Some Thoughts on the Management of Technology with Special Reference to *N. gonorrhoeae* and Penicillin

(Preliminary Draft)

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ABSTRACT

A number of experiments are proposed to obtain factual data on the effect of relaxed selection pressure on the build-up of resistance of bacterial disease organisms to antibiotics. One possible scheme for retaining a level of susceptibility in a population of disease organisms is set forth. Similar procedure could be utilized with pesticides.

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1. INTRODUCTION

The first seventy-two years of the twentieth century have been associated with fantastic advances in technology from the horseless carriage and Model T Ford to the routine Apollo missions to the moon. There is no question but that the development of new technology has been most rapid, but there is also no question that some of these developments have been misused or mismanaged with sometimes serious consequences. Pollution by chemicals, by human wastes, by noise, by discarded or obsolete appliances, by overpopulation, of the mind, of the body, of the water, of the air, etc. is in evidence everywhere. The side-effects of technology, whether it be electronic or medical, are becoming evident. It is also becoming evident that the physical and biological scientists have been doing an excellent job at innovation but that the legal, political, and social scholars have fallen flat on their faces in presenting ways for man to adjust and to live with the rapid advance of technology. Should the physical and biological scientists address themselves to this problem? It appears that they will have to if man is to avoid a serious, or perhaps even fatal, catastrophe.

It would appear that it will be necessary for the physical and biological scientists to address themselves to the management (use) of the technology developed to date. New technology will continue to be developed since it is almost impossible to

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eliminate man's innovative and creative nature even under the most dictatorial of political regimes. This characteristic has allowed him to survive and to evolve through the years, and, barring a fatal catastrophe, it will enable him to survive in the future and to use technology without serious side effects. In order to accomplish this, the physical and biological scientists will need to divert a sizeable portion of their energies in this direction in the next few years.

The developers of new technology have been content to let others study and report on side-effects and spin-offs of the new development. They have tended to let the legislative and executive branches of a government and their regulatory agencies worry about side effects. These have failed and are failing in many areas as evidenced by some of our present problems, with one reason for these failures being the very rapid advances in technology. By the time a problem is resolved, it is no longer needed because a new product has been developed in the interim. Hence, it may be necessary to delay the applications and uses of technology until a thorough study has been made of side effects.

2. A SPECIFIC PROBLEM

As many of you may know, the disease known as gonorrhea is in epidemic proportions at the current time. It is estimated that 50% of all high school students in 1980 will have or will have had the disease. However, as statisticians should know, extrapolation can be highly inaccurate. Despite this, gonorrhea is a serious disease, and it may become even more serious during the next decade unless steps are taken to control the disease. We know that the spread of the disease is through contact with sexual organs in both heterosexual and homosexual contacts. The rate of infection from sexual intercourse with no precautions is of the order of 50%, depending upon the strain of the bacteria N. gonorrhoeae. There are numerous strains as Bristol

Laboratories has over 250 isolates in their possession. The strains or isolates exhibit different reactions to specified dosages of an antibiotic. One incident reported was that of a girl who took a six-weeks trip on the Eastern Coast of the U.S. During this period she had sexual intercourse with 163 different men. Eighty-one of the 163 contracted the disease gonorrhea from her. If the sexual parts are washed with soap and water both before and after intercourse, the rate of infection for some strains can be reduced to ten per cent or less.

The detection of the disease can often be made through external symptoms on the sexual organs and/or through blood tests. However, for certain strains, the female may be a carrier of the disease and have no external symptoms. A new strain has recently been reported which exhibits no symptoms in the male but does in the female. To my knowledge, blood tests by trained medical observers will detect the presence or absence of the disease in nearly all cases, even if no symptoms are present in the carrier of the disease organism.

The medical treatment for this disease can take many forms such as the use of soap and water, abstinence both voluntarily and nonvoluntarily (for example, through isolation of the sexes or through the use of Big Brother's chastity belt), by the use of a mercury treatment which was in vogue before the advent of antibiotics, penicillin, and other antibiotics. One of the big questions now is the licensing of other antibiotics to treat the disease; another problem is to develop new medical treatments, perhaps for specific strains of *N. gonorrhoeae*. This problem is accompanied by the need for methods for the rapid identification of strains of the bacterium involved in a particular diseased patient.

The problems associated with the moral, social, and legal aspects of the disease are not even formulated, let alone being resolved. For example, a boy contracted gonorrhea from his "steady" girl friend. It was discovered that this "steady" girl friend had also infected thirteen other boys at the College. In a second example, two members of a commune in Michigan killed a girl because she had infected one of them with gonorrhea. These examples illustrate the fact that there are moral, social, and legal problems involved when one person transmits a disease to another. Of course, our present social and moral codes prohibit one person from bringing damage suits against the person from whom the disease gonorrhea was contracted, but the present course of events also indicate that this may be a real possibility in the 1980's or 1990's. This would appear to be an area in which the social scientists, political scientists, and legal experts should become active. Scholarly work should be done prior to legislation being enacted. The "right" to "do your thing" without considering the effect on others may become a thing of the past.

3. THE LICENSING OF DRUGS

A new antibiotic must possess no "significant correlation" with penicillin in the reactions of n isolates of *N. gonorrhoeae* to the two drugs. This criterion is used because "the ability of *N. gonorrhoeae* isolates to develop resistance to multiple antibiotics is very troublesome". A relatively large number of randomly selected isolates, as well as a large number of known antibiotic resistant isolates, must be studied prior to reaching conclusions about the correlation between the reactions of isolates to the two drugs. Many gonococcal strains are required before it is considered possible to make a comparison of cross-antibiotic resistance of two antibiotics.

From a statistician's view of the preceding paragraph describing the procedure, it would appear that the null hypotheses of zero-correlation between the two drugs was being considered for licensing a new drug. We shall show in the next sections that this is a nonsensical procedure if it means that new drugs cannot be licensed for treating gonorrhea. Furthermore, what is large, what is significant, and what is many? A statistician or anyone else is unable to work with such vague terms and imprecise definitions.

4. THE REAL PROBLEM OF TREATMENT

The real goal of any health program on the disease gonorrhea should be to keep the incidence of the disease low (which needs to be defined) and to keep the population of gonococcal strains as susceptible as practically possible to treatment with antibiotics. We know that a population composed mainly of individuals from strains which are resistant to allowable dosages of an antibiotic means that the antibiotic is useless in the treatment of the disease. This could easily become the case with penicillin. The build-up of resistant strains in the population of *N. gonorrhoeae* could render this excellent antibiotic useless. The build-up of resistance is a real possibility due to what I consider to be a serious misuse and mismanagement of the use of all antibiotics. The indiscriminant use of antibiotics in animal foods and by the medical profession for any infection, including the common cold, hastens the development of a population of resistant strains of the bacteria. Thus, we must devise ways to manage the use of antibiotics unless they are to be rendered useless through malpractice. A wonderful development in technology such as that related to antibiotics can easily be rendered unusable by industry and medical profession mismanagements. As we shall see later, the problem is even more complicated than indicated above.

With regard to the validity of the null hypothesis of zero cross correlation between reactions of strains of *N. gonorrhoeae* to different dosages of two drugs, we know from genetic breeding theory and practice that it is possible to locate strains which are both resistant or both susceptible to treatment by two antibiotics. Hence, the null hypothesis is false and finding significance is merely a matter of having a large enough sample size. Therefore, the present criterion on a "nonsignificant cross-correlation" which is utilized in determining whether or not a new antibiotic is licensed and which is described in the preceding section, is nonsensical on both biological and statistical grounds. "Nonsignificant correlations" will then be a matter of sampling variation in a population wherein the null hypothesis does not hold.

There is also the possibility that changes occur in the model of resistance to an organism. In stem rust infections of wheat, one theory is that if there are major genes for resistance in the wheat strains being grown, the organism develops a resistance to these major genes and continues to survive. If now only wheat strains are grown which do not carry these resistant genes, the frequency of the resistant genes in the rust organisms tends to decrease, perhaps because they have a lower reproductive and lower survival rate. It may be that the mode of resistance of wheat varieties to rust is changed rather than this being a loss of resistance. There is some work by Van der Plank and in Australia on these ideas associated with the simultaneous build-up of resistance in both wheat and in the rust organism with one type of resistance counteracting the other.

About 1958 a Japanese researcher reported that organisms of one bacterial species could transfer a chunk of RNA to organisms of a second species, making them resistant to treatment with antibiotics. This is called a "resistance factor". Hence, organisms such as *E. coli* which inhabit the intestinal region of man are capable of transferring the resistance factor to other bacteria which cause bacterial diseases, such as gonorrhoea and spinal meningitis. The "resistance factor" makes the organisms resistant to all antibiotics. Thus, the build-up of a population of organisms carrying the "resistance factor" could render antibiotics useless for the treatment of all bacterial diseases. Hence, a goal should be to keep the frequency of the "resistance factor" in the population as low as possible. It is also known that the reproduction and survival rate of organisms carrying the extra piece of RNA is lower than for other organisms, and this fact could be utilized in a drug management program.

The picture relative to the use of antibiotics appears pretty dismal if present antibiotic practices by the animals foods industries and the medical profession are continued. Also, the practice by regulatory agencies of limiting the licensing of antibiotics for the treatment of gonorrhea will lead to the untenable situation that antibiotics will be relatively useless for the treatment of the disease. This would mean a return to previous treatments for treating the disease or the development of a new treatment through an advance in technology.

5. SOME QUESTIONS AND PROPOSALS

Urgently needed for biological and medical theory is the answer to the following questions:

(i) After a build-up of a specified level of resistance in a population of organisms due to continued selection pressure, how many generations does it require for the level of resistance to return to its original state if the selection pressure is removed?

(ii) Is the return to the original state dependent upon the level of resistance developed?

(iii) How long and under what kind of selection pressure does it take to attain a specified level of resistance?

(iv) Do the answers to the above questions vary with species and with strains within species?

(v) What types of back-selection pressure may be useful in returning to the original state of resistance?

(vi) Are there selection regimes which would lower the frequency of resistant strains in a population while at the same time reducing the incidence of the disease?

(vii) What are the roles of linkage, inversions, translocations, mutations, and of the transfer of genetic material between individuals both within and between species (e.g. the "resistance factor")?

(viii) What published information is really available to answer these questions and where is research being initiated to obtain answers to the above questions?

(ix) Should biological scientists continue their current studies in which they have vested interests or should they obtain answers to questions related to the management of technology?

(x) What are the roles of the biologist and of the biometrician in this research?

From conversing with a number of biologists it would appear that there is very little in the way of published literature or answers to the above questions. There is the work by Alan Robertson on back selection; also, there are results by K. E. Papa on selection in Neurospora and by D. Pimentel on selection studies in the house fly, and the results by Van der Plank mentioned previously. These are insufficient to provide answers to the above questions. It would appear that a large research effort will be required to obtain the desired answers necessary to implement some of the following proposals.

Suppose that the generation or selection interval is known for gonorrhea, for example, say a three-month period. Also, suppose that one knows that the level of resistance built up in a selection period of three months is diminished to its original level if selection pressure is eliminated for nine selection periods (27 months).

Then, one management scheme for the use of ten antibiotics and/or other treatments for the disease would be to divide North America up into ten areas. The prevalent treatment in one of the ten areas would be determined by its location in a 10 x 10 latin square arrangement where the columns would be the ten areas, the rows would be the ten time periods, and the ten treatments would be the ten medical treatments. Any patient not responding to one medical treatment would be treated with other treatments until he was cured. Starting in the eleventh period, the treatments would be repeated in the same area that they were in the first period, and the entire process would be continued in the 12th to the 20th periods. Thus, if the resistance of the population could be kept at the original level by this management scheme, the ten medical treatments would retain their effectiveness in treating the disease and in lowering its incidence rate.

Many experiments need to be conducted with laboratory organisms. Perhaps the work should first be done on *E. coli* or some other laboratory organism prior to experimenting directly with gonococcal strains. However, the two plans below use *N. gonorrhoeae* to illustrate the procedure.

Plan for experiment 1

Step 0: Obtain isolates from ten (or more) randomly selected strains from the 250 or more strains of *N. gonorrhoeae* to form ten populations.

Step 1: Treat a subpopulation from each population with .1 units/ml of penicillin for g generations.

Step 2: Treat a second subpopulation from each of the ten populations with .2 units/ml of penicillin for g generations.

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Step s: Treat the sth subpopulation from each of the ten populations with s(.1) units/ml of penicillin for g generations.

At the end of each step place one-half of the population in an environment with no penicillin for as many generations as are necessary to bring the population to its original level of resistance. At all steps and all generations for each population, measure the amount of resistance present to penicillin.

Plan for experiment 2:

Obtain a random selection of isolates from a number of strains (say 15). Make up 15 populations for each of the 15 strains and a 16th population which is a composite of the 15. Use a number of antibiotics (say 10) and use a number of levels of dosages (say 3) for each antibiotic. For each dosage level treat each of the 16 populations for a number of generations (say 4) for a specified period of time (say 3 months), then switch to a second antibiotic at the same dosage level for the second period of time for each population; continue this until all ten treatments have been used on each antibiotic. At the end of each period measure the level of resistance present before proceeding to apply the next treatment. The goal here would be to obtain some evidence for the number of generations and the length and number of the periods required to keep the resistance of a population to a particular drug at a constant level.

Data from experiments of this nature would provide some answers to the questions raised at the beginning of this section and to the problem of a sensible program for using antibiotics to treat gonorrhea.

Similar experiments should be utilized to study management schemes for pesticides and fungicides. DDT was a wonderful invention but its misuse has led to a ban on the use of the advance in technology.

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REFERENCES

Clark, A. V. The Mode of Action of Drugs on Cells. Edward Arnold & Co., London, 1933, pp. vii + 298. (On the theories of action of drugs on cells with nothing on selection of resistant strains.)

Falconer, D. S. Introduction to Quantitative Genetics. The Ronald Press Company, New York, 1960, pp. ix + 365 (see pages 210-1). (See chapters 11, 12, 13 and associated references.)

Wright, J. W. and Pal, R. Genetics of Insect Vectors of Disease. Elsevier Publishing Co., Amsterdam, London, New York, 1967, pp. xix + 794. Library of Congress No. 67-12781, $67.50. (Mainly on the genetics of different species with little on selection.)