged dangers of smoking. Not one of the leading insurance companies, who consider health hazards in terms of monetary risk, has raised the life insurance rates for heavy smokers.” To this day it has proved virtually impossible to induce lung cancer in animals by the inhalation method.\(^{30}\)

Another case is asbestos-induced lung cancer.\(^{31}\) The first reports of an association between asbestos and lung cancer came from America, England and Germany during the 1930s following examination of people who had died with the lung disease asbestosis. By 1938 there were six reported cases and five years later the German government declared asbestos-induced lung cancer an occupational disease. But in some countries, notably the United States, the carcinogenic action of asbestos was doubted until the 1960s because it proved impossible to induce the disease in animals. By 1955, six separate animal studies had been carried out but only one appeared to show that asbestos might cause cancer and even this was discredited by scientists. Researchers were also concerned that the early autopsy findings might not be representative of all asbestos workers. The issue should have been resolved in 1949 when more cancer cases were found among workers seeking compensation for asbestosis than for silicosis, and again in 1955 when Doll reported the incidence of lung cancer in asbestos workers was ten times that in the general population. But the debate continued. Only in 1967
were experimenters finally able to induce cancer in animals by dosing them with asbestos.

In 1983 attention was drawn to an increased number of childhood leukaemia cases in the vicinity of a nuclear reprocessing plant at Sellafield in Britain. Although the incidence of leukemia was ten times the national average, the official Committee of Inquiry decided that the nuclear facility was not the cause. Their conclusions were based on information from animal experiments. By preferring animal data to direct human observations, the effect was to minimize the risks of radiation. Nevertheless, subsequent human studies revealed that radiation was indeed to blame. It was found that those at highest risk of leukemia were born to fathers who worked at the
nuclear plant. This suggests an effect of radiation on fathers which leads to cancer in their offspring.\textsuperscript{33}

For over 80 years doctors have known that too much alcohol can cause cancer but once again this well-established fact has been questioned because it proved impossible to induce the disease in laboratory animals. Indeed, some researchers insist that alcohol should not be classified as a human carcinogen because there is no evidence from animal experiments!\textsuperscript{34} The same is true for benzene, an industrial chemical widely used in manufacturing processes. According to the August 1982 issue of the scientific journal \textit{American Statistician},

\begin{quote}
“Although there are reliable human data linking benzene to leukemia, scientists have been reluctant to categorize benzene as a carcinogen because there are no published reports that it induces leukemia in rodents.”
\end{quote}

Arsenic is yet another well known human carcinogen for which animal tests have proved persistently negative. Human population studies have identified cancers in people following exposure to arsenic in drinking water and medications, as well as in chemical and agricultural workers, and also in those mining the ore.\textsuperscript{35} By 1947 an historical review of the subject described how dozens of animal tests had given “only doubtful results,” but that some human cases seemed definitely linked to the chemical.\textsuperscript{36} In 1969 researchers at the National Cancer Institute stated\textsuperscript{37} that “arsenic has been suspected by many investigators as a carcinogen in man, though there is no supporting evidence from animal experiments.” And in 1977 a further scientific review still concluded\textsuperscript{35} that there is little evidence that arsenic compounds are carcinogenic in animals.” Finally, in 1987, scientists managed to produce cancer in animals. This was 180 years after arsenic was first suggested as a human carcinogen and over 70 years since the first attempt to induce the disease in animals.
Animal experiments have also given contradictory results in studies of diet and cancer. Epidemiological research has shown that too much fat in the diet can cause cancer of the colon with saturated fat the chief culprit. However, according to animal tests, it is the unsaturated fats that are the most dangerous. With regard to dietary fibre, animal research is again confusing with some experiments showing a reduced risk of cancer and others an increased risk. The human evidence, which is all that matters, suggests that fiber can protect against cancer of the colon. But the absurdity of animal experiments is especially highlighted by tests carried out on the natural substances present in fruit and vegetables. These chemicals have been evolved by the plant as a defense against predators and parasites. When tested on rats and mice at high doses, many of these substances were shown to cause cancer. Yet it is well known from human experience that diets rich in fruit and vegetables actually reduce the risk of cancer!

Nevertheless, proponents of animal tests argue that they do have validity since nearly all human carcinogens have (eventually) been shown to cause cancer in some species of animal. But this is misleading: if substances like asbestos, tobacco, arsenic, benzene, alcohol, naphthylamine and soot were not already known to be human carcinogens, scientists would not have persisted with attempts to induce the disease in animals. Reliance would have been placed on one or two
routine feeding or inhalation tests of the type to which new chemicals are now submitted. As a result, many of the most dangerous human carcinogens would have been deemed safe. For new substances, where epidemiology has had no opportunity to assess risks, researchers should be calling for more reliable test systems rather than a continuation of the biologically flawed approach with rats and mice.

It is not only in cancer research where animal data is preferred to epidemiology. There is direct epidemiological and clinical evidence to show that a proportion of the population reacts adversely to food additives such as colors, preservatives, antioxidants and flavor enhancers. Symptoms include hyperactivity, asthma and eczema. But failure to produce corresponding symptoms in animals has been cited as grounds for doubting the human data.\textsuperscript{32}

In another case, reliance on animal experiments rather than epidemiology delayed a full realization that lack of food early in life can harm the brain.\textsuperscript{41} During the first quarter of the 20th century, there was considerable interest in the possibility that lack of food during childhood might interfere with the proper development of the brain and therefore affect the later achievement of the individual. Unfortunately, almost all the research was carried out on animals and showed that starving baby or adult rats had no effect on the brain. Not surprisingly, the topic was abandoned and was only resumed in the late 1950s when children with histories of undernutrition were persistently found to underachieve both in school and in formal tests.
Many of these problems arise from the mistaken belief that human findings must be replicated in the laboratory before they can be accepted. The 19th century microbiologist Robert Koch actually incorporated the idea into a set of rules for establishing proof that a specific germ caused the disease under investigation. When inoculated into animals, Koch argued, the microbe should reproduce the same condition seen in people. The concept was soon discredited by Koch's own study of
cholera\(^1\) but nevertheless remained influential. Only recently, the failure to induce AIDS in laboratory animals has been used as an argument against HIV as the cause.\(^{42}\)

In 1928 Bridge and Henry set out similar rules for *non-infectious* disease, stating that epidemiological evidence must be confirmed in the laboratory before a cancer can be classified as industrial. The preference for animal experiments is so ingrained that even as late as 1964, the World Health Organization was still recommending further animal testing of tobacco smoke,\(^{34}\) despite overwhelming epidemiological evidence for its effects in people. Epidemiologists have argued that population studies should stand alone in assessing the causes of chronic illness.\(^{34}\)

**Drug Safety**

It is well known that animal tests are very imperfect indicators of human toxicity so epidemiology has a vital role in monitoring the side effects of new drugs once they reach the market. Indeed, population studies have often come to the rescue after animal experiments have given a false sense of security. For instance, careful observation of women taking oral contraceptives revealed an increased risk of blood clots leading to heart attacks, lung disorders and strokes. The pill’s estrogen content was subsequently reduced. Not only had animal tests failed to identify the hazards but in rats and dogs, high doses of estrogen had entirely the opposite effect, making it more difficult for the blood to clot.\(^1\)

Epidemiology also had a major impact on the treatment of asthma. During the 1960s, at least 3500 young asthma sufferers died in the UK following the use of isoprenaline aerosol inhalers. Population studies showed that deaths occurred in countries using a particularly concentrated form of aerosol. The findings were sufficiently suggestive to change prescribing habits, with isoprenaline no longer available over the
counter at drug stores. Animal tests had given no warning and even after the disaster, it proved difficult to reproduce the drug's harmful effects in the laboratory.¹

One of the leading bodies involved in identifying hazards is the Boston Collaborative Drug Surveillance Program which set out to monitor adverse drug reactions by continuously observing patients admitted to hospital wards and taking their histories.¹¹ The Program first alerted doctors to the possible cancer-causing effects of reserpine, a drug used to treat high blood pressure.⁴³ Animal tests reported by Ciba Geigy, which markets the drug, had shown no sign of cancer.⁴⁴

Such cases highlight the need not only for effective monitoring of patients receiving drug treatment, so that hazards can be spotted at an early stage, but also for more relevant pre-clinical toxicity tests.

**Epidemiology - Underrated and Underfunded**

Despite impressive achievements, epidemiology has never received the credit it deserves. Although it is able to identify the underlying causes of illness and premature death, epidemiology does not have the prestige or financial support of laboratory research. The National Institutes of Health spends about twice as much on animal experiments as it does on research with human subjects,⁴⁵ while the preference for molecular explanations over social and environmental ones is backed by much of the medical establishment, by the drug companies and by the institutions of science themselves: there are no Nobel prizes for epidemiology. Furthermore, the high technology approach to medicine is far more glamorous and newsworthy than the preventive measures achieved through population studies. While epidemiological findings are saving millions of would-be heart patients, it is the transplant program and attempts to develop an artificial heart that gain media coverage, even though they can only hope to prolong the lives of a tiny
proportion of sufferers. As Dr David Nash, Clinical Professor of Medicine at the State University of New York Health Service Center, explains,  

“While it may be dramatic to demonstrate our technical skill in replacing blocked arteries, or even replacing the human heart with a mechanical device, risk factor reduction is a far more realistic, cost-effective and humane approach to resolving this serious health issue.”

Unless proper attention is given to epidemiological studies, there will be little prospect of reducing the incidence of major diseases such as childhood diabetes, epilepsy and Alzheimers, and medicine will be restricted to the often painful and costly control of symptoms with powerful drugs and surgery.

Nevertheless, population studies do have their limitations. Critics argue that epidemiologists cannot always carry out experimental trials with volunteers and are “limited” to observing what has already occurred, whereas laboratory scientists can manipulate animals in any way they see fit: after all, animals are regarded as disposable. In addition, when poorly designed population studies produce conflicting results, scientists may feel justified in turning to animal experiments. But as Professor Matanoski of the Johns Hopkins University explains,  

“Resolution of conflicting data will not be achieved by abandoning human data, but rather by examining more thoroughly the available information on humans to identify and eliminate the flaws in the existing (study) designs and methodologies so that eventually risk estimates can be based on data from the true reference population, the human.”

Whatever its limitations, the overwhelming advantage of epidemiology is its direct relevance to human disease. Not only that but observations can be made on hundreds of thousands of people whereas experiments on similar numbers of animals would be prohibitively expensive. No practicable animal experiment, for instance, could have proved that small doses of X-rays to a foetus in its mother’s womb, would result in one
cancer in every 2000 individuals during childhood, as was shown by epidemiological studies in Britain and the United States in 1958 and 1962.\textsuperscript{23}

Apart from saving lives and alleviating suffering, epidemiologists have made one other important, though inadvertent, contribution to medicine. By showing that diet, lifestyle and environment are the main causes of disease, they have shown that animal research is not only irrelevant to the major factors which govern our health but is also a serious waste of resources.

\begin{itemize}
  \item Mice are \textbf{not} miniature people. As Alexander Pope said \textit{"The proper study of mankind is man!"}
\end{itemize}
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