The Golden Staph: Medicine's Response to the Challenge of the Resistant Staphylococci in the Mid-Twentieth Century

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During the first two decades of the antibiotic era the problem of microbial resistance to antibiotic therapy was discovered, challenged and, in part, the battle was won. The chemotherapeutic agents, antibiotics, were often touted as «miracle drugs», but were not without severe tests and not uncommon lost skirmishes. The refractory resistance of one particular pathogen, *Staphylococcus aureus,* the Golden Staph, was to cause considerable difficulties for the new medicine of the 1940s and 1950s. It seemed that no sooner had penicillin become available than Charles Rammelkamp (b. 1911), one of the first physicians to employ it, discovered resistance to its antimicrobial abilities (1).

The subject of antibiotic resistance, and the medical community's responde to it, is the central focus of this paper. There are good reasons for considering this subject matter. In the first place, antibiotic resistance was a major topic in biomedical literature at the century's midpoint. That had a great influence on the search for new antibiotics. Secondly, it is informative to ask how the medical community responded to the challenge during those first halcyon days of discovery and development in antibiotic medicine. This history specifically considers the challenge posed by the resistant staphylococci and delineates the quite empirical manner by which the medical community met that challenge. Like the story of the antibiotic era itsef, this history must remain incomplete. Continual new discoveries of antibiotics and molecular manipulation of known agents eliminates the possibility of as full a historical perspective as one might wish. It is possible, however, to consider the period from Rammelkamp's discovery of resistance (i.e. 1942), at least, to about the mid-1950s and the appearance of vancomycin (2). For conve-

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(1) RAMMELKAMP, C.; MAXSON, T. (1942). Resistance of *Staphylococcus aureus* to the Action of Penicillin. *Proc. Soc. Exper. Biol. Med., 51,* 386-389.

(2) Vancomycin was discovered by and remains proprietary with Eli Lilly and Company. A full history of the antibiotic can be found in Mc GRAW, D. J. (1976). *The Antibiotic Discovery Era (1940-1960): Vancomycin as an Example of the Era* (Oregon State University, doctoral

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nience the discussion is ended with the period of vancomycin's first availability as it remains the only known antibiotic to which multiply-resistant *Staphylococcus aureus* was (and still is) not refractory.

I. *ANTIBIOTICS AND THE GOLDEN STAPH*

If the appearence of penicillin initiated a new era in the history of Medicine, it was not without some immediate difficulties. The curative power of penicillin was impressive. Because of this it was used in great quantities. In fact, «the American public is like a huge sponge that absorbs antibacterial agents like water» (3). This excessive use of the new tools (penicillin and others) had resulted in the resistance seen with certain bacteria. Diseases formerly susceptible to the action of penicillin were no longer so. And disease organisms treated later by streptomycin became resistant so rapidly that after a patient had been undergoing streptomycin therapy for four weeks, chances could be as much as 93 per 100 that he would harbor totally resistant microbes (4).

The antibiotic industry grew rapidly after the early technological difficulties in the production of penicillin were overcome. The discoveries of new antibiotics came quickly and industrial technology and production facilities grew just as fast, supplying the demands of the new medicine. By the early 1950s there were 13 producers making available at least 17 different antibiotics. The production levels had expanded greatly. In 1943 only 29 pounds of crude penicillin were produced. In 1953, 756,000 pounds of much purer penicillin was made available to be absorbed by the «sponge» of the American public. At the same time there was a rapid increase in streptomycin production from 3,800 pounds in 1946 (its first year on the market) to 375,000 pounds by 1953 (5).

The increase in the availability of an antibiotic, particularly in that period when the oft-heard phrase «miracle drugs» could not be stilled, led to an increase in their employment. It was this extensive utilization of these new tools that threatened their very utility. Some bacterial

dissertation). The author wishes to thank the many people at Eli Lilly and Company and at Oregon State University who helped bring the original dissertation to fruition. Of particular aid was Mr. Gene McCormick, then Corporate Historian, at Lilly, to whom the warmest of thanks are given.

(3) WELCH, H. (1958). Antibiotics 1943-1955: Their Development and Role in Present Day Society. *The Impact of the Antibiotics on Medicine and Society*, 85.

(4) HOBBY, G. L. (1951). Microbiology in Relation to Antibiotics. *J. History Med.*, *6*, 380.

(5) WELCH, H. (1958), *op. cit.*, pp. 25, 72, 76.

strains had been found to resist the effects of many antibiotics and in some cases (as with streptomycin) even became dependent upon them to survive. In order to appreciate the role of *Staphylococcus aureus* in medical practice, it is germane to briefly consider the history of man's knowledge of the organism.

Prior to 1880 concepts of blood poisoning etiology were chaotic (6). But soon thereafter much light was shed on the subject. That came only after the careful investigations of Sir Alexander Ogston (1844-1929), a Scottish bacteriologist. He studied the origin of acute suppurative processes in man. His studies were not aimed so much at scientific nosology as at practical application in surgery and Medicine. During the course of his investigations Ogston made clear the etiology of suppuration, septic wounds, and related infectious processes.

The use of aseptic surgery led physicians and surgeons to question whether surgical sepsis was not, in fact, of bacterial origin. Ogston, like others, wondered at what may cause sepsis. He «often meditated on the subject and became the more convinced that there was a single cause... some special germ» (7). During that period several individuals reported seeing cocci or micrococci in various pathological processes. But others strongly opposed any suggestion that such organisms could be implicated in the disease mechanism (8). Both Elek and Bulloch credit Ogston as having settled the debate clearly in 1880-81 (9). By infecting laboratory animals with micrococci and demonstrating typical suppurative lesions, Ogston was able to implicate the microorganism. The organisms were grouped, he said, «like the roe of fish, into clusters», and to them Ogston gave the name *Staphylococcus*.

The turning point in the understanding of the etiology of various septic disorders set off many investigations during the decade of the 1890's on the staphylococci. It was generally felt, even before Ogston's

(6) ELEK (1959). *Staphylococcus pyogenes: And Its Relation to Disease,* Edinburgh, Livingston, p. 2. See also the excellent review of the half-century period prior to Ogston's work in relation to septicemia given in: BULLOCH, W. (1960). *The History of Bacteriology,* Oxford, London, Chap. VI.

(7) Cited in ELEK, *op. cit.,* p. 2. The quotation is a remake of another one cited by Elek, but for which he gives no source.

(8) *Ibid,* p. 4. Such others included Louis Pasteur who grew the organisms in broth in 1880. His thoughts on the role such cocci played were not well known to others. The Pathological Society of London held (in 1879) that the cocci might be the agents of suppuration. BULLOCH, W. (1960), *op. cit.* (Chap. VI), considers a great many workers in his discussion.

(9) OGSTON, A. (1881). Report Upon Micro-Organisms in Surgical Diseases. *Brit. Med. J., 1,* 370.

reference to it, that the golden, yellow, or orange hue of pus should be considered a sign for much concern by the physician. Septic wounds often led to fulminating septicemias and, as Ogston demonstrated, *Staphylococcus* was the agent. As Ogston had shown the virulence and pathogenicity of staphylococci in animals, others would, within a half dozen years, demonstrate it in man.

The first attempts at classification were based upon wheter or not the organisms were pathogenic for man and/or animals, or were nonpathogenic commensals. The method was not satisfactory, however, as it was impractical to test every culture for pathogenicity by animal inoculation. Serological typing, used to great advantage with the streptococci later, was attempted at the turn of the century, but also proved fruitless. Development of a feasible systematics matured over a very long period of time. Additionally, the history of nomenclature in the staphylococci is very complex and an examination of it here is not necessary. The monograph by Elek (1959) discusses in detail the subject of nomenclature. The work on staphylococci during the 1940s and early 1950s, which is the central period of interest here, employs several synonyms, but all refer to the same organism (10).

II. *THE DISCOVERY OF RESISTANCE*

Wesley Spink reminded us (in 1954) that «while other species of bacteria have demonstrated resistance to some of the antibiotics, the *Staphylococcus* has been been the most consistent in exhibiting prompt resistance to each of the antibiotics, and infections due to this species pose the most serious clinical problem of antibiotic resistance today» (11).

What led up to this situation began with the first appearance of penicillin. But in fact, microbial resistance in general had been of significance very much earlier than that. Coincident with the very beginnings of modern chemotherapy, resistance had been encountered. Thus Paul

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(10) The name *Staphylococcus* was applied by Ogston in 1880. Nevertheless, it is a *nomen nudum* and the valid publication of the name falls to Rosenbach (1884). This organism is the species most commonly indicted in staphylococcal diseases and is the species of central interest to this history. Other synonyms will be seen in the literature: these include *Micrococcus pyogenes aureus* (Rosenbach) Zopf, 1885; *Micrococcus aureus* (Rosenbach) Zopt, 1885; *Micrococcus pyogenes* Lehmann and Neumann, 1986; and others. For further amplification the reader is referred to BUCHANAN, E., *et al.* (eds.). *Index Bergeyana,* Baltimore, Williams and Wilkins, p. 1062, ff.

(11) SPINK, W. (1954). Staphylococcal Infections and the Problem of Antibiotic-Resistant Staphylococci. *Arch. Int. Med., 94,* 167-196.

Ehrlich, even before 1910 and the release of salvarsan, the famed «magic bullet», discovered that the microbes were able to repulse the attacks of chemotherapeutic agents. The trypanosomes with which he was working are very different from the eubacteria and their biochemical defense system is not analogous to that of the bacteria. Be that as it may, it is clear that the earliest workers could foresee problems in chemotherapy presented by the resistance phenomenon. Ehrlich found that the dyes, atoxyl, trypan red, trypan blue, and parafuchsin could be ignored by strains of resistant trypanosomes. In the case of atoxyl-resistant microbes in mice the dose required to inhibit or kill the parasite exceeded the lethal dose for the host (12). Such resistance was often long in coming *in vivo,* but could develop as quickly as in two weeks after the onset of treatment.

Mutual resistance, as Ehrlich termed it, was also seen in the case of his dyes resistance to trypan red would also obtain for trypan blue. That general type of resistance in the broadest sense, much later would make the broad spectrum antibiotics virtually ineffectual against the staphylococci. Ehrlich surmised that use of related compounds against parasites might lead to mutual resistance and, in fact, saw a great research tool in this. A physician, but yet a consummate scientist, Ehrlich was much intrigued by mutual resistance. He realized he could use it as a technique to differentiate between various antimicrobial agents whose chemical structure might not otherwise be known. He felt various specific resistance might help to classify a new agent within its proper chemical family (his therapeutic sieve or *"cribrum therapeuticum"*) (13).

Resistance, then, was not the exclusive property of the antibiotic era. Not only did Ehrlich find it during pre-antibiotic times, but it was seen later with the sulfonamides acting against bacteria. In the first publication on this sulfonamide resistance the authors reported the resistance of various bacteria, including the staphylococci, to sulfa drugs (14). This resistance was seen not only *in vitro,* but *in vivo* as well. And as Ehrlich had noticed with the trypanocide atosyl, the onset of resistance could be sudden. In that first sulfonamide case investigated a *Staphylococcus* strain became resistant in man within eight days. The speed of resistance development, as shown later, could be very rapid with some antibiotics as well. This was true of streptomycin against staphylococci, for instance.

(12) EHRLICH, P. Chemotherapeutic Studies on Trypanosomes (Third Harben Lecture), *in: Collected Papers, 3,* 131.

(13) *Ibid,* p. 132.

(14) VIVINO, J. J.; SPINK, W. (1942). Sulphonamide-Resistant Strains of Staphylococci: Clinical Significance. *Proc. Soc. Exper. Biol. Med., 50,* 336-338.

The year 1942 must have been a depressing one for the medical community, for not only was sulfonamide resistance first reported, but so also was penicillin resistance. Rammelkamp's paper, not surprisingly, bears the name of *Staphylococcus* in it, for from the very beginning of antibiotic resistance history the staphylococci would be in the foremost role. In contrast to this, other bacteria (such as many streptococci) have remained highly sensitive to penicillin for four decades. For example, Rammelkamp noted in his report that, unlike *Staphylococcus,* a strain of hemolytic *Streptococcus* did not develop resistance to penicillin. That encouraging observation proved to point out that the staphylococci were primary offenders. Even in the mid-1950s when the resistant staphylococci had grown to be a problem of major proportions, streptococci remained penicillin sensitive (15). They continue to remain so with few exceptions.

On the dismal side of the situation, however, Rammelkamp had shown a rapid adquisition of resistance by staphylococci (in one case 16-fold in two days). The mechanism of that resistance seemed unclear, because he could not demonstrate penicillinase as Howard Florey's Oxford team had done only a short time before. [Penicillinase was at that time assumed the only mechanism of penicillin resistance (see below).]

The matter of bacterial resistance to antibiotics became for the clinician a matter of great concern. What was he to do when a resistant staphylococcal sepsis ocurred in a patient? If he could not turn to penicillin, would some other antibiotic resolve the dilemma? Much success, but many failures, marked antistaphylococcal antibiosis over more than a decade from Rammelkamp's observation to the early vancomycin period (later 1950s).

III. *THE NATURE OF RESISTANCE*

How resistance developed and what its mechanism was occupied various investigators beginning in the mid-1940s. Most significant was the work of M. Demerec (1895-1965). A geneticist at the Carnegie Institution (Cold Spring Harbor, New York), Demerec elucidated the mechanism of penicillin resistance. The organism of choice was *Staphylococcus.* It is a fact that investigations into general bacterial resistance to antibiotics and specifically staphylococcal resistance to antibiotics go hand and hand. Studies on general resistance seemed invariably to employ

(15) BERNTSEN, A. (1955). Unaltered Penicillin Susceptibility of Streptococci. *J. Amer. Med. Assoc., 157,* 331-333.

staphylococci: the history of our knowledge of mechanisms of bacterial resistance is based essentially upon that one genus. This is not surprising because *Staphylococcus* was the first bacterial taxon to be implicated in antibiotic resistance phenomena and has proved to be the most refractory to chemotherapy. It if had not been one of the most central concerns of infectious medicine prior to the antibiotic era, it certainly became so quickly after the inauguration of that period. Perforce it must be the star organism in this history.

By the mid-1950s, a great many papers had been published on bacterial drug resistance. In the 1940s, there was tendency toward controversy on which mechanism might be correct. But by the mid-1950s those controversial questions had «lost most of their original interest» (16). The reason being that one (or two) mechanisms were generally conceded at that time to be the most likely ones operative. The central mechanism, mutation and selection, was suggested by Demerec. Since then the entire issue has been shown to be much more involved (see below). But in 1945 Demerec set out on a quantitative study to «clarify the genetic aspect of the mechanism through which resistance is formed» (17). He posited two possible mechanisms: 1) resistance is an acquired characteristic, or 2) it is an inherited characteristic arising through mutation which origin was not penicillin-dependent. That is, resistant mutants would occur at random and be selected for in the presence of penicillin: the drug killing the sensitive or non-resistant individuals. Demerec, after some very elegant experimentation, decided in favor of the second postulate. The penicillin seemed to affect only the dividing bacterial cells (18). The pattern of the appearance of resistance was step-wise and distinctive. In a somewhat later study (1948) Demerec found a second pattern distinctive for streptomycin (19). In more recent times antibiotics have been shown to develop resistance to penicillin

(16) SZYBALSKY, W.; BRYSON, W. (1955). Origin of Drug Resistance in Microorganisms, *in:* SEVAG, M. G. *et al.* (eds.). *Origins of Resistance to Toxic Agents,* New York, Academic Press, page 22.

(17) DEMEREC, M. (1954). Production of Staphylococcus Strains Resistant to Various Concentrations of Penicillin. *Proc. Nat. Acad. Sci., 31,* 16.

(18) Demerec's discovery, though it had no special historical significance then, helps now to illuminate another problem. HARE, R. (1970), *Birth of Penicillin: And the Disarming of Microbes.* London, Allen and Unwin points out *in extenso* reasons why Alexander Fleming's discovery of penicillin was so extremely fortuitous. The fact that penicillin affects dividing cells sets a definite temporal relationship for the appearance on the culture dish of the *Penicillium* spore and its subsequent product penicillin. Had, as Hare points out, the spore arrived on Fleming's Petri dish at a somewhat different point in time than the seeding of the plate with *Staphylococcus,* penicillin would have been missed.,

(19) DEMEREC, M. (1958). Origin of Resistance to Antibiotics. *J. Bacteriol., 56,* 63-74.

and other antibiotics by a number of mechanisms (20). How these mechanisms operate is fascinating, but for the clinician they did not solve the practical problem of the resistant staphylococci. Yet the literature of bacterial resistance is filled with a discussion of these various modes.

The penicillinase problem, however, was a refinement of one of Demerec's two possibilities and would, in the broadest use of the term acquired (avoiding any Lamarckian implications) fit as an example of that hypothesis. The production of penicillinase is adaptive and homogeneous throughout the population challenged by penicillin. Not all penicillin-resistant staphylococci which were isolated from infective processes were found to produce penicillinase, although in general that was found (during that period) to be «the main source of their resistance to penicillin» (21). Also the cells were not necessarily permanently penicillin-resistant, as Ehrlich's trypansomes were to atoxyl. By the mid-1950s «mutation, associated with a process of selection» explained the emergence of penicillin-resistant staphylococci (22). Those were not all resistant due to the ability to produce penicillinase, though. At least three other types of penicillin resistance had come to be noticed by 1954. Cells which do not produce penicillinase, but were penicillin-resistant: 1) did not combine with penicillin [reason(s) unknown]; or 2) did not degrade the penicillin intracellularly; or (3) had components of the cell which would be penicillin-vulnerable and which had a low reactivity with penicillin (23). Those were the mechanisms for explaining bacterial resistance by the mid-1950s. Resistance against streptomycin, chloramphenicol and other early antibiotics seemed primarily due to random mutation as no adaptive enzymes (such as penicillinase) were then demonstrable with those agents (24).

The conclusions of workers in the field of antibiotic resistance were uniform. A number of highly similar publications became available (25). Each stressed the importance of Demerec's work. Each concen-

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(20) BARBER, M. (1953). Antibiotic-Resistant Staphylococcal Variants, *in: Adaptation in Micro-Organisms*, Cambridge, University Press, p. 235. See also: ABRAHAM, E. P. (1981). The Beta-Lactam Antibiotics, *Scientific American*, June.

(21) BARBER, M. (1953), *op. cit.*, p. 238.

(22) *Ibid.*

(23) EAGLE, H. (1954). The Multiple Mechanisms of Penicillin Resistance. *J. Bacteriol., 68*, 615.

(24) BARBER, M. (1953), *op. cit.*, p. 243 ff.

(25) In addition to those publications on bacterial resistance mentioned in the preceding few footnotes, several others should be consulted. These include BRYSON, V.; DEMEREC, M. (1955). Bacterial Resistance, *Amer. J. Med., 18*, 723-737. HUSSAR, A. E.; HOLLEY, L. (1954). *Antibiotics and Antibiotis Therapy*, New York, Macmillan, pp. 19-27, 34-39,

trated on resistance in staphylococci in particular. None offered a basis by which a specific antistaphylococcal agent could be purposely designed. Such an agent would have to come from an empirical search; and that did come as a result of the realization of the threat the resistant staphylococci offered.

The use of penicillin against the staphylococci presented in most instances a none too hopeful picture. Though there were repeated successes, failures in treatment became more and more common. The reason for this was not so much because the staphylococci could grow in high concentrations of penicillin, but because they inactivated the antibiotic outright. That was usually due to the action of penicillinase.

The enzyme penicillinase was first observed by Florey's penicillin team at Oxford in 1940 and was recognized, by 1953, to be the main source of penicillin resistance in the staphylococci. *Staphylococcus aureus* was not the only bacteriam capable of generating penicillinase, indeed its production was shown to be wide-spread among the eubacteria. The Oxford team (specifically E. P. Abraham) had originally demonstrated it, not in the staphylococci, but in the mammalian gut bacterium *Escherichia coli,* Shortly thereafter (1944), penicillinase production had been demonstrated in such diverse bacteria as *Bacilus cereus, Bacillus anthracis* (anthrax bacillus), *Enterobacter* (then *Aerobacter*) *aerogenes, Shigella dysenteriae* (etiologic agent of bacterial dysentery), *Pseudomonas* species, and a great many others (26).

In 1943 case histories of penicillin failure against the resistant staphylococci began appearing in the literature. In its early use the new antibiotic was in competition with the sulfa drugs as well as being in short supply. Its use as a last resort effort in some cases made and observer wonder if it was being used against a resistant *Staphylococcus* or merely being used too late on a given patient (27). Mary Florey (1900-66) and the other physicians on the Oxford team had gotten remarkably rapid recoveries many times during that period of the early 1940s. But that physicians were dealing with penicillin and sulfonamide resistant staphylococci was only too clear in many instances (28). Within a few

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59-60; WELSCH, M. (1955). La Resistance Bacterienne aux Antibiotiques. *Schweiz. Med. Woch., 85,* 274-279; Resistance of Micro-Organisms to Antibiotic, the editors, *Research Today, 13,* 22-41 (1957); and SPINK, W. W. (1954). Staphylococcal Infections and the Problem of Antibiotic Resistant Staphylococci, *Arch. Int. Med., 94,* 167-196, among others.

(26) BONDI, A.; DIETZ, C. C. (1944). Production of Penicillinase by Bacteria. *Proc. Soc. Exper. Biol. Med., 56,* 133.

(27) CASE. Records of the Massachusetts General Hospital. Case 29371 (1943), *New England J. Med., 229,* 481-485.

(28) *Ibid.,* Case 29162, 519-522.

years individual case history reports were being displaced in the literature by impersonal lists of statistics attesting to antibiotic failures against the resistant staphylococci (29).

IV. *FIRST RESPONSES FROM THE MEDICAL COMMUNITY: NEW AGENTS*

In 1947 Mary Barber (1911-1964), an astute observer of staphylococcal resistance, noted that the incidence of strains of *Staphylococcus aureus* resistant to penicillin was «increasing rapidly (and had become) somewhat alarming» (30). That understatement underwent a maturation over the next several years. Soon all such articles opened in much the same manner – each showing an increasing tendency toward greater alarm. In 1955 one typical opening statement was: «the enormous increase in resistance of staphylococci has raised... important questions for physicians» (31).

The cause of the increase was that the intensified use of penicillin (Welch's «sponge») was causing a shift in the gene pool; therefore, strains that were more resistant were appearing in greater numbers in the population. Demerec had demonstrated the mechanism for this and the growing literature attesting to the increasing rate of resistance was a proof of it. The work of Mary Barber was by no means isolated, for other investigators world-wide were making similar discoveries (33).

Until the oral form of penicillin became available in the later 1950s the only way one could receive the antibiotics' benefits was in a hospital. Early administration was by intravenous infusion only. Somewhat later intramuscular injections were possible, but a rapid decrease in blood levels of the active penicillin required repeated administrations. Finally, longer lasting intramuscular preparations made possible a workable regimen less offensive to patient and physician alike. Because oral penicillin was later in coming, the observations on the increase of staphylococcal resistance to penicillin were primarily hospital associated. The

(29) REISS, E., *et al.* (1952). Penicillin Sensitivity of Staphylococci. *New England J. Med., 246,* 64.

(30) BARBER, M. (1947). Staphylococcal Infection Due to Penicillin-Resistant Strains. *Brit. Med. J., 2,* 863.

(31) KNIGHT, V.; COLLINS, H. S. (1955). A Current View on the Problem of Drug Resistant Staphylococci and Staphylococcal Infections. *Bull. N. Y. Acad. Sci., 31,* 549.

(32) BARBER, M.; ROZWADOWSKA-DOWZENKO, M. (1948). Infection by Penicillin Resistant Staphylococci. *Lancet, 2,* 641.

(33) KNIGHT, V.; COLLINS, H. S. (1955), *op. cit.*, p. 551.

so-called «hospital staph» was recognized early and to this day the major problems of staphylococcal resistance are in hospitals. When vancomycin, for example, became available the earliest advertising literature introduced the new antibiotic as of special importance in hospitals. This situation has not changed.

Mary Barber's work had «aroused much interest and not a little alarm» by 1949 (34). The rising resistance was clearly hospital oriented (35). The question of the origin of those resistant strains was asked. The discovery that carriers were present on the staff of the hospital provoked much discussion in the literature. The longer one stayed in the hospital, of course, the greater the risk of exposure. Hence, more «hospital staph» was available from more hospital staff. It behooved the patient to stay but a short time in the hospital lest he acquire an unwanted infection (36). The staff who carried the resistant strains included everyone from doctors and nurses to maids. Of 50 ward nurses, 46 per 100 carried resistant strains in their anterior nares. In a comparison study a number of office workers, totally unrelated to the hospital environment workers, were shown to have among them only 2 per 100 who were carriers (37).

Not unexpectedly staphylococcal resistance in the community at large was increasing as it had done therefore in the hospital community. The 12.5 per 100 of outpatients with resistant strains demonstrated in 1949 (above) had increased to 38 per 100 by 1956 (38). Staphylococcal infections of varying types were not uncommon in the general population, though in the hospital they were much more common. A cycle of reinfection of patient and staff continued to occur and a good many staff members in a large hospital could at any one time be carriers, convalescents, or patients themselves. That was especially true in earlier years and was demonstrated as Boston City Hospital at one point in the mid-1950s. A survey of nosocomial infections indicated just how severe hospital staphylococci had become. Of the in-house physicians with varying staphylococcal infections, 18 had carbuncles of furuncles, nine other were convalescing from other staphylococcal diseases, seven nurses

(34) FORBES, G. B. (1949). Infection with Penicillin-Resistant Staphylococci in Hospitals and General Practice. *Brit. Med. J., 2,* 569.

(35) *Ibid.,* p. 570.

(36) CAIRNS, H. J. F. (1950). Penicillin-Resistant Staphylococci: Incidence in Relation to Length of Stay in Hospital. *Lancet, 1,* 446.

(37) FORBES, G. B. (1949), *op. cit.,* p. 571.

(38) FINLAND, M.; JONES, W. F. (1956). Staphylococcal Infections Currently Encountered in a Large Municipal Hospital: Some Problems in Evaluating Antimicrobial Therapy in Such Infections. *Ann. N. Y. Acad. Sci., 65,* 193.

were out with similar ills, eight ward attendents had known ongoing infections, and other similar infections were suspected (39).

Clearly from as early as penicillin became available, until well into the mid-1950s the staphylococci had presented a difficult problem. Penicillin resistance was not (and is not) universal among the staphylococci, but it's occurrence was so notable that it soon became apparent that alternatives would have to be sought.

The first response to the resistant microbes by clinicians was to seek alternative antibiotic therapy. By the mid-1950s there was a goodly number of different antibiotics available. As of 1954 the antibiotics in common use included: penicillin, streptomycin, chlortetracycline, oxytetracycline, tetracylcline, chloramphenicol, bacitracin, polymyxin, neomycin, tyrothricin, erythromycin and carbomycin (40). Not all of those were effective against the staphylococci, however. Tyrothricin, though antagonistic to gram positive organisms (such as are staphylococci), could not be used systematically, and hence was never of any particular value except in topical application. The antibiotics chlortetracycline, oxytetracycline, tetracycline and chloramphenicol formed the group known as the broad spectrum antibiotics. They antagonized both gram positive and gram negative bacteria, but their antimicrobial activities were all virtually the same. When resistance to one occurred it automatically occured with the others (though mechanisms vary greatly); hence they possessed mutually susceptible cross resistance in the broadest sense (41). For that reason only one, chlortetracycline, was heavily employed against the staphylococci. Streptomycin, since its greates activity is against gram negative organisms, was never particularly significant as an antistaphylococcal agent. Streptomycin also lost its effectiveness against the staphylococci very rapidly (see below). Erythromycin was heavily used against the staphylococci; and since carbomycin was subject to mutual cross resistance with erythromycin, it was rarely employed. Bacitracin, though active against staphylococci, appeared to operate like penicillin. Resistance to it developed much as it had with penicillin, so it never played a major role. Polymixin was only a gram negative antagonist and neomycin was somewhat cross resistant with streptomycin, as well as being very toxic (42).

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(39) *Ibid.*

(40) HUSER, A. E.; HOLLEY, H. L. (1954). *Antibiotics and Antibiotic Therapy.* New York, Macmillan, p. XII.

(41) *Ibid.,* p. 410. See also note 20 herein.

(42) *Ibid.,* p. 171.

Other antibiotics became available during the 1950s. A variety of semisynthetic penicillins are now available, as well as more tetracyclines. Many of the antibiotics available in 1954 are still available three decades later while others have fallen into disuse (e. g. tyrothricin, carbomycin). Many other new classes of antibiotics exist today. One group, the cephalosporins, in that they share the betalactum ring structure with the penicillins, are similarly successful.

The literature of the pre-vancomycin period concentrated upon three antibiotics as penicillin alternatives in staphylococcal treatment. Those were chlortetracycline, erythromycin, and to a much lesser extent, streptomycin. In 1952 chlortetracycline (and related tetracyclines) and streptomycin were considered the principal penicillin alternatives (43). In that same year erythromycin became available and at first looked extremely promising. Streptomycin, though, was the first alternative considered when it became apparent that the staphylococci were becoming penicillin resistant. Chlortetracycline and erythromycin then were increasingly employed once streptomycin became an inviable alternative. This latter agent is considered first.

The discovery of streptomycin was first announced in the literature in 1944, but it became available for clinical use only in 1946. Streptomycin resistant organisms were reported that same year, and there were even more reports the following year. Several reports concerning staphylococcal resistance to streptomycin had appeared by 1946. By 1948 some strains of *Staphylococcus aureus* (as well as four pathogens) had actually been shown to be streptomycin dependent for their growth (44). This dependence was not as permanent a characteristic as simple resistance. Under conditions of dependence strange pleomorphic forms were demonstrated (45). Although resistance to penicillin did not seem to be permanent, that to streptomycin evidently was. These findings seemed to suggest that the application of streptomycin in staphylococcal diseases was of little value. At any rate, it was early appreciated that streptomycin was much more active on gram negative organisms that

(43) LINSELL, W. (1952). The Antibiotic Sensitivity of Pathogenic Staphylococci. *J. Clin. Path., 5,* 166.

(44) PAINE, T. F.; FINLAND, M. (1948). Observations on Bacteria Sensitive to, Resistant to, and Dependent Upon Streptomycin. *J. Bacteriol., 56,* 209.

(45) In 1948 Klimek, Cavallito, and Bailey reported that they witnessed pleomorphism and conversion to the gram negative state in penicillin-grow *Staphylococcus aureus.* They had been ridiculed by various authors. Such things must have been contaminants, so it was thought. The observation by Paine and Finland, however, tends to lend credence to that of Klimek, *et al.* See KLIMEK, J. W., *et al.* (1958). Induced Resistance of *Staphylococcus aureus* to Various Antibiotics. *J. Bacteriol., 55,* 139-145.

on positive and it was not suprising that there were «rather wide variations in the sensitivity (of staphylococci) to streptomycin» (46). The pattern of development of resistance (noted earlier), by its nature, led to a very rapid increase in streptomycin resistance by many microorganisms. The success of streptomycin was primarily in the treatment of tuberculosis, where it had had a great impact.

Chronologically, the next alternative to penicillin against the resistant staphylococci was the tetracycline group. Chlortetracycline was discovered in the very year (1948) that streptomycin dependence was demonstrated (47). Chlortetracycline, like streptomycin and vancomycin, and in fact most major antibiotics, was derived from the bacterial species of the genus *Streptomyces* (48).

A survey done in 1950 showed a «rather high susceptibility» of most strains to chlortetracycline. The study did not conclude as optimistically, however. There was «some intimation» that some strains had a «relatively high» resistance to chlortetracycline. And «it seems not unlikely that (with increased used)... more strains which are relatively resistant... will be found» (49). Evidently, strains varied widely in the response to chlortetracycline for in 1952 one investigator still saw «an optimistic picture» (50). But a quantitative examination of the rise of resistance to chlortetracycline by staphylococci, showed the rise to be statistically significant. That was found to be true with streptococci, *Proteus* species, and colon bacilli, in addition to the staphylococci (51).

In 1953 the level of chlortetracycline resistant staphylococci in the general population was unknown, but in the hospital it was on a strong increase (52). The related members of the tetracycline family experien-

(46) FINLAND, M., *et al.* (1950). *In vitro* Susceptibility of Pathogenic Staphylococci to Seven Antibiotics. *Amer. J. Clin. Path., 29,* 332.

(47) NICHOLS, R.; NEEDHAM, G. M. (1949). Aureomycin in the Treatment of Penicillin Resistant Staphylococci Bacteremia. *Proc. Staff Mett. Mayo Clin., 24,* 310 ff. It should be noted that the definitions of «sensitive» and «resistant» are not fixed as to so much weight or volume of antibiotic being the dividing line between these classes. The definitions were routinely set by the various investigators in each of their respective studies. For that reason statistics vary over time in their qualitative interrelationship. Nevertheless, this points out a trend, not absolute mathematically, but very real.

(48) CHANDLER, C. A., *et al.* (1949). Observations on Staphylococcal Infections Treated with Aureomycin. *Pediatrics, 4,* 149-156.

(49) FINLAND, M. (1950), *op. cit.,* p. 333.

(50) LINSELL, W. (1952), *op. cit.,* p. 168.

(51) SCHNEIERSON, S. S. (1952). Changes in Bacterial Sensitivity to Aureomycin and Chloramphenicol in the Course of the Past Three Years. *J. Lab. Clin. Med., 40,* 56.

(52) DOWLING, H. F., *et al.* (1953). Observations on the Epidemiological Spread of Antibiotic-Resistant Staphylococci, With Measurements of the Changes in Sensitivity to Penicillin and Aureomycin. *Amer. J. Pub. Health, 43,* 860.

ced increasing resistance as did chlortetracycline (53). It had become abundantly clear, particularly in hospitals, that not only was streptomycin not a viable alternative to penicillin, but also neither was chlortetracycline.

During that very period (1952) a new antistaphylococcal agent, the bacteriostatic erythromycin, became available. The range of antimicrobial activity of this new agent was found to be quite large. It antagonized both gram positive and gram negative bacteria. Although the early failures of erythromycin against staphylococci seemed dismal, due especially to the agents bacteriostatic, not bactericidal nature, those failures were related primarily to the hospital staphylococci. Even into the 1970s erythromycin was still antagonistic to most staphylococci, but the resistant forms remain a hospital problem generally untreatable by the agent. But in its first year only rarely had a strain of *Staphylococcus aureus* been found that was resistant to erythromycin (54). Provided endocarditis (requiring a bactericidal agent) had not developed, septicemia was well controlled by erythromycin (55). Because it was only bacteriostatis investigators recommended against erythromycin when treating staphylococcal endocarditis.

By 1947 Mary Barber had been alarmed. Her sentiments were expressed again by other investigatos a half dozen years later. If the alternatives to penicillin were not alternatives in fact, where could one go from there? The answer was to combine two antibiotics. That approach was taken — and with success at times.

V. *THE SECOND RESPONSE: ANTIBIOTICS IN COMBINATION*

The trends in antistaphylococcal therapy were event-dependent. The introduction of a new antibiotic was an event. After the appearance of each antibiotic a series of studies of clinical applications of the agent would appear. In the case of new antistaphylococcal agents, great hope would be expressed early. Some time thereafter the warning aura of the decline of the new agent would become clear. Hopes of something new coming to fore were then expressed. That cycle was repeated several ti-

(53) KNIGHT, V.; COLLINS, H. S. (1955), *op. cit.*, 551.
(54) HERRELL, W., *et al.* (1953). Erythromycin for Infections Due to *Micrococcus pyogenes*. *J. Amer. Med. Assoc., 152,* 1601.
(55) *Ibid.*, p. 1602.
(56) BIGGER, J. W. (1944). Synergic Action of Penicillin and Sulphonamides. *Lancet, 247,* 142-145.

mes and by 1953 no new antistaphylococcal agents were in ascendence (except vancomycin). The only apparent alternative was to use the previous antibiotics of choice in combination against the resistant staphylococci.

The rationale of antibiotic combination therapy was not ill-founded. Although combination therapy had been employed as early as 1944 (see below and n. 57), the practice became common only in 1953. That latter year seems to have marked the point at which the clinicians felt obliged not to hope further for the ideal antistaphylococcal agent. Instead they looked at the older antibiotics and asked: if manipulated differently, might they yield improved results? Manipulation by combination proved a not entirely ill-based hope.

The use of sulfa drugs had enjoyed great success on many gram-positive cocci, but not on *Staphylococcus aureus*. By 1944 not only were the antibacterial sulfas extant, but so also was penicillin. Because there was reason to believe that the two agents antagonized bacteria by different modes of action, the use of them in combination seemed justified. The rationale of combination therapy was based upon the realization of the differences in modes of actions of antibiotic A versus antibiotic B. If A destroyed a significant sector of the invasive microbial population it may still leave survivors which were resistant to A. Had B been employed instead in the first place, similar results may have been obtained. A simultaneous use of both, however, would tend to eliminate the survivors to either.

When, in 1944, Joseph Bigger (1891-1951), a British army physician, attempted to use the combination of penicillin and sulfathiazole against *Staphylococcus aureus*, he found it highly effective (56). Not only did the two functions well together, but in fact seemed to exceed the expected. Bigger had discovered that the presence of a small amount of sulfathiazole actually enhanced the action of an amount of penicillin which, by itself, was non-inhibitory to the test bacterium. He had discovered a synergistic action (57). Much later, when many more antibacterial agents were available, the importance of synergism had become the central rationale for the employment of combination therapy. It could be said that «The ultimate justification for combined therapy then should be

(57) Bigger noted that the only previous combination therapy was done in 1943 by J. Ungar who used sulfapyridine and penicillin. Although Ungar found evidence of synergism, Bigger showed his sulfathiazole to be much more synergistic than Ungar's sulfapyridine. See BIGGER, J. W. (1944), *op. cit.*, p. 145.

based on a combined effect that is greater than that achieved by the *safe margin* dosage of either drug alone» (58).

From 1944 to 1953 nothing more was seen in the literature on combination therapy. Nor does this seem surprising even given the good results shown by Bigger. New antibiotics were appearing rapidly and penicillin's success was growing as well. Not until the continued rise of resistant *Staphylococcus aureus* untreatable by single agents did combination therapy once again seem appealling.

The use of penicillin, streptomycin, and erythromycin singly had led to the development of resistance to each. By combining them it was hoped that the development of resistance could be eliminated or delayed. If one could delay this development within a single patient during therapy, he might be cured. Doubly resistant strains could be generated in the process, nevertheless. There may or may not be a threat to the initial patient, but would likely be so to the population at large later on (the heritage of Welch's «sponge»). It was found that the development of resistance to streptomycin when in the presence of penicillin was «uniformly rapid». Such development was less rapid when erythromycin was substituted for streptomycin, but still ocurred. Carbomycin caused cross resistance much like erythromycin. When carbomycin was combined with the penicillin, poor results were obtained. Those studies were done, unfortunately, with levels of penicillin, which when used singly, constituted an ineffective dose. Nevertheless, they demonstrated that synergism was not a universal result of combination therapy.

More investigations with various agents, paired in different permutations, led to the recognition that the results of such therapy varied considerably. After several years of combination therapy the reason for the variations was explained in the literature. Four results were possible when using a given combination. The combination could be indifferent, additive,. synergistic, or antagonistic. When indifferent the total effect was not greater that the effect of the more potent member alone. If additive the total effect equaled the mathematic sum of both drugs' percentage efficacy when used singly. The synergistic action exceeded the mathematic sum expected. If antagonistic the total effect was less than that expected from the more potent member when used alone. In recent ti-

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(58) KLEIN, M.; SCHORR, S. E. (1953). The Role of Bacterial Resistance in Antibiotic Synergism and Antagonism. *J. Bacteriol., 65,* 454. Emphasis is Klein's and Schorr's.

(59) FINLAND, M.; WILCOX, C. (1953). Antibiotic Combinations and Resistance to Antibiotics: Penicillin With Other Antibiotics Against Penicillin Resistant Staphylococci. *Proc. Soc. Exper. Biol. Med., 83,* 605.

mes the clinical significance (i. e., *in vivo*) remains obscure for the antagonistic phenomenon.

A partial explanation for those findings lay with variations in strains of the staphylococci themselves. Although it had been shown that the penicillin-erythromycin combination (in a 1:1 ratio) was often of no utility, with some strains a different ratio of the two agents did produce positive results (60). The ratio varied widely with the strain and to determine which ratio was most efficacious on a given strain sometimes required extensive testing *in vitro*. The physician attending a moribund patient, of course, had no time to vary the ratio of a combination whose effective ratio may not be known against a given strain. It may not have even been determinable given the time involved.

Erythromycin was commonly used as one member in combined therapy against *Staphylococcus aureus*. But other combinations were tried, too. When streptomycin-penicillin ratios were varied away from a 1:1 ratio, an increase in efficacy was sometimes possible. But an increased resistance was easily demonstrated with pairs containing members of the tetracycline group. Some hope was generated by those various reports, but the mechanisms by which combined antibiotic worked remained unknown and useful combinations unpredictable (61).

The recognition of antagonism did little to boost morale among the physicians. Chloramphenicol, chlortetracycline, oxytetracycline, and some sulfas were all shown to antagonize penicillin and streptomycin under certain conditions, but such antagonism varied in an «unpredictable fashion» (62). A clinician had no real referent upon which to base any intended combination therapy. Only if all singly used antibiotics were without positive results would he choose combination therapy. And there were situations where combination therapy was actually contraindicated. Under any circumstances the two members of a combination must have different modes of action. Two tetracycline antibiotics used together, for example, would be useless in light of the rationale of combination therapy and could even produce additional cross resistance.

The organization of antibiotics into three families of cross resistance

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(60) PURCELL, E. M., *et al.* (1953). Antibiotic Combinations and Resistance to Antibiotics: Penicillin-Erythromycin and Streptomycin-Erythromycin Combinations *in vitro*. *Proc. Soc. Exper. Biol. Med., 82,* 124-313.

(61) WRIGHT, S. S., *et al.* (1953). Antibiotic Combinations and Resistance to Antibiotics. *J. Lab. Clin. Med., 42,* 891.

(62) KLEIN, M.; SCHORR, S. E. (1953), *op. cit.,* p. 454 and p. 462.

(as perceived then) had occurred in the literature by 1953 (63). The clinician sould expect possible positive responses only in he employed no combination in which both members of the pair were from the same cross resistance family. It seemed clear, too, that no combination sould prevent the appearance of resistant staphylococci, but could only delay such appearance.

VI. *THE PARTIAL VICTORY*

There were only two suggestions beyong combination therapy to treat the resistant staphylococci in the mid-1950s it seemed. The first was to completely withhold an antibiotic during therapy once resistance emerged. This appeared to have some benefit in reducing the resistance. In the moribund patient, though, that would certainly seem inadvisable. However, in such a situation the moribund patient did not likely have a chance anyway.

The second was to hope that during the active and continuing antibiotic screening programs conducted by the major pharmaceutical houses a new anti-staphylococcal agent would be discovered. Vancomycin soon filled that wish (n. 2).

But in the mid-1950s, prior to vancomycin's appearance, the wheel of first optimism, then wariness, and finally pessimism, had made many a complete cycle. The resistant staphylococci had not diminished as a threat. The organisms continued to pursue their refractory ways.

(63) DOWLING, H. F. (1953-1954). The Effect of the Emergence of Resistant Strains on the Future of Antibiotic Therapy. *Antibiotics Annual*, p. 27.