Given to 12 Knap Graduate Students at Dinner Talk 1-14-58 Madison

EPIDEMIOLOGY

Let us consider for the moment the problems facing a lone influenza virus. A disembodied creature consisting of little more than a gene a hundred millimicrons across. It floats in the air of this room billions of millimicrons across in search of just one nostril ten million millimicrons across. Millimicrons may mean as little to you as they do to most of the people who use them, so let's enlarge all of the objects a half million times. The virus is now the size of a hen's egg, 2½ inches across and the nostril, the size of Lake Monona, 4 miles across, and this room is as big as the eastern half of the United States. The influenza virus has the problem of finding the nostril in this vast space and a further problem if it reaches the nostril of avoiding the forest of hairs and the swamps of slimmy mucus that surround the channel from the nostril to the lungs. Only if it reaches an epithelial cell in the lungs and if it can penetrate the protective layers of mucopolysaccharide on the cell surface and wrest control from house-size cell can it reproduce.

Viruses must have hosts and they must have means of reaching them. Some travel by air as the influenza virus. Some hitch-hike as the yellow fever virus does in the mosquito, and some hide in food and water as does

poliomyelitis or in the moist kiss of a girl as does the virus of mononucleosis. Viruses appear to be resourceful.

It is now evident that I'm going to talk about the problems confronting microbes in their role as parasites of animals and that I'm going to confine myself to one kind of microbe, the virus. But I'm also going to discuss the problems the epidemiologist has faced in studying these problems of microbes. The history of epidemiology is a story of concepts, contagion, the germ theory, carriers, vectors and parasitism as an evolutionary goal. The ancients did not understand contagion although the early Hebrews isolated lepers and described plagues. Boccaccio in his Decameron described the black plague which his characters were fleeing as a fire that consumed tinder, passing from one piece to another. A hundred years later, about 1500, Fracastoro, elaborated on the idea of contagion in a treatise. It is frustrating today to read his paper and know that his logical interpretation of events was not to be appreciated for another 400 years. Without experimental science and with only logic, other systems which were proposed had equal or greater appeal to thinking men of those days. This was illustrated as late as the yellow fever epidemic of 1793.

There was a similar fever in New York in 1791, and in Charleston 1792, but the major storm of yellow fever broke in Philadelphia in 1793 and of

the total population of about 50,000 people, 11,000 were attacked and some 4,000 died. It is probable that terror ran deeper in Philadelphia September 1793 than in London in the last stages of the black plague. Few went outside of their homes without having at their nose handkerchiefs or sponges impregnated with vinegar or camphor. Some carried tarred rope in their hands or camphor packs around their necks. Many took the middle of the road to avoid houses in which the disease had occurred. Acquaintances and friends avoided each other in the street and no one shook hands.

What did the people particularly those who were trained in medical science believe to be the cause of this epidemic? Some of the College of Physicians of Philadelphia said that the disease was imported into the city by vessels which arrived in the port after the middle of July. Benjamin Rush, the leading physician, scoffed at this idea of importation. He said that while yellow fever existed in the West Indies from which these vessels came, it was present only in certain areas where marsh exudations and the vegetable putrefaction was present and was intensified by the hot and dry weather. These same causes must also produce the same effects elsewhere; therefore, since vegetable exudations and hot, dry weather produce yellow fever in the West Indies, the same causes produce it in the United States and the cause of the epidemic was the rotting of damaged coffee on a wharf

near Arch Street. Dr. Redman of the College of Physicians supported Benjamin Rush. Daniel Webster of dictionary fame became interested in the epidemiology of yellow fever and published a series of papers on the subject, all arguments against contagion, chiefly because cases occurred without exposure to pre-existing cases of the disease. He showed the blankets and clothing of diseased individuals failed to infect healthy people and he showed that individuals who became diseased had not been out of the house in weeks in certain instances and had no contact with anyone who had the disease. He also pointed out that the epidemic was localized in in a given area, ran its course and died out. All of these he felt were incompatible with the idea of contagion. He believed the epidemic was caused by a local miasma due to organic to organic decomposition. He laid stress on unhealthy conditions, dampness and an accumulation of decomposed organic matter.

Not everyone agreed with Benjamin Rush and Daniel Webster. John Mease, a Philadelphia physician, believed that apparently healthy individuals could transmit the disease. He pointed out that during the Revolutionary War in the United States the mixture of Southern and Northern troops led speadily to disease when camped together; although, both had been previously healthy. In the like matter, the mixture of crews of ships of different nations at

sea has produced disease. The arrival of a stranger at St. Kilda on the remote western islands of Scotland produced influenza among the inhabitants. Mease discussed the healthy carrier of Texas fever of cattle before the Philadelphia society for promotion of agriculture. His supposition on this disease and influenza were correct.

The experimental foundations for epidemiology were laid even before the epidemic in Philadelphia by Leeuwenhoek, a Dutchman who observed bacteria in tooth scrapings in 1683. Neither he nor any of his correspondents at the Royal Society saw the significance of this new order of microbial life. One hundred and fifty years later, Pasteur demonstrated that the microbes of Leeuwenhoek, like other forms of life, rose from their own kind. Each generation of bacteria begot another generation. Spontaneous generation of lower life did not occur.

In 1878, Koch demonstrated that the microbes of Leeuwenhoek and Pasteur could cause disease in man and animals. It was not miasma or the wrath of God but microbes that caused disease. How they grew and passed from one host to another was still a mystery. An American, Sternberg, learned in 1880 that bacteria which caused disease could also hide in animals without causing disease. He found the Diplococcus of pneumonia in the saliva of healthy men. Then Loeffler isolated the diptheria organism

from throat washings. Koch recognized the establishment of this milestone in epidemiology. The incubative and subclinical carriers of disease were one of the mysterious sources of infection.

The role of vectors in transmission of disease was uncovered by two Americans. Theobald Smith and Frank Kilbourne, who proved in 1893 that ticks transmitted Texas fever from one cow to another. This was the same disease that had concerned John Mease years earlier. The tick was not only capable of transmitting it to cattle but also transmitted the infection to its own off spring. Within 7 years Reed and his co-workers had reported transmission of yellow fever by mosquitoes. Now Daniel Webster could be answered and John Mease could be vindicated. Theobald Smith went further and supplied the philosophical structure for epidemiology in his book, Parasitism and Disease. He applied the evolutionary concept to disease organisms. "The struggle for existence among living things, both plant and animal, which may be translated into a struggle for food and a search for the easiest way of obtaining such food has developed two universal habits, the predatory and the parasitic. The predatory habit has probably led by gradual, evolutionary steps into the parasitic habit which has been defined as finding of lodgment and food by one organism on or in another. Parasitism may be regarded not as a pathological manifestation but as a

normal condition having its roots in the interdependence of living organisms. The success of the parasite can be measured then by the number of hosts that it parasitizes not by the number of hosts that it kills. To kill a host is a mark of inexperience on the part of the parasite. Those are the fathers and their concepts.

Epidemiology is still a new science. We know the story of only a few viruses; some are simple, some complex. The disease that kills dogs along the Pacific Coast in Washington and Oregon is of the latter type. This virus-like parasite escapes from its host in the egg of another parasite, the fluke. The fluke egg hatches and its first stage larvae containing the virus infects a species of snail. Several larval stages pass in the snail and then the still immature fluke escapes and enters the salmon. The virus riding along waits while the fluke encysts in the salmon and while the encysted fluke waits for a carnivore to catch the spawning salmon. In the stomach of the carnivore, the fluke is liberated and migrates through tissues to the liver. Now the latent virus escapes and if the carnivore is a dog, a fatal infection develops. Obviously, tracing such a devious cycle is a fascinating job of detective work.

Here in Wisconsin we have been working on the story of vesicular stomatitis. We do not know yet whether the disease cycle is simple or

or complex. Some of the chapters are still missing. Our interest in the disease began in September 1949. An epizootic involving thousands of cattle occurred in northwestern Wisconsin. We isolated the virus and collected what information we could about this outbreak. What we learned did not fit textbook accounts at all. The textbooks described the disease as primarily affecting horses, as being spread by contact, as having neither a seasonal incidence or a geographical prevalence. We found the disease primarily in cattle, we could not spread it by contact, we learned that the disease almost always appeared in August and September and never during the winter. Furthermore, it appeared in some communities and never in others where one might expect it. A good deal of this information was available in the literature but had been ignored because it didn't fit the concepts of the textbook writers. Other information we obtained by writing to veterinary pathologists in all parts of this country and many places abroad. We tested some ideas by experiments. We stabled infected and normal cattle side by side, allowed them to eat hay from the same manger and to drink water from the same bucket. No infection of the normal cattle occurred. Yet these cattle were fully susceptible to inoculation. What inoculated cattle in the natural outbreak? Not an artificial needle. The seasonal incidence of the disease, its disappearance when cold weather came

on, its rapid spread in pasture land and along streams suggested that some biting arthropod was involved. For three summers two graduate students spent part of their time in northern Wisconsin collecting biting insects that attacked man and cattle. We learned that there were many species of Tabanids, horseflies and deerflies, but their primary season of abundance was during June too early for the outbreak. There were many species of mosquitoes and of other biting Diptera. These species were found throughout the warm season with two peaks, one in spring and one in late summer. We fed representative species upon infected animals and then on susceptible animals and demonstrated that it was possible for a number of mosquitoes and a number of the Tabanids to transmit the infection from one host to another. The arthropods acted as flying needles. The virus did not multiply in the insect but it could carry the virus from one site to another on the infected mouth parts.

An interesting thing about vesicular stomatitis was that the epizootics in Wisconsin occurred at infrequent intervals. The outbreak in 1949 had been preceded by an outbreak in 1937 which was in turn preceded by one in 1926. On this basis one might expect another outbreak about 1959 or 1960. There was little opportunity then for a chance to study the disease in nature in Wisconsin in the early 1950's. Our inquiries about the distribution

of the disease in other parts of the United States had revealed that the periodicity in the northern areas were much the same as they were in Wisconsin once a decade, but further south the disease appeared with greater frequency along the Gulf Coast and in southeastern United States the disease was seen every year. The disease was also a constant problem in all of the countries surrounding the Carribean.

In 1955 we were invited by the U. S. Department of Agriculture to investigate vesicular stomatitis of swine in southeastern Georgia. At this point I would like to distinguish several words. Epidemiology concerns the occurrence of disease in human populations and epizootiology is the study of the occurrence of disease in animal populations. Consequently, an epidemic is an outbreak of disease in the human population and epizootic in an animal population. An endemic area is a region in which disease does not die out. It is a focus from which disease spreads. An enzootic area has the same meaning. Southeastern Georgia then was an enzootic area for vesicular stomatitis; a region in which the disease kept alive and from which it could spread to an epizootic area such as we have known in northwestern Wisconsin. Our problem was to compare the epizootic and enzootic areas to find what made them different; why the disease persisted in one area and not in another.

Graduate students who were sent south in 1955 were enterprising. Within a week after arrival they had met the right people and acquired a rent-free headquarters where they and their families could stay, a crew of six trappers and the full-time assistance of an Okeefinokee guide. The laboratory was set up at Fort Stewart with the blessing of officialdom and a minimum of red tape. The first step as we saw it was to determine whether or not the disease existed in the wildlife population. Before the summer was over we knew that many of the raccoon and the deer and the bobcats had had vesicular stomatitis. Possums, cottontails, vultures and other creatures that we tested had not had vesicular stomatitis. The past history of the animal was readily determined by a serological procedure. Neutralizing antibodies were detected by mixing them with the specific virus. If antibody was present, the virus did not kill the indicator host in the embryonating egg. If antibodies were absent, the virus killed the embryonated eggs.

We also attempted that summer to find virus in mosquitoes and yellowflies of southeastern Georgia. In this we failed. The disease was seen in domestic swine and we found that it frequently occurred in the feral swine. The latter are true pigs that have escaped anytime within the past three hundred years into theswamps and lowlands of South Carolina, Georgia and

Florida. These pigs are present in thousands. They are hunted as game animals.

The success of the summer of 1955 depended upom Smith, the ex-poacher gamewarden, upon Randall, the local veterinary practitioner who got his license ten years after he began to practice, and Sargeant Register, an Okeefinokee native who knew the ways of the swamp.

The next summer extended our findings but did not add a great deal more. Whatdid it mean? We found that the wildlife on the lower coastal plain of Georgia and not on the upper coastal plain or in Wisconsin was infected with the virus of vesicular stomatitis. We had exposed cattle, swine, deer and raccoon to the virus in the laboratory so we knew something of the nature of the infection. All of these animals recovered from the disease within four to six days at the most and do not shed the virus thereafter. How could the disease be maintained with such a transitory beachhead in animals?

Although the disease was seen every summer in the coastal counties of Georgia, it had not been seen after October and did not appear again until the month of May. Where did it hide in the meantime? The raccoon, deer, bobcat and feral swine did not appear to provide any better possibility for a winter hide out of the virus then did the domestic swine or cattle.

In spite of the fact that we had demonstrated in the laboratory that the virus could be transmitted by arthropods, we had failed in the enzootic area to demonstrate the virus in any of the insects that we captured from premises where the disease appeared. Nevertheless, we did not feel too badly about this. Investigators of eastern equine encephalomyelitis had worked for years without demonstrating the presence of the virus in insects in the field; although we know that the disease is insect transmitted. We did succeed in finding the virus of equine encephalomyelitis in three pools of insects in 1956 so we knew that our techniques were satisfactory. It seemed time to change our research approach and our location. Several other things that happened independently caused us to leave Fort Stewart as a site of operation. Boccaccio could probably describe the situation much more effectively. Drew Pearson's column said that the General in charge of the Camp Stewart did not approve of the prostitution in Heinsville at the east end of the reservation. He pointed his finger at the sheriff of Liberty County as the chief propriator of the houses in Heinsville. According to Pearson the General had reason as conditions were worse than at Phoenix City. A Grand Jury investigation of the sheriff dragged along for a period of time. Finally through the intervention, said Pearson, of a Georgia senator the General was suddenly retired without the customary

promotion and the Grand Jury dropped the investigation. Our only concern in this matter was the fact that the new General came onto the post and for some reason he and our good friend from the Okeefinokee, Sargeant Register, did not understand each other and so Register was transferred to Germany. Furthermore, the army trapping program was suspended.

In 1957, we turned our attention further south to a place on the coast near Darien. We felt that it was necessary to establish a sylvan cycle of the disease and this could best be done on the land held by the Georgia Fish and Game Commission near the coastal waterway. Here on an island separated from a contact with the mainland and away from domestic animals we could determine whether or not the disease could be perpetuated in species native to the island. We found the place in the Altamaha Wildlife Refuge. The headquarters of the refuge is on Butler Island which lies below the level of the sea. The dikes which protects the island were built by slave labor prior to the Revolutionary War. This island was a source of rice during that early days. Of the original plantation buildings only the brick chimney of the old rice mill still stands. The present buildings were erected by one of the Vanderbilts some fifty years ago. We were surprised to learn that John Mease who described the epizootiology of Texas fever and gave a very excellent account of rabies went south from

from Philadelphia for the winter to the Golden Isles of Georgia. He met and married the daughter of Colonel Butler of Butler Island Plantation. His son some years later took the name of Butler to gain the inheritance and married an English actress by the name of Fanny Kemble. ~~We learned~~ about this from her journal. ~~Fanny Kemble's~~ description of the island in the month of February was set down in the journal which was later published. The colors of the swampland, the deep blue skies, the dead-gray moss-hung trees, the brown river, the great birds were ~~fully appreciated by this~~ English girl. Her account of the life on the plantation or in Darien as a slave or as a white was cut so sharp that she is remembered to this day. We first heard of her as the woman who started the Civil War. She minced no words in describing southern decadency and in reporting the parentage of certain mulattoes. We learned on Butler Island that vesicular stomatitis could persist in a sylvan cycle, that domestic animals were not needed for its existence. We became much more intrigued with the possibility that the feral swine might be the host of this virus the year round. A study area was set up on a 23 acre peninsula on Champney Island. Separated from the rest of the island by a double fence. The study area consisted of typical cypress and grass swamp a foot or two above the water. In this area we placed feral swine and later domestic swine. Their disease

status is being determined at selected times throughout the year. It may be that the virus of vesicular stomatitis is transmitted throughout the winter among the swine of the swamp regions that man has ignored. From the swamp region of Georgia came another discovery that vesicular stomatitis is a disease of man. Thirty percent of the human sera from the swamp regions of Georgia contained antibodies to vesciular stomatitis. On farms where the disease was reported the incidence was 50 percent and among women taken at random 10 percent had antibodies. It appears that vesicular stomatitis on the lower coastal plain may be a disease of man fully as important as encephalitis. Vesicular stomatitis of man resembles influenza and incapacitates the individual for four or five days. The Georgia Board of Public Health has become interested in the problems and has supplied us with a laboratory at Waycross where experimental work may be carried out on the significance of this disease in both human population and in the wildlife reservoirs.

How is the disease maintained in the enzootic foci? We postulate that vesicular stomatitis virus exists on the lower coastal plain in South Carolina Georgia and Florida, as a disease of feral swine and accidently of man, deer, raccoon and cattle. We postulate that it is transmitted by biting arthropods and maintained throughout the entire year by insect

transmission. How does the disease spread out of the enzootic area?

In some years probably because of the meterological conditions vesicular stomatitis spreads to the upper coastal plain and at infrequent intervals by means which we do not know the disease spreads into other parts of the United States as far north as Wisconsin, Minnesota, and Manitoba. This dissemination may be accomplished through the transportation of infected livestock. It may be through the agency of birds which are occasionally found to possess antibodies. It may be by the means of Diptera on winds of a storm, as are the leaf-hoppers which carry diseases of field crops far north into areas in which the disease can be propagated. Why does the disease appear as an epizootic in one area (northwest west) and not in another (southwest). We believe that the disease is found in northwestern Wisconsin and not southern Wisconsin, in central Minnesota and not in southern, and into eastern Manitoba and not into western because of the ecological conditions which favor the abundance of a suitable vector. Our investigation of ~~this subject~~ the epizootiology of V.S. has uncovered more problems than it has solved. This is true of many of the investigations in the field of epidemiology.