Gonorrhea: More of a Problem but Less of a Mystery

The spread of gonorrhea is easy to model, according to at least one mathematician. You can assume that everyone is susceptible to the disease and that a core of asymptomatic carriers keeps the disease endemic in the population (see box). Unfortunately, these traits, which make gonorrhea easy to model, make it difficult to wipe out. The current gonorrhea epidemic in the United States is a serious health hazard, especially since the gonorrhea microorganisms tend to spread from the urogenital tract, causing arthritis and other complications.

Until recently, research on the pathogenesis of gonorrhea was characterized by many open questions and few answers. Now, however, several recently reported results are giving new direction to gonorrhea research. Reasons why some strains of gonococci are pathogenic and others are not have been proposed and the proposals have been tested. Reasons why people do not seem to develop immunity to gonorrhea are emerging, as are ways that immunity may be induced. And the development of a blood test, if not a vaccine, for gonorrhea is thought to be imminent.

More than a decade ago Douglas Kellogg of the Center for Disease Control in Atlanta observed that gonococci can be divided into four groups, which he called colonial types, based on the appearance of the colonies formed when the bacteria are grown on agar plates. In tests on male volunteers, he found that two of these colonial types cause gonorrhea, whereas the other two do not. The avirulent types arise when freshly isolated virulent gonococci are subcultured for many generations in the laboratory. These observations by Kellogg led to the questions of what makes a colonial type virulent or avirulent and whether virulence can be controlled.

Richard Finkelstein and his associates at the University of Texas Southwestern Medical School in Dallas are investigating the relation between pathogenicity and colonial type by infecting chick embryos with gonococci of each of the four types. They found that the two colonial types that are pathogenic for humans are also pathogenic for chick embryos. When they inoculate a chick embryo with as few as 10 to 100 of these bacteria, the embryo dies within 24 hours. More than 10,000 bacteria of the avirulent colonial types must be inoculated into a chick embryo before a lethal infection will develop.

Recently, Finkelstein and Shelley Payne reported that they can alter the pathogenicity of the various colonial types of gonococci by manipulating the amount of iron available to these bacteria in chick embryos. When they inoculate embryos with gonococci of a virulent colonial type along with an iron binding protein, the pathogenicity of these bacteria greatly decreases. On the other hand, when they inoculate the embryos with gonococci of an avirulent type along with iron compounds, the virulence of these bacteria greatly increases.

According to Finkelstein, their discovery may provide clues to understanding why some people are more susceptible than others to gonorrhea and why some people have more severe infections than others. Differences in iron metabolism among laboratory animals have been shown to affect their susceptibilities to several bacterial diseases other than gonorrhea. Many investigators believe that whether various bacterial infections become established depends on whether the bacteria can acquire sufficient amounts of iron from their hosts. Finkelstein's studies indicate that gonococci are likely to belong to such a class of iron-requiring bacteria.

Gonococci from virulent colonial types are distinguished from avirulent types not only by their iron requirements but also by one aspect of their surface morphologies. Virulent gonococci have hairlike appendages (pili) on their surfaces, but avirulent gonococci do not (Fig. 1). Since there is a correlation between the presence of pili and pathogenicity for many gram-negative bacteria (bacteria are classified as gram-negative or gram-positive according to the way their surfaces take up a certain dye), researchers are asking whether pili play a role in the establishment of gonorrhea infections and, if so, how.

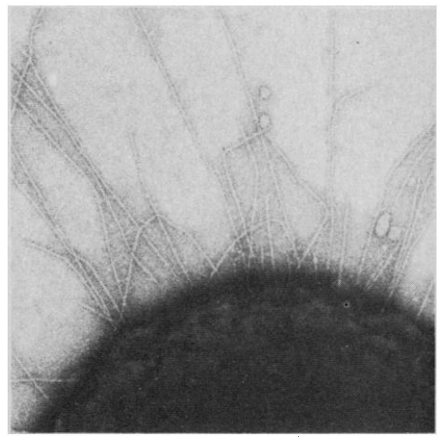

Fig. 1. Pili on the surface of a gonococcus (× 40,000). [Source: John Swanson, University of Utah]

One hypothesis is that pili enable gonococci to stick to host cells and thereby avoid being washed away. Gonococci that stick to sperm would also have an advantage in entering the reproductive tracts of women. In support of this hypothesis, John Swanson and his associates at the University of Utah showed that gonococci with pili attach to various human cells, including cells of the lining of the mouth and sperm cells, more readily than gonococci without pili. Swanson showed, by electron microscopy, that pili extend from the surfaces of gonococci to the plasma membranes of host cells when the gonococci stick to host cells. Thomas Buchanan and W. A. Pearce of the University of Washington find, in addition, that isolated, purified gonococcal pili bind more readily to human cells that would normally come in contact with these bacteria than to other kinds of human cells. For example, cells from the human cervix or vagina bind about 1000 pili per cell. Sperm bind fewer pili but HeLa cells, each of which bind only one to ten pili per cell.

It has been proposed that pili offer the gonococci protection from ingestion by human leukocytes. This is a common way for other virulent bacterial strains to protect themselves against their host's defense mechanisms. About 3 years ago, two groups of investigators reported that gonococci with pili are less readily ingested by human leukocytes than those without pili. More recently, however, Swanson and his associates found that although different colonial types of gonococci vary in their resistance to leukocytes, this variation is not correlated with the presence or absence of pili. In fact, one colonial type without pili is more resistant to leukocytes than others with pili. These investigators report that the ability of gonococci with pili to attach to host cells is not inhibited by the proteolytic enzymes trypsin or chymotrypsin. The ability of gonococci to resist ingestion by leukocytes is, however, inhibited by these enzymes. Swanson and

his colleagues suggest that a genetically controlled surface component, which they call leukocyte association factor, determines how susceptible various genetic strains of gonococci are to leukocytes. This factor occurs independently of pili.

A few years ago, Buchanan and his associates developed a radioimmunoassay for antibodies to pili and thereby showed that people often produce antibodies to pili when they are in-

Strategies for the Control of Gonorrhea

More than 1 million cases of gonorrhea were reported last year, and at least three times that many are estimated to have occurred. More cases of gonorrhea are reported each year to the U.S. Public Health Service than cases of all other communicable disease combined, including chicken pox, syphilis, mumps, hepatitis, tuberculosis, and measles.

Most disturbing to public health officials is the fact that the incidence of gonorrhea in the United States keeps increasing each year despite the fact that effective antibiotics to treat this infection are readily available. The number of reported cases has tripled in the past 10 years and, according to investigators at the Center for Disease Control (CDC) in Atlanta, these increases represent changes in incidences rather than changes in the proportion of cases reported.

To combat this epidemic, the CDC began, in 1972, a nationwide gonorrhea screening program. Last year, about 8 million people were screened, and those infected were treated. In the past year, the rate of increase in the number of gonorrhea cases in the United States leveled off. The screening program, however, may not be solely responsible for this effect. European countries with good health statistics, such as Norway, Finland, Denmark, and Great Britain, report similar slowdowns in their gonorrhea epidemics, although they started no new gonorrhea control programs in recent years. And Sweden witnessed a remarkable decline in gonorrhea incidences over the past 6 years. The number of cases reported in Sweden last year was only about half the number reported in 1969.

Since Sweden is showing that gonorrhea epidemics can be controlled, the reasons for Sweden's success are currently a subject of much speculation and interest. Lennart Juhlin of the University of Uppsala and others believe that an increased use of condoms in Sweden is a major reason why gonorrhea rates are falling there. The Swedish government has successfully promoted condoms by widely displaying a national condom symbol (Fig. 1) and by making condoms attractive and easily available. Gonorrhea rates declined as condom sales increased, and the changes occurred in the same proportions. However, Finland, Norway, and Denmark did not promote condoms and do not report decreases in their gonorrhea rates.

Some critics point out that, among the Swedish university students surveyed, many claim they do not use condoms, and hence the young people most at risk for gonorrhea may not be using these devices.

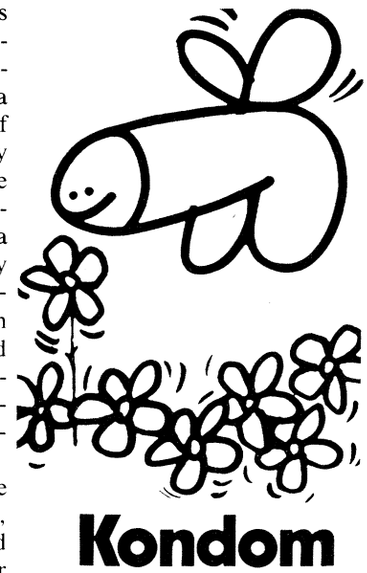

Fig. 1. The Swedish condom symbol.

These critics postulate that other events, such as changes in social mores, may have been of greater importance in causing Sweden's decline in gonorrhea cases. Yet many investigators recognize that these other events also occurred in Finland, Norway, and Denmark. Only the condom promotion is unique to Sweden.

Ralph Henderson of the CDC and others believe that the worldwide economic recession probably affected the gonorrhea epidemic in Sweden and also in the United States and other countries. Restriction of the amount of free time, mobility, and the spending money that people have is thought to be a factor in limiting sexual contact. If the recession did play such a role in reducing the number of cases of gonorrhea in the United States, then the effects of the CDC's screening program may have been minimal at best.

The CDC evaluation of the dynamics of gonorrhea epidemics in other countries and its analysis of its own gonorrhea control program led officials at the CDC to change their strategies. They are now focusing their screen on groups likely to have high incidences of gonorrhea, such as people between the ages of 20 and 24, and are retesting infected people 4 to 6 weeks after they are cured of their original infections.

The reason for retesting was derived in part from a mathematical model developed by James Yorke of the University of Maryland. Yorke argued that the dynamics of gonorrhea are controlled by a small "core" of sexually active people. At least 20 percent of this core population is infected at any time, and the core represents the main source of gonorrhea cases. Thus, the only way to decrease gonorrhea rates would be to decrease the number of people in the core. Since these people are likely to become reinfected once cured, members of the core would be detected and the number in the core would be reduced by rescreening infected people.

About 6 months ago, the CDC put its new program into operation, and already it seems to be more effective than its former program. Henderson reports that they are detecting more people with gonorrhea and are apparently finding some core members since 15 to 20 percent of retested patients have gonorrhea. Only 4 percent of all those tested in the previous program had gonorrhea. Thus as the epidemiology of gonorrhea becomes better understood, it seems increasingly likely that the disease may be brought under control in the United States.—G.B.K.

fected with gonococci. The finding of antibodies to pili supports the proposal that these antibodies may provide people with some immunity to reinfection by gonococci. Buchanan now reports, however, that pili are antigenically heterogeneous. He finds, so far, at least six antigenic types of pili. Thus it remains possible that antibodies against pili from one strain of gonococci will not protect against infection by gonococci with antigenically different pili. He reports results of studies of the role of antibodies in blocking the attachment of isolated pili to cells that support this hypothesis.

Despite the complication of antigenic heterogeneity of pili, Charles Brinton of the University of Pittsburgh reports that he can successfully protect chimpanzees from gonococcal infections when he vaccinates them with pili. Last year, he vaccinated five animals with pili and found that they were subsequently more refractory to gonorrhea. He finds this year that the three vaccinated chimpanzees that are still alive remain resistant to challenge with gonococci of the same strain as that with which they were vaccinated, although whether they are protected against other strains remains open to question. The immunized animals require 7100 times more gonococci to establish an infection than do chimpanzees that had not been immunized.

Blood Test Possible

Of interest to both pharmaceutical firms and clinicians is the possibility that an antigenic classification of strains of gonococci may lead to a blood test for gonorrhea. Most investigators agree that, in order to stop the spread of gonorrhea in the United States, it will be necessary to identify and treat carriers of the disease. At present, tests to identify carriers involve the taking of specimens and the culturing of the bacteria. Such tests are difficult and time-consuming.

Since infected people do produce antibodies to gonococcal pili, it remains possible that these antibodies could form the basis of a blood test for gonorrhea. Buchanan and his associates found, a few years ago, that men with asymptomatic infections and men with symptomatic urethritis who are treated within 10 days of being infected have very low concentrations of antibodies to pili in their blood. They suggested, then, that a radioimmunoassay for pili antibodies might best be used to detect gonorrhea in women. Recently, a firm has begun field testing this method as a means to screen women for gonorrhea.

Rather than attempt to develop an antigenic classification based on pili, several investigators are starting to classify strains of gonococci in terms of their cell surface proteins. This method is being developed by Kenneth Johnston of the University of Texas Southwestern Medical School at Dallas, King Holmes of the University of Washington Medical School, and Emil Gotschlich of Rockefeller University.

The outer membranes of gonococci, like those of other gram-negative bacteria, contain relatively few kinds of proteins. This simplifies the isolation of membrane antigens from these organisms. Johnston and his associates find that, for some strains, more than 60 percent of the total outer membrane protein of gonococci is of one type, and that

Speaking of Science

Concern Over Climate: Researchers Increasingly Go Public

The possibility of famine caused by greater incidence of bad weather is increasingly troubling many climatologists. The Indian monsoon, they note, has failed twice already in the 1970's, compared with only once in the 1960's. Definitive evidence of impending climate change is not in hand, however, nor likely to be very soon. But the stakes—literally millions of lives—do not make it easy for those with a knowledge of the extreme variability of climate in the past and the number of plausible causes of change to adopt an attitude of complacency. Wary of crying wolf too soon and critical of a few individuals who have publicly predicted disasters ahead, climatologists and atmospheric scientists have nonetheless been expressing growing concern to each other and to government officials. This has for the most part taken the form of cautiously worded reports emanating from the National Academy of Sciences and other agencies. Climate, they say, especially the remarkably uniform and favorable climate of the period 1955 to 1970, cannot be taken for granted. Higher priorities and more money for climate research have also been requested.

In trying to convey their message to federal policymakers, however, those concerned with climate have had little apparent success. A National Climate Program, in the process of formulation within the bureaucracy for the past 18 months, has died aborning. Top officials of the U.S. Department of Agriculture (USDA), urged to consider the possibility of grain reserves as a hedge against bad weather, have turned a deaf ear and asserted that adequate food can be supplied come what may, thanks to the miracle technologies of the Green Revolution.

The upshot of all this seems to be that more climate scientists, despite the still unresolved internal debates over the causes of climate change and the prospects for the future, are beginning to seek a wider audience for their concerns. One example is a forthcoming book by Stephen Schneider, a young climatologist at the National Center for Atmospheric Research in Boulder, Colorado, and his wife, a freelance journalist.* Intended for a popular audience, the book summarizes both the history and the theory of climate to illustrate its variability and the complexity of the mechanisms that control it. The book focuses on the potential impact of climate change on world food supplies and takes its theme from the Old Testament story in which Joseph warns the Pharaoh to store up food during the years of plenty for the lean years to come. Schneider proposes a similar "Genesis strategy" for the modern world that would include large grain reserves and similar policies to maintain "margins of safety" in the face of potentially adverse climatic changes, whether of natural or human origin. He suggests a host of new institutions and international agreements to cope with the pressures of growing populations on supplies of food, energy, and natural resources—pressures that he believes could be drastically increased by unfavorable shifts in climate.

*Stephen H. Schneider with Lynne E. Mesirow, *The Genesis Strategy* (Plenum, New York, in press).

major protein may serve as the basis of an immunological classification scheme.

Johnston, Holmes, and Gotschlich have found, so far, 16 different antigenic types of gonococci, classified by this outer membrane protein. Johnston points out that the distribution of these types is of epidemiological interest since the types serve as markers of the spread of gonorrhea. He reports that the distribution of these antigenic types varies across the country and that the types found on the West Coast of the United States are the same as types found in Vietnam.

The apparent lack of immunity to gonorrhea is a major reason why the disease remains endemic in human populations. This lack of immunity could be due to the antigenic diversity of the pili and surface proteins of the gonococci. It could also be an effect of a recently discovered enzyme secreted by gonococci and by closely related organisms that cause meningitis. The enzyme was found by Andrew Plaut of Tufts University Medical School, the late Malcolm Artenstein of Walter Reed Army Institute of Medicine, and their associates. This enzyme cleaves a type of antibody, IgA, secreted by mucosal surfaces. Similar enzymes have only rarely been found associated with bacteria, so its significance as a defense mechanism is under active investigation. Plaut and his associates speculate that the secretion of this enzyme may explain why patients recovering from gonorrhea have IgA antibodies in their urethral secretions, but still are susceptible to reinfection by gonococci.

The cleavage of IgA by the gonococcal enzyme, however, may not be the entire reason why people are subject to reinfection by these bacteria. Immunity to bacterial meningitis does occur, even though these bacteria also secrete an IgA-cleaving enzyme. In addition, not all the IgA antibodies to gonococci may be cleaved. The secretory antibodies of the IgA class are divided, on the basis of their structures, into two groups, called IgA_1 and IgA_2. The enzymes secreted by the gonococci break only IgA_1; hence IgA_2 antibodies to gonococci could still provide immunity if they are produced in sufficient amounts. No one has determined the relative proportions of IgA_1 and IgA_2 produced in response to gonococcal infections.

Another indication that the IgA-cleaving enzyme may not destroy all immunity to gonococci is that the enzyme has not, as yet, been associated with pathogenicity. Plaut and his associates report that all four colonial types of gonococci produce the enzyme, although only the two colonial types with pili are pathogenic. These investigators point out, however, that they do not know whether all four colonial types secrete equal amounts of the enzyme, or whether the enzymes of each type have similar activities in vivo.

The gonococci, then, are becoming less of a mystery at the same time that gonorrhea in the United States is becoming more of a problem. The leads are there, many believe, for the development of improved methods of dealing with gonorrheal infections. The difficult task of finding and treating gonorrhea carriers may be a bit easier in the future.—GINA BARI KOLATA

The book is strongest—and most revealing of the state of affairs in the research community concerned with climate—in its assessment of existing knowledge. Schneider is extremely candid about the weaknesses of virtually every climate prediction, whether a historical extrapolation or a model calculation. He admits there is no unanimity among researchers as to what degree of certainty should be attached to various potential climate changes. But he concludes that "the survival of human beings is still strongly dependent on the climate" and that "uncertainty . . . does not imply that there are no problems; nor does it deserve a 'wait and see' attitude."

This last point, however, seems to be a difficult one to impress upon those officials who control U.S. agricultural policy. A 1973 debate between them and Iowa State University's dean of agriculture, Louis Thompson—which is aired for the first time in Schneider's book—illustrates the problem. Thompson and James McQuigg, then a climatologist at the University of Missouri, concluded on the basis of a statistical study of crop and climate data back to 1890 that grain yields throughout the 1960's had been favored by extremely good weather; they warned that "any national policy that does not take into account the fact that less favorable weather is far more likely than recent nearly optimum conditions" is likely to create severe problems in the future. The USDA, which has based optimistic forecasts on extrapolations from the 1960's, criticized the study and asserted that gains in technology not only were the main reason for high yields during that period but also had decreased the susceptibility of crops to adverse weather. Ironically, this extended and ultimately fruitless exchange of views took place shortly before the disastrous 1974 harvest, which produced a U.S. corn crop 30 percent below USDA projections as a result of fluctuations in rainfall and an early freeze.

The 1974 grain crops are not the only recent indication of adverse weather affecting food production. The severe drought that damaged the 1972 Soviet grain crops and led to massive purchases on the world markets was repeated, on a smaller scale, in 1975. Canadian grain yields have also suffered in recent years, and many investigators have pointed out that arid, high-latitude granaries such as those in the Soviet Union and Canada are very susceptible to climatic fluctuations. In addition, drought afflicted the African Sahel, and there are preliminary indications in the wheat-growing region of the United States of what some investigators believe may be an extended drought like the one that produced the dust bowl of the 1930's. But the United States, which carried huge government-owned surpluses of grain throughout the bumper years of the 1960's, now has no grain reserves, other than the limited private stocks of the major grain companies.

Schneider does not predict climate-related disaster, but he does convey a sense of urgency and pleads for a strategy that, in food and in other areas, would allow for contingencies. "Ill-founded certainty is far worse than a realistic appreciation of the confusing issues," he says. Decision-making in the face of uncertainty, however, is never easy. On major public issues, it ultimately becomes a political process—witness the current debate over the risks and advantages of nuclear power. A similar course is likely for the problems posed by climate change and its impact on our future, a subject that in the long run may be of far more moment to the world than nuclear power, and the process can only be enhanced by broadening the discussion beyond the specialists and the politicians.—ALLEN L. HAMMOND