EPIDEMICS, OLD AND NEW

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Wide spread occurrence or epidemics of infections have been recorded in human societies for several thousand years. As early as 1570 BC Egyptian mummies were noted to have skin lesions characteristic of small pox. In 541 AD a major plague epidemic spread throughout the Roman Empire. Starting in 1346 the most serious plague epidemic, called the Black Death killed about one third of the population of 14th century Europe (about 25 million people). It is said that the Spanish most likely introduced small pox, measles and other epidemic diseases to Central and South America, and by the mid 16th century the Aztec population in Mexico decreased from 30 million to 1.5 million. The microscope, discovered in the 17th century, revealed microscopic creatures of uncertain significance. By the late 19th century it was established that some of these "things" seen under the microscope caused disease. Pasteur was able to reduce the incidence of tuberculosis transmitted in cow's milk by heating milk to a temperature which destroyed offending organisms

but did not chemically alter the milk. This process is called pasteurization. In 1870 Pasteur said "It is in the power of man to make parasitic maladies disappear from the face of the earth." He was so wrong. Epidemics of infections continue to feast on humans.

An epidemic of streptococcal infection swept through the armed forces in 1944 and 1945. While in boot camp at Great Lakes in the winter of 1944 (Company 2298) approximately 25% of our company developed a streptococcal infection in one form or another and were temporarily relieved of duty, some being hospitalized. I think some of you already know that during the boot camp experience at lest twice a day members of each company were required to steel wool the deck (wooden floors of the barracks) to remove spots of any kind, mostly spots that were caused by rubber composition soles of boots that all recruits wore. Each time after steel wooling there was so much dust in the air that it was impossible to see from one end of the relatively short barracks to the other. Several of us in my company wondered if the dust and streptococcal infection were in any way related. One day a small group of us screwed up our courage and asked our chief, the company commander, if he thought there was any relationship between the extraordinary incidence of infection in our group and the dust in the barracks. The chief of the company met our observations graciously by saying "Get the hell out of here. That is none of your damn business." A week or so later an edict came down from on high announcing that there would no longer be a requirement to steel wool the decks of our barracks. The steel wooling stopped and the floors were oiled instead. Almost immediately there was a striking reduction in the incidence of streptococcal infection at Great Lakes. I am quite sure that our observations never left the chief's office.

No one could have predicted the changes for the better in regard to disease management and understanding since the mid-twentieth century. In mid

May of the year 2002 my class celebrates its 50th anniversary of graduation from the college of Medicine here in Cincinnati. My beautiful wife and I also celebrate our 50th wedding anniversary. Let me review briefly the status of clinical medicine in 1952. For example, there was no effective treatment for hypertension. Treatment for the failing heart or what was called "dropsy" in those days was only minimally successful for a short period of time. The only treatment for cancer was surgery sometimes followed by low voltage radiation. The antibiotic era had begun but there were many infectious illnesses that were poorly diagnosed and untreatable. There was little or no treatment either preventive or therapeutic for patients with arterial disease. All patients with all forms of acute leukemia died shortly after diagnosis. No treatment was available. Streptomycin and Paraminosalicylic Acid (PAC) were available to treat tuberculosis, but thousands did not respond to this treatment and were housed for indefinite periods of time, sometimes years, isolated from society because of the threat that they would spread infection. Heart operations involved only manipulations of one or two of the heart valves. Valve replacement therapy was considered to be experimental. Coronary artery therapy was being dreamed of but had not yet begun. Organ transplantation, kidney, liver, pancreas, bone marrow and so forth, was on the drawing board but no projects were underway. Obviously great progress has been made in these past five decades.

Now hypertension, when diagnosed, is treated successfully with one or several of a wide variety of drugs. The therapy of cancer now includes high voltage or isotope radiation and multiple chemotherapy drugs. Improvement of survival, for instance in patients with breast cancer and colon cancer, increases every year because of improved therapeutic modalities.

In my field of special interest, more than 75% of children with acute leukemia are treated successfully with very elaborate chemotherapy programs. In adults

the success rates are not quite as good but are improving yearly. Adults with lymph node tumors called lymphomas and Hodgkin's Disease can be cured with combinations of radiation therapy and chemotherapy. Sometimes bone marrow rescue or bone marrow transplant is necessary. It seems likely in the audience tonight that there are several who have had coronary bypass surgery and/or valve replacement or both. Hardly anyone of our "mature age group" has not been offered a drug to lower cholesterol and triglycerides.

Organ transplantation, although still a very serious therapeutic endeavor, has become relatively commonplace. Kidney and bone marrow are the most frequently transplanted. Liver, pancreas, heart, lung and intestinal transplants are on the rise.

The progress in the management of infectious diseases has been astonishing. In 1952 there was a world-wide tuberculosis epidemic. That year Isoniazid was added to the previous therapy of tuberculosis and thousands more were cured. Throughout the country domiciliary units and tuberculosis hospitals which had housed active tuberculosis patients emptied out and began to close down. TB still occurs in the United States presenting mostly in the homeless and the elderly in immunosuppressed patients (AIDS) and others with far advanced chronic illness. Worldwide it is estimated that there is still 30 million cases of active tuberculosis with 10 million new cases diagnosed yearly. There obviously is still a lot of work to do, especially at the international level.

As a medical student and as an intern and resident in the early days of my career, it was not uncommon to see and treat patients with far advanced or tertiary syphilis. The syphilis spirochete was known to invade every organ leading to dementia, inability to walk properly, heart disease, skin disease, liver disease and so forth. As a medical student I remember attending the night VD (venereal disease) clinic at the then General Hospital where multiple patients with

advanced central nervous system syphilis were being treated and followed. The treatment at that time, which was reasonably successful, was with a lengthy series of heavy metal injections which were referred to by patients as the "hip and arm shots". By the mid 1950s penicillin had become the treatment of choice for all forms of syphilis and currently is still the highly successful treatment of choice.

Of interest are the discussions which continue to this day regarding the origin of syphilis. Some "experts" believe that syphilis was brought to Europe by members of Columbus' crew having contracted the syphilis in Haiti. Others believe that syphilis had been present in Europe prior to the voyages of Columbus originating possibly in Central Africa. It is well known that syphilis may follow sexual contact with infectious lesions. Currently populations at highest risk to develop syphilis parallel the risk groups of HIV infections.

Following graduation members of my class took three days of state board examinations in Columbus, Ohio prior to starting the internship. A small group of us rented adjoining rooms in a motel near the OSU campus where each evening before the upcoming examinations we reviewed briefly some of the subjects. I remember at that time scanning through a Columbus newspaper and noting in the news with some interest that Anthrax was found in a few sheep in west central Ohio. Subsequently that flock was isolated and destroyed. Having spent a summer working on the line at the Stearns and Foster Mattress Factory six years previously we were told that the wool used in some of the mattresses was sterilized and there was no danger of wool sorters disease, a cutaneous form of Anthrax. My review of the details of Anthrax the night before the exam in microbiology paid off. There were multiple questions about Anthrax. Until recently I had not thought about that disease for some 50 years. Prior to the current outbreak only a rare case of Anthrax had been reported in the United States during the past 20

years, although 20 to 40 thousand cases per year continued to occur in the rest of the world.

Following an internship at the General Hospital and a year of residency in Internal Medicine at a local community hospital I entered the general practice of medicine in the summer of 1954 and continued with this general practice of medicine until 1961 when I returned to the College of Medicine to complete my training in Internal Medicine and later Hematology in large measure through the encouragement of Dr. Richard Vilter. In the winter of 1957 there was an influenza epidemic in the USA. This particular variety of the influenza (flu) virus was not as virulent as the 1918-1919 strain where it was estimated that there were 20 million fatalities world wide. During the epidemic in 1957 our office was open seven days and five nights a week tending to our group of patients. In addition to seeing approximately 100 or more patients in the office on any given day, there were always a number of house calls to do, babies to deliver, and patients to visit in each of several hospitals. Most of our days began before 7:00 AM and were sometimes complete before midnight. To my knowledge none of our patients who developed influenza died.

The summers from 1954 through 1960 were always times of great stress and emotion, not only for physicians and their staff, but for most of our families, especially those with small children. Several times each day, either in the office or in the patient's home, we evaluated the children with fever, sometimes high fever, hoping to find evidence of the infection in their ears, lungs or throat rather than weakness or pain in one or more muscle groups. I can still see the relieved expressions on the faces of the parents who had just learned that their child had a sore ear or a sore throat and that polio was not part of the picture. As parents of small children during those days we had similar frightening experiences. In 1960 the worry about polio came to end. April 24, 1960 was the first of three consecutive polio Sabin Sundays

where in our offices we administered the oral vaccine to all comers. Obviously we needed to keep a record of the vaccinations for each patient. Many who came to our office were not members of our regular practice group but obviously that made no difference. The vaccine was supplied to us free of charge. Our entire office staff which included a clerk, two nurses, two physicians, and two physicians' wives managed to administer hundreds of doses of vaccines on each of these three Sundays at no charge to the patient. It was interesting to hear the grumbling of some of the patients who wondered why the vaccine had to be distributed on Sunday taking away their family time. We did, however, receive one note from one father thanking us for the effort on behalf of our practice community.

All of you in the audience tonight know that Albert Sabin and his colleagues developed the polio vaccine while he served as Professor of Pediatrics here at our Children's Hospital Medical Center. Born in Poland in 1906 he came to this country when he was 15 years old. He attended New York University and started out his professional education as a dental student but soon shifted to the College of Medicine. It is said that the ultimate direction of his career was influenced greatly by his reading Paul DeKruif's "Microbe Hunters" where he recognized the challenges of unanswered problems in infectious diseases. It is common knowledge that the Sabin vaccine, administered orally, was developed using attenuated live poliovirus. The Salk vaccine developed at almost the same time used dead poliovirus. This latter vaccine was only available for use by injection or parenterally.

Beginning in 1960 and completing its cycle in roughly 1964, approximately 100 million people in the United States received the Sabin vaccine. It is estimated that from 1965 to 1966 the worldwide use of the vaccine prevented about five million cases of paralytic polio and approximately 500,000 deaths.

I had heard that Dr. Sabin could be and was a difficult task master, although I had only one personal experience with him, I found him to be gracious and charming. I should note that he and his family lived in the house at the corner of Rawson Wood Lane and Middleton Avenue in the heart of the Gaslight District in Clifton. I lived a block away up the hill and around on Rawson Wood Circle. One day upon arriving home from the hospital at about 6:00 PM one of Dr. Sabin's teenage children ran up the street to see me requesting that I come to see Dr. Sabin as soon as possible. He had injured himself at home and a "lot of blood was all over the house." I ran down to the house with her and found the great man bleeding profusely from a cut on his leg, actually more than one cut on his leg, injuring himself in some way that I no longer recall. In any event I asked him to sit, which he did. I asked someone to bring me a towel which was done. I wrapped the leg and tied the bandage and the bleeding stopped. Obviously it needed the further attention of a surgeon and this was carried out promptly by one of the faculty surgeons at the College of Medicine. Sometime after I received a handwritten note from him thanking me for my prompt attention to his need. He would be forever grateful, he said. I have that note tucked away somewhere. Maybe one of these days we can find it again. I do not understand why he did not receive the Nobel Prize in medicine.

By 1967 the threat of poliomyelitis was no longer present. The US Surgeon General, William Stewart, boldly predicted in 1967 that the book on infectious diseases was closing. He was so wrong! In 1980 a "new" disease appeared on the medicine scene in the United States and soon became a frightening epidemic.

The AIDS epidemic was ushered into the United States officially in June of 1981 when five previously healthy homosexual men became desperately ill with pneumonia caused by pneumocystis carini, an organism of uncertain taxonomy. In December of 1981 it was learned that these patients and similar patients had a

deficiency of CD4 T cells watchdog (lymphocytes derived from the thymus gland). In September of 1982 the term acquired immunodeficiency syndrome was used for the first time to name the illnesses of this unfortunate and growing number of patients with this unusual viral infection. In May of 1983 the AIDS virus was isolated from a patient and found to belong to the group of viruses called retroviruses. Since 1980 there has been an astonishing globalization of infected patients. It is estimated as of June 2001 that there are 36 million people worldwide infected with the HIV virus. An additional 22 million had died. Thirteen million children have become AIDS orphans having lost their mother or both parents to the disease. More than 14,000 new infections occur daily, five million alone in the year 2000 including 600,000 children younger than 15 years. Approximately 70% of the cases occur in sub-Saharan Africa where, in some regions, the HIV prevalence among adults exceeds 25%. The Caribbean, Southeast Asia and Eastern Europe are also struggling with substantial rates of new infection. We now have learned that AIDS is rapidly becoming a problem in China. Until the virus was isolated and the screening tests became available in March of 1985 the HIV virus had been transmitted via infected plasma to at least 50% of the 16,000 hemophiliacs in the United States and to an additional 12,000 non hemophiliac recipients of blood transfusions.

It seems reasonable to ask the question about the origin or site of origin of the HIV virus. Epidemiological data show that the HIV1 virus has been present in a subspecies of chimpanzees for centuries. However, why the virus jumped from chimpanzees to humans is a matter of scientific conjecture. Chimpanzees, as I am sure some of you know, have been a source of nutrition for humans in certain parts of sub-Saharan Africa for hundreds of years. Infected blood could have entered the human during the process of dressing a slaughtered chimp for human consumption. Ultimately complex demographic and social issues allowed the spread of this virus from Africa to

America. Transmitted by sexual contact in humans as well as contact with contaminated blood, AIDS became a major problem years ago among members of the gay community. Despite the frightening news regarding the prevalence of AIDS, it is now known that the spread of AIDS can be controlled or prevented with social behavioral modifications as well as the use of antiviral drugs.

Recently I talked with Dr. Peter Frame who is Director of the Infectious Diseases Center formerly known as the AIDS Treatment Center at the University Hospital. Dr. Frame initiated this treatment program in 1985. Currently they serve over 2,000 patients. For those who regularly seek medical attention and for those on optimum antiviral therapy, AIDS becomes a manageable chronic illness, not curable, that may lead to a normal life span in most people. Prior to the current program AIDS was 25% fatal within a decade. At the present time Dr. Frame notes that there are 16 licensed antiviral drugs in the management of AIDS. New drugs are arriving frequently. Treatment programs cost several thousand dollars yearly. This cost is of major concern to all patients, even those in the United States. I think that it is perfectly obvious that in the poor countries, especially in sub-Saharan Africa, AIDS is going largely untreated. There should be and could be a major humanitarian effort at an international level to see to it that all patients who have acquired AIDS get optimum treatment. I asked Dr. Frame about the possibility of there being a vaccine against AIDS in the foreseeable future. "It is my understanding that currently available HIV vaccine show some promise, but a uniformly successful vaccine may still be several years off." Triple drug therapy is 90% effective in improving the immunological course of infected patients, and as a result strikingly reduces the incidence of debilitating opportunistic infections.

Now another "new disease" is present in our society. This "new disease" was first described in an aboriginal population 50 years ago.

New Guinea is a large bird-shaped island extending east to west off the north coast of Australia, and is second only to Greenland as the largest non-continental land mass. Although discovered in the early 16th century by Portuguese explorers, civilized development of the island has moved forward very slowly except for isolated coastal areas. Aboriginal people then, as now, inhabited the New Guinea highlands and vast areas still remain undeveloped or even unexplored. During World War II Coast watchers established small outposts in some of the highland areas where they could monitor the flow of Japanese naval vessels and airplanes in and around the Solomon Islands which lay north of New Guinea. These observers often came into contact with the Aboriginal natives. Rumors were brought back by some of these observers that in one or more of the Aboriginal tribes there was a peculiar illness thought by some to be related to evil spirits that caused patients to die with a shaking illness which progressively led to inability to walk, eat, talk or think. Usually those involved were women. In 1953 J.R. Macarthur serving as a patrol officer for the Australian Trust Territory of New Guinea in the eastern highlands of New Guinea put the following comment in his journal: "Proceeding southwest across the range and down and across a small creek ascending to Amousi villages, nearing one of the dwellings I observed a small girl sitting down beside a fire. She was shivering violently and her head was jerking spasmodically from side to side. I was told that she was a victim of sorcery and would continue this shivering unable to eat until death claimed her within a few weeks." Officer Macarthur continued to encounter this shaking illness which was called by the Foray people Kuru, a word which they used for trembling from fear or cold. Mr. and Mrs. Berndt made similar observations among the Foray people, Jatay people, and Osurufa peoples during the years of 1952 and 1953. In 1956 Dr. V. Zigas, the district medical officer for the region, was able to obtain blood serum samples from 26 patients with Kuru, and the brain from one dead patient. All of this material was sent to a Dr. S.G.

Anderson at the Walter Eliza Institute of Medical Research in Melbourne, Australia. No infectious agent was isolated from the brain and antibodies against a local encephalitis virus were not present in the serum. Early in 1957 Dr. D. Carlton Gajdusek, a Cincinnati trained pediatrician, joined Dr. Zigas in New Guinea. These two initiated a Kuru Research Center where examinations and additional studies could be conducted and continued. In a relatively short period of time 154 active cases of Kuru were identified, many of whom died shortly after identification.

It became clear during the early days of this study that almost all of the patients came from tribes of the eastern highlands of New Guinea where the combined population of all the villages and hamlets was approximately 16,000, and two-thirds were of the Foray tribe. The disease itself, from beginning to end (end being death), was lasted 6-9 months with an occasional patient who seemed to have remissions and then relapses. The disease usually began with the patient noting difficulty in walking and, slightly later, tremor. The tremor and the ataxia progress to the point where the patients could no longer balance themselves even in a sitting position. As the disease progressed speech became unintelligible. Progressive dementia developed. At the end patients were totally helpless, unable to communicate, move or eat. Other than the abnormal neurologic function, no abnormal physical finding such as gross organ enlargement were noted. Extensive laboratory evaluations were performed using serum, and in the deceased, samples of body parts. No diagnostic abnormalities were noted. Treatment was attempted using a variety of antibiotics available in those days and these were not helpful. It was of interest to note that the disorder affected principally adult females and their children. Adult males were rarely involved. Autopsy samples of the brain showed degenerative changes in the cerebellum as well as the extra pyramidal system in the form that we now call spongiform encephalopathy.

The concept of a relationship between cannibalistic habit and the disease Kuru evolved slowly. In the areas of high Kuru incidence, cannibalism was practiced mostly by the women. Corpses with leprosy as well as those who died with severe diarrheal illnesses were excluded from the cannibalistic orgies. The bodies of Kuru victims were thought to be particularly tasty. Various forms of cannibalistic feasting were observed in several separate tribal areas. The brain was considered the prize morsel of the deceased corpses and was exclusively eaten by women. For at least a decade the etiology of Kuru remained an enigma. Working with two other colleagues, Dr. Carlton Gajdusek inoculated several primates intracerebrally with brain tissue obtained from deceased Kuru patients. Three chimps named Georgette, Daisey, and Joanne, inoculated as noted above developed a Kuru like illness approximately two years after the inoculations. The illness progressed and each one of the chimps died. An autopsy of the brains of the chimps revealed the presence of the human variety of spongiform encephalopathy. In 1956, Gajdusek and his coworkers inoculated a three-year-old chimp with homogenized brain tissue from a 59-year-old English male patient suffering with what was called Creutzfeld-Jakob's disease. Thirteen months after the inoculation the chimp developed a similarly progressive disease and at autopsy once again showed the spongiform encephalopathy. This latter experiment suggests that at least in some patients Creutzfeld-Jakob's is a transmissible illness. Kuru is now included among the several diseases caused by prions (proteinatious infectious particles). Prior molecules contain no nucleoprotein, have no cell walls, and yet are able to reproduce. With appropriate educational emphasis, cannibalism has largely disappeared from the tribes in New Guinea and Kuru has now dropped out of sight. For his work with Kuru Dr. Gajdusek received the Nobel Prize for Medicine in 1976.

Other "strange" diseases have now been confirmed to be "prion" diseases. Scrappie is one of these prion

diseases found in sheep and goats. The infected animals become irritable with intense itching that leads them to scrape their wool or hair, hence the name Scrappie. Mad Cow disease began to appear in Great Britain in the mid 1980s. The source of this prion disease in cattle was traced to a food supplement that included meat and bone meal from dead sheep. Some of these sheep carried the Scrappie prion and hence there was a species jump from the sheep to the cattle leading to the "Mad Cow Disease". Infected cows were found to have "spongiform encephalopathy", similar in form to "Kuru" brains. In Great Britain since the mid 80s over 150,000 cattle have been destroyed, ones either suspected of having or actually having prion disease.

In the human being there is a rare degenerative illness of the central nervous system called Creutzfeld-Jakob's disease (mentioned previously), similar in form to Kuru. There are several forms of Creutzfeld-Jakob's disease in humans: familial, sporadic and new variant. This latter form is acquired by ingestion of infected animal protein, prion protein, present in "mad cows".

In April of 2001 I drove to Lexington, KY where I spent 90 minutes with Dr. Joseph Berger, Chairman of the Department of Neurology of the University of Kentucky, and an acknowledged expert in prion diseases. We discussed bovine encephalopathy and Creutzfeld-Jakob's disease in some detail. He showed me data that suggests that the rate of occurrence of a new variant Creutzfeld-Jakob's disease was doubling every 23 months, but fortunately the numbers are extremely small.

A story was published in the New Yorker magazine July 17, 2000 authored by Burkhardt Bilger where it was noted that in four years five patients in western Kentucky had been diagnosed with Creutzfeld-Jakob's disease, a variant, as you now know, of Mad Cow disease. All five of these patients had one thing in common: they ate squirrel brains. These observations

were brought to the attention of Dr. Joseph Berger and his associate Eric Wiseman. Subsequently a letter regarding these findings was published in a British medical journal called "The Lancet". Their conclusion was "caution might be exercised in the ingestion of these arboreal rodents." At the time of my visit I asked Dr. Berger about the status of "Mad Squirrel Disease". His answer was that there was no evidence of spongiform encephalopathy in 50 captured squirrels from western Kentucky and that there were no further patients.

Finally, I asked Dr. Berger briefly about Hoof and Mouth disease, or Foot and Mouth disease which is recently being found in increasing numbers in some herds of cattle, currently a non-epidemic in Man. I asked if there was any risk of this being one of those organisms that could exhibit a species jump and move from animal to man. Hoof and Mouth disease is caused by a Coxsackievirus. There are Coxsackievirus viral infections in man. His answer was that he thought it would be highly unlikely. Just to be on the cautious side, however, I think you all ought to keep careful watch of your fingernails and toenails. I think you should also become especially worried if, when answering a question or an inquiry, you begin to shake your head and "whinny"!

The recently announced completion of the human genome will bring, ultimately, further understanding of known diseases and the discovery of many others. Despite significant progress, the battle against infective diseases is far from being won.
