On Leaving the Mine: Historiographic Resource Exhaustion in Antibiotics History

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SUMMARY

I.—First suggestions of the mining out phenomenon. II.—Latter day lessons: The vancomycin history redivivus. III.—On leaving the mine. IV.—Beyond penicillin. V.—Inspecting the mine.

RESUMEN

La literatura crítica sobre historia de los antibióticos ha producido muy pocas novedades en relación con la penicilina o cualquier otro antibiótico principal durante las dos últimas décadas. Aquí mantenemos la hipótesis de que las fuentes primarias pudieran estar exhaustas por cuanto a información se refiere. Este hecho puede reflejar la propia naturaleza de la historia de los antibióticos, en la cual se observa identidad en los procesos de descubrimiento y desarrollo de cada agente terapéutico, con la consiguiente falta de opción para nuevas aproximaciones historiográficas.

Few would deny that the introduction of antibiotics in about 1940 brought about a revolution in the treatment of infectious diseases. Those maladies had played a central role in both human mortality and morbidity for millenia. For the few historians who have sought to tell the story of these chemotherapeutic agents, the raw materials that constitute the stuff of historiography must have seemed rich indeed. Those not specialists in this niche might well assume from the high calibre of studies on the history of penicillin (almost exclusively) that have appeared during the last two decades that

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a view of a richness of resource is correct. But, as we slip further away in time from the century's midpoint, a period that has been viewed as the antibiotic discovery era, something disturbing about both the historiography and the resource itself appears. Evidence exists, as I will argue, that even though the primary materials are rich in a quantitative way, a curious depaupereteness in those resources is nevertheless present.

The contention that the resource may have been, at least in some respects, «mined-out» is made with regard to aspects of both history of science and of technology. Matters of sociology are left untouched. There is reason to believe that a considerable vein of valuable primary source materials may await the investigator who wishes to study, say, corporate decision-making in the pharmaceutical industry, or, as another example, to further analyze several of the personalities involved in the streptomycin story (below). But with regard to elaboration concerning the history of the science and technology of antibiotics, and also their medical testing, especially between about 1940 and about 1960, a certain exhaustion of the subject seems evident.

One must be mindful of the, possibly apocryphal, tale of the inventor who committed suicide, about 1900, giving the reason that there was nothing left to invent. Apropos of the inventor's general assessment, there are scholars out there who have very recently voiced some concern along the lines of mining out intellectual resources. John Maddox, editor of the journal *Nature,* has in an opinion piece noted that a dean of the «D. H. Lawrence industry», Emile Lavernay, fears the mining out phenomenon. Lavernay wonders, according to Maddox, if a number of graduate students are dissecting well-known literary works in ever-finer detail such that the «consequences that the theses that result are of interest only to their authors and the supervisors thereof». Maddox concluded his own analysis of the Lavernay fear by offering a caveat.

> «Natural scientists will —certainly they should— naturally be sympathetic, knowing as they do that the process of discovery necessarily raises more questions than it answers. But they should also be careful not to patronize the [English literature] fraternity, at least until they can be sure that their own PhD thesis topics are not also salami slices» (1).

The immediate possible rejoinder to suggesting that the posited argument of exhaustion in antibiotics historiography is not directly comparable

(1) MADDOX, John (1990). PhD by Dissection. *Nature,* 345, 752.

to «Lawrence industry» problems, or, more to the point, does not exist at all, may not be so easily proved. The published literature (in English) in antibiotics history has for the better part of two decades shown itself to be, in a manner of speaking, moribund. The reason for this state of affairs, as this study will attempt to demonstrate, is due to a fundamental sameness of the nature of the processes of both discovery and development of antibiotic agents: the primary historical sources then mirror this sameness and the secondary literature further repeats it.

I. *FIRST SUGGESTIONS OF THE MINING OUT PHENOMENON*

During studies in the mid-1970's on the history of vancomycin (vancocin, Lilly), evidence was provided for the clear existence of a pattern of antibiotic discovery and development (2). The essential elements of the pattern had been more generally recognized for some years previously by several workers, most notably L. H. Conover and Selman Waksman. While the concept of use of the pattern elements as a tool to probe the history of numerous other antibiotics was envisioned (in the mid-1970's) by the present author, the inherent depauperateness of the primary sources, alluded to above, was then opaque. It was argued that the appearance of successive antibiotics from about 1940 to about 1960 followed a distinctive, repeatable, indeed predictable, pattern of first discovery and thence development to a marketed chemotherapeutic agent. What are the pattern elements and, more central to this current study, what historiographic hints are there to lead to the contention that mining out may be a very real problem in antibiotics historiography?

Penicillin provided the model for laboratory researchers in the 1940's and later, in their quest to discover and develop an armamentarium of antimicrobial (primarily antibacterial) agents. The discovery of penicillin was quite fortuitous. The likely mechanism for Alexander Fleming's extraordinary serendipity, though having since been occasionally debated, has been best explicated by Hare (3). Discovery of other, i.e., post-penicillin, antibio-

(2) McGRAW, Donald J. (1976). *The Antibiotic Discovery Era (1940-1960): Vancomycin as an Example of the Era.* Oregon State University, doctoral dissertation.

(3) HARE, Ronald (1971). *The Birth of Penicillin and the Disarming of Microbes.* London, Allen and Unwin.; Hare has maintained his 1971 argument concerning the source of, and timing of discovery of the *Penicillium* culture in more recent publications: see HARE, Ro-

tics found no pattern element for discovery per se in the penicillin story, due simply to the fortuitous nature of that event. But from the technique (vast soil screening programs) employed in the discovery of the microorganisms that would produce later antibiotics, a pattern element for discovery quickly became established. Once this element was established, all parts of the full pattern of discovery and development were then present; penicillin having provided the lion's share of the lead (4).

The pattern elements of discovery and development of essentially all successful (defined here as having come to market), as well as virtually all unsuccessful, antibacterial antibiotics of the period 1940-1960 were first suggested by L. H. Conover (5). While detailing the vancomycin story, it was demonstrated that Conover's general outline could be both confirmed and expanded. The vancomycin-inspired version of the discovery/development pattern is as follows.

a. Facile collection of a wide variety of microbial types from nature, especially from soils,
b. Isolation and characterization, of not only morphologically, but biochemically (physiologically), disparate groups of microorganisms,
c. Demonstration of antibiotic potential, most commonly by team appraoch, within a given industrial firm capable of all aspects of production of chemotherapeutic agents,
d. Employment of several significant techniques including massive sam-

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nald (1982). New Light on the History of Penicillin. *Med. Hist.,* 26, 1-24; see p. 4ff. The term serendipity has been used by several authors, but see ELLIS-PEGLER, R. B. (1986). Serendipity and the Discovery of Penicillin. *NZ Med. J.,* 99, 545-549, who said that «Professor Ronald Hare...is the originator of most of the information in this paper...» (p. 548); this is taken as a piece of evidence for the central contention of a mined out resource.

(4) While it is nearly universally agreed that penicillin should be considered the first clinically useful antibiotic, a symposium was held (October 23, 1989, at the Rockefeller University) which, according to later observers, was to «'right? the antibiotic record» (1989, *Science,* 246, 883-884). See Carol L. MOBERG and Zanvil A. COHN (eds.) (1990). *Launching the Antibiotic Era.* New York, Rockefeller Univ. Press. At that symposium, celebrating the 50th anniversary of Rene Dubos' discovery of gramicidin (1939), arguments were made urging gramicidin as precedent over penicillin. The fact remains that gramicidin never had the impact that obtained for penicillin, nor is it even possible to use it systemically, as is the case with the latter.

(5) CONOVER, L. H. (1971). Discovery of Drugs from Microbial Sources, in B. Bloom and G. E. Ullyot (eds.) (1971). *Drug Discovery: Science and Development in a Changing Society.* Washington, D.C., American Chemical Society.

pling programs and sophisticated biochemical testing capable of selecting for desirable variations in active fractions of naturally-occurring compounds,

e. Willingness to expend very large sums of money on research and development,

f. The capacity (through law) to employ living organisms in test situations, even in apparent incurable human ailments,

g. Use of widely varying microbiological methods (mutagenesis, strain improvement, phage manipulation) to attain high-producing strains of microorganisms, and

h. The development of industrial-scale production of naturally-occurring agents by techniques previously unknown or untried, such as submerged fermentation, and, in recovery, the precipitation and ion exchange of the product (6).

A much more wieldy, though less informative, set of pattern elements is simply a listing of five major features of the above (the terms were, and are, common to the industry):

1. Discovery,
2. Fermentation,
3. Recovery (i.e., isolation of the active compound(s)),
4. Purification, and
5. Finishing.

It was argued, in 1976, that the discovery era closed about 1960. There are three reasons for choosing that year. First was penicillin-pioneer Ernst Chain's comment that semisynthetic penicillin could become a possibility once the complete molecular structure of the natural compound became known. In 1955, an American team of researchers elucidated the structure of penicillin. In 1957, the first semisynthetic penicillin was created in the laboratory (7). A period (still extant) possibly best characterized as an era of semisynthetic antibiotics seems to have begun by the late 1950's-early 1960's.

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(6) McGRAW (1976), *op. cit.* (fn. 2), pp. 206-7.

(7) CHAIN, Ernst B. (1965). Twenty-Five Years of Penicillin Therapy in Perspective, *in:* Gladys L. Hobby (ed.) *Antimicrobial Agents and Chemotherapy — 1965,* New York, American Society for Microbiology, p.4. The term semisynthetic implies that the nucleus of the penicillin molecule is created through fermentation then substituent sidechains are manipulated, in the laboratory and, later, in further fermentation, to produce various penicillin subtypes, each with slightly different structures and antibacterial activities.

The second reason for choosing 1960 is rooted in an argument provided by Selman Waksman, modern developer of soil microbiology and co-discoverer of streptomycin. He held that, while soil screening continued during the early 1960's, and still does to some extent, useful new antibacterial antibiotics were not being found in nature at the rate they were in the 1940's and the early 1950's. The same antibiotics discovered earlier were being found repeatedly in soil with new compounds rarely occurring as the discovery era wore on (8). Waksman himself called the period from 1939-1960 «The Golden Age of Chemotherapy», well aware that diminished discoveries and the rise of semisynthetics seemed to mark the close of an epoch.

Finally, Conover concluded (in 1971) that during the period of 1940-1959 «every important class of antibacterial antibiotic known was recognized» (9). The technical literature to date seems to suggest that this has not changed (see, however, fn 51 below). And while it would have been unwise to make a prediction in the mid-1970's that in yet another decade and a half the situation would remain unchanged, the very seeds, earlier unseen, of the mined-out contention made here were present. This is best seen in the vancomycin history.

II. *LATTER DAY LESSONS: THE VANCOMYCIN HISTORY REDIVIVUS*

A few allusions will serve to illuminate the argument that had been made for the existence of a clearly definable discovery era pattern. The fuller vancomycin history (fn 2) elucidates the elements point by point, elaborating upon Conover and expanding upon his earlier ideas.

The soil sample that would yield the streptomycete that produced the first molecules of vancomycin was dug near Tengeng, Borneo in 1953. By that time, the idea of maintaining far-flung soil sampling programs was already an industry standard. Waksman established the sagacity of such programs when he began a concerted effort to discover a cure for the scourge against which penicillin was not effective — tuberculosis. He played a crucial

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(8) WAKSMAN, Selman A. (1967). A Quarter Century of the Antibiotic Era. *Antimicrobial Agents and Chemotherapy — 1967.* New York, Amer. Soc. Microbiol., p. 10. Waksman's contention about rediscovery was given overwhelming statistical support in a paper by A. NEELAMEGHAN (1968). Discovery, Duplication and Documentation: A Case Study. *Library Sci. with a Slant to Documentation, 5,* 264-288.

(9) CONOVER (1971), *op. cit.* (fn. 5), p. 39.

role in helping to formulate, about 1943, what would become the discovery era pattern by seconding for streptomycin so much of what had been the developmental history of penicillin. Indeed, in reviewing those times, he said that the rapid progress he enjoyed for streptomycin research was due, in part, to the «spectacular rise of penicillin between 1941 and 1943» (10).

To make the argument, in the mid-1970s, that there was a clearly definable pattern of discovery and development during the 1940-1960 era, it was held that some antibiotic from the period would have to be examined in considerable detail. This would be accomplished by turning especially to the primary sources that could be found only in corporate records (very few antibiotics were either discovered or developed outside of the pharmaceutical companies' spheres after penicillin and the discovery, per se, of streptomycin). While vancomycin provided such an antibiotic, it further seemed necessary to compare it with at least a few other such agents of those times to bolster the pattern argument. Penicillin was an obvious choice as the development pattern had its genesis with that agent. Streptomycin, given its locus in time and knowing that Waksman (and others later) had been so influenced by the penicillin story, was chosen as well. Two other discovery era agents, aureomycin (chlortetracycline) and terramycin (oxytetracycline), were chosen because of their importance in medical practice and because a large technical literature, and some historical writings, existed concerning them (11). These four agents were representative of that period because only about one dozen antibiotics comprised the available spectrum for medical practice prior to the semisynthetics era (12).

Streptomycin was the first antibiotic in which a «privately financed, nationally coordinated clinical evaluation» was accomplished (13). This became fixed as a pattern element of the next nearly two decades (and continues today). Another strand of the pattern elements that would be repeated with other agents of the time was seen then, as well: strain selection (by various methods) of the producing microbe for maximal yield of product. Aureomycin, terramycin, and vancomycin would all later be developed within a

(10) WAKSMAN, Selman A. (1949). *Streptomycin: Nature and Practical Applications,* Baltimore, Williams and Wilkins, p. 1.

(11) McGRAW (1976), *op. cit.* (fn. 2), Chap 3.

(12) HUSSAR, A. E. and H. L. HOLLEY (1954). *Antibiotics and Antibiotic Therapy,* New York, Macmillan, p.viii.

(13) WAKSMAN (1967), *op. cit.* (fn. 8), p. 2.

major pharmaceutical house and each would, similarly, require concerted efforts in the strain selection arena.

By the time of aureomycin, certain aspects of both production (e.g., use of the corn steep liquor growth substance pioneered in penicillin efforts) and extraction of the active molecule would follow in the established footprints of penicillin and streptomycin — each, however, with suitable variations peculiar to the chemistry of the given molecule. (Vancomycin would later reaffirm these pattern elements, too.). In fact, aureomycin was chosen as an era example because of one statement in particular that had later been made by one of that agent's development team:

> «Our personal experience in this area 'antibiotics science and technology? led to the idea that an *analogy* could be possible with the already known types of basic antibiotics and aureomycin. That is the reason we undertook a general study on the production and isolation of aureomycin. *We followed the general plan designed by other investigators*» (14).

So well had the industry worked out the basics of discovery and development that, by the period of terramycin, the lag time between discovery and finished product became, not years, but only months (albeit, vancomycin and some others were rather chemically recalcitrant and cannot be said to have been so quickly brought to market).

It is unnecessary to review the vancomycin story here. Suffice to say, nothing in that full history could have been said to have been a surprise, vis-a-vis the nature of the discovery era pattern. In the writing of that history, though, enthusiasm was generated in the belief that a detailed pattern description could be used in informing histories of yet other agents. However, what was not then apparent was that the very pattern itself, as I now argue, may be the seed of what is here being suggested as a phenomenon of a mined-out resource. That is to say, if an essentially predictable pattern of discovery and development does exist, then will something new be learned by slogging through the history of each agent of the discovery era one by one? And, if not, is that why no further detailed histories have been forthcoming on other discovery era agents? Are we presented, then, with a qualitatively depauperate resource?

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(14) VAN DYCK, P.; DESOMER, P. (1948). Production and Extraction Methods of Aureomycin, *Antibiotics and Chemotherapy, 2,* 184. Emphases added.

The literature of both the discovery era itself, and that since, is remarkable in its lack of thorough-going histories of antibiotics other than penicillin and vancomycin. Even streptomycin, about which Waksman wrote a book (fn 9), lacks a critical history. And though numerous short articles of an historical nature exist on other discovery era agents, none has been chronicled in the detail present for that of either penicillin or vancomycin (15).

Doth the gentleman protest too much? Is it that we merely lack enough graduate students inclined to tackle terramycin or erythromycin, or others, using the corporate primary sources (for that is the required archive)? Is it that we would be slicing salami, to borrow Maddox's engaging phrase, if such works were undertaken? Might we not make some valuable finds for the history of science or technology? Surely other reasons might be brought to bear, but the extant literature suggests, at least at this juncture, that mining out may be the cause of the lack of any recent major studies. What lines of evidence are there to lead to what seems a rather harsh conclusion?

III. *ON LEAVING THE MINE*

Lamentations were made recently in the form of a book review of yet another history of penicillin and of the individuals who brought that agent to fruition (16). The reviewed book, otherwise fine scholarship, is symptomatic, in its repetitiveness, of the literature of the last few decades, especially with regard to penicillin. The premier antibiotic remains the most alluring, it would seem, for historians. Yet the literature smacks of sliced salami.

John Malkin, in 1981, disintered the Fleming story for another retelling and, in the process, demonstrated a lack of knowledge concerning the biology of microfungi (conidiophores with attendent conidiospores are simply termed spores in a photograph; p. 31) and of the history of the origin of the

(15) See McGRAW, Donald J. (1986). The History of Antibiotics: A Critical Bibliography. *Bulletin of Bibliography, 43,* 103-107, for one line of evidence; see also remainder of text above for further argument. A number of studies published during the last two decades are reviewed in this noted reference and hence are not again mentioned in the main text of the current article.

(16) McGRAW, Donald J. (1987). Review of Trevor I. Williams. *Howard Florey: Penicillin and After,* Oxford, University Press, 1984. *Isis, 78,* 499-500). It was argued in the review, among other features, that 219 (of 404) pages were repetitious of a number of earlier works.

word lysozyme (Fleming did not coin the word; Sir Almroth Wright did at Flemings request; p. 27) (17). This is not carping, for this and others of the histories written during the 1970's and the 1980's introduce new errors into the secondary literature. W. Howard Hughes in his Fleming biography misreads a dedicatory plaque in the Oxford Physic Garden that assigns credit to those individuals reponsible for bringing penicillin to final development, thus adding an unnecessary burden of imprecision (18). David Wilson's history of penicillin adds nothing new (19).

The same is not true for some other works concerning penicillin that have appeared of late. Nevertheless, each is, by necessity, quite repetitious in many respects: a feature of a mined-out resource? How many ways can the biography of Fleming or Florey be told; how many for penicillin? To be just, of the several high quality studies recently written, each brings some addition to the overall story, but these addenda are often minor. Gladys Hobby, grand dame of antibiotic history and, to a lesser degree, antibiotics historiography, has provided the single best source for grasping the complex production history of penicillin (20). John Sheehan has helped us to understand how the nucleus of the penicillin molecule could be manipulated to provide the basis for building semisynthetic versions; but little is new beyond that in his history (21). The late Gwyn Macfarlane has done signal service for this whole field of scholarship by providing the definitive biographies of both Alexander Fleming and Howard Walter Florey, who, much more than Fleming, is truly responsible for bringing penicillin to the world (22).

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(17) MALKIN, John (1981). *Sir Alexander Fleming: Man of Penicillin,* Ayrshire, Alloway. The work is quite short (81 ppg. total) and exhibits somewhat large print. It may have been intended for younger readers, though this is not certain. Lady Amalia Fleming (Sir Alexander's second wife) wrote the Foreward for the book noting (in her view) its accuracy.

(18) HUGHES, W. Howard (1974). *Alexander Fleming and Penicillin,* London, Priory Press. The reference to the incorrect plaque reading is found on p. 273 in MACFARLANE, Gwyn (1984). *Alexander Fleming: The Man and the Myth,* Cambridge, Harvard, which is the premier biography of Fleming (see text later above).

(19) WILSON, David (1976). *Penicillin in Perspective,* London, Faber and Faber.

(20) HOBBY, Gladys L. (1985). *Penicillin: Meeting the Challenge,* New Haven, Yale. Much of the newest information, and some retelling, of the worldwide production story begins in Part II — «Reaching for Mass Production».

(21) SHEEHAN, John C. (1982). *The Enchanted Ring: The Untold Story of Penicillin,* Cambridge, MIT Press.

(22) MACFARLANE, Gwyn (1979). *Howard Florey: The Making of a Great Scientist,* Oxford, University Press; see fn 18 above for citation of Macfarlane's Fleming biography.

As with the «Lawrence industry», the Fleming industry has been busy, not only with regard to booklength works, but within the journal pages, as well. A spate of such journal offerings varies from simple antiquarianism to truly unnecessary restatement. It is with some of these publications that the complaints that burgeoning journal titles and that total pagination has reached unmanageable proportions become realized. Elmer Bendiner's long biography of Fleming in the pages of *Hospital Practice* is difficult to justify (23). Nothing new is presented, paper is wasted, and one becomes further convinced that the mined-out contention may well be true.

The year 1979 was the golden anniversary of Fleming's publication of the discovery of what he intially termed «mould juice». Lawrence Garrod, a major physician in medical testing of potentially useful new antibiotics over many decades, introduced a reprinting of Fleming's 1929 publication announcing penicillin's discovery and presumed value (to bench bacteriology, not human medicine, which use Fleming did not clearly perceive) (24). Nothing new was offered by Garrod, save the tidbit that an original reprint of the 1929 paper fetched 1,500 British pounds at a then recent auction. Curiously, Edward Abraham, a central figure in the penicillin and cephalosporin stories, cites the figure at 1,600! (25). Minor imperfection, yes, but again, symptomatic of uncritically retold tales.

Numerous letters to the editors of several medical journals, especially in Great Britain and the Commonwealth, were penned during the years around the 50th anniversary period and were of the reminiscence genre. One author, quite unknowingly, summed up well what was then occurring in the literature:

> «It is surely time to reflect in gratitude and with admiration on the genius,

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(23) BENDINER, Elmer (1989). Alexander Fleming: Player with Microbes, *Hospital Practice, 24,* 283-316, passim.

(24) GARROD, Lawrence P. (1979). Alexander Fleming: A Dedication on the 50th Anniversary of the Discovery of Penicillin, *Brit. J. Exper. Pathol, 60,* 1-13. The British Society for Antimicrobial Chemotherapy published a collection of Garrod's editorials extracted from the *British Medical Journal* (see WATERWORTH, Pamela, M. (1985). L. P. Garrod on Antibiotics. *J. Antimicrob. Chemother., 15* (Suppl.B), 1-46) which is valuable in providing much of the tenor of the times in the biomedical world, vis-a-vis antibiotics, over the middle third of this century.

(25) ABRAHAM, Edward P. (1980). Fleming's Discovery, *Rev. Inf. Dis., 2.*, 140-141. The auction apparently took place at Sotheby's in 1975, according to Abraham.

> the ingenuity and the extraordinary motivation of those who, within the past 50 years, have been the authors of such beneficence» (26).

The reminiscence style paper is not without the problems that accompany use of oral history, especially when such publications derive from lectures. V.D. Allison, whose experimentalist- physician role in Britain was not dissimilar to that of Garrod in America, is exemplary of those who have continued to confound the literature with errors of various proportions. Attributing the axiom that chance favors the prepared mind to Claude Bernard instead of to Louis Pasteur is grating, but to continue the, by then discredited (by Hare) idea that Fleming's mold spore «blew in through the window from the air in Praed Street», is less easily accepted (27).

There has long been established a subset of the penicillin literature, not unlike that in many other areas of science, that by title, but seldom by content, purports to be historical. Typically, works of this genre are review articles on use of certain agents often prefaced by an historical introduction. There have been a number of recent publications along this line (28).

A newer type of genre can be of some value to the scholar who wishes a quick and effortless introduction to an historical area not otherwise familiar: the video/film history. While film, as a venue for historiographic recording, has its own history of legitimacy for the scholar, videotape presents a newer approach. The well known, and well respected, NOVA series of WGBH/

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(26) SCOTT-YOUNG, Margery. (1979). Florey and After, *Med. J. Austral., 2,* 652. Florey was well remembered during this period as well as was Fleming. See especially Sir Ian FRASER (1974). Penicillin: Early Trials in War Casualties, *Brit. Med. J., 289,* 1723-1725, who pointedly reminded his readers that «Fleming had put penicillin on the map, but Florey really put it on the market» (p. 1723). See also MCEWIN, Roderick (1982). Florey and Cairns — Early Work on Penicillin, *Med. J. Austral., 1,* 12-13 and BREATHNACH, C. S. (1981). Biographical Sketches No. 8 — Fleming, *Irish Med. J., 74,* 214-215, who decried what he refered to as an «era of denigration» concerning what Hare (see fn 3 above) refered to as luck that Fleming found penicillin at all.

(27) ALLISON, V.D. (1974). Personal Recollections of Sir Almroth Wright and Sir Alexander Fleming, *Ulster Med. J., 43,* 89-98; the work is peppered with minor errors. Pasteur's famous quotation reads: «Dans les champs de l'observation, le hasard ne favorie que les esprits préparés».

(28) Examples include KAMPMEIER, Rudolph, H. (1981). The Introduction of Penicillin for the Treatment of Syphilis, *Sexually Transmitted Dis.,* 8, 260-265; SELWYN, Sydney (1982). The Evolution of the Broad-Spectrum Penicillins, *J. Antimicrob. Chemother., 9* (Suppl. B), 1-10, among others.

Boston, tackled the penicillin story utilizing both Hare's and Macfarlane's works as references. The 58 minute capsulization does an excellent job of demythologizing Fleming and, simultaneously, giving Florey his proper place in the pantheon, just as do Hare and Macfarlane in their respective books. The video could do immense service for younger viewers by placing Florey, especially, into the proper perspective, but the level of the production is not suitable to that age level. And this work too (though only in the Teacher's Guide), is not without the errors of retelling (here the 'spore through the window' problem) (29).

A second video production (Pyramid Film and Video) of recent times offers a printed insert which boldly speaks of Fleming's «chance observation» of a culture of «mold-inhibiting bacteria» — quite the biological reverse of reality. Unlike the NOVA production, which emphasized the human aspects of penicillin history, the Pyramid version is strongly technological emphasizing the biology and chemistry of penicillin (30). While the production is truly outstanding, once again nothing new is added to our historical knowledge. The works by both Hare and Macfarlane, as with the NOVA version, function as the primary reference sources in the Pyramid product.

There has long been a fascination both with who first discovered the penicillin effect (i.e., the destruction of bacteria) and who first put it to practical use. The fact that the *Penicillium* mold has lytic effects on bacteria had been well established long before Fleming pursued the phenomenon. Florey first noted the early literature on it in his *magnum opus* on antibiotics, and numerous others have sought to push the initial «discovery» year ever further back in time (31). In his C.E. Wallis Lecture, W. Fraser-Moodie reminds us that not only had Pasteur fallen upon the penicillin effect and presciently suggested a human therapeutic use for it, but that Lister had even made a concerted effort to employ a culture of *Penicillium glaucum* (identified by Pasteur at

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(29) NOVA (1986). *The Rise of a Wonder Drug,* Northbrook, Illinois, Coronet Films and Video; the Coronet — produced *Teacher's Guide* sheet regrettably provides a large drawing of an open window with spores blowing in onto a Petri plate (already, incidentally, growing a microfungal colony); the picture is accompanied by text which reads: «Most people have heard the story: how mold spores accidentally blew in the window [sic] of an attic [sic] laboratory in England...» See the review by McGRAW, Donald, J. (1986). *Sci. Books Films, 22,* 133-4, concerning the many excellent features of this video.

(30) *Penicillin: First of the Miracle Drugs,* Santa Monica, California, Pyramid Film and Video (1987).

(31) FLOREY, Howard W., *et al.* (1949). Introduction, Vol. I, *Antibiotics,* London, Oxford.

Lister's request) in a human infection (32). Sydney Selwyn, however, seems to have done the most thorough job in the 'who-discovered-it-first' genre and, while there is much that is repetitious in his publication, he has presented valuable new information, as well (33).

The use of moldy bread, or other moldy foodstuff, as a wound poultice had been a practice in many societies in a number of places world-wide over centuries, if not millenia. This use was widely known by the pioneer bacteriologists of the 19th century and also by the medical community of the last century, if not before. It is in this therapeutic-use literature that we may find one of the more notable recent contributions to the penicillin story — one not repetitive of earlier historiographic facets. Allan Dumont has shown that a New York surgeon, Dr. Frederick S. Dennis of Bellevue Hospital Medical College, presented a paper («The Action of Microorganisms on Surgical Wounds with Demonstrations») before the second annual meeting of the New York Medical Association in 1885. And, as Dumont correctly states, «'Dennis'? article seems to have escaped the notice of those who have chronicled the history of antibiotics» (34). Along with new revelations by Selwyn (above), this aspect of the penicillin story has made recent, albeit minor, gains.

Closely related are those articles noting the first uses of penicillin per se, as opposed to the raw products of a *Penicillium* culture. The physician Charles Fletcher was asked by Florey (in January, 1941) to find a patient «with some inevitably fatal disorder who might be willing to help» by being the first human upon whom to try penicillin (35). Fletcher offered a «pleasant 50

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(32) FRASER-MOODIE, W. (1971). Struggle Against Infection, *Proc. Roy. Soc. Med., 64,* 87-94.

(33) SELWYN, S. (1979). Pioneer Work on the 'Penicillin Phenomenon,' 1870-1876, *J. Antimicrob. Chemother., 5,* 249-255. An excellent review of the greater history of chemotherapy, including antibiosis (and antibiotics), which supplements its text with useful time-lines, is to be found in ROLINSON, G. N. (1988). From Pasteur to Penicillin — The History of Antibacterial Chemotherapy, *Zbl. Bakt. Hyg.* (Ser. A), *267,* 307-315 (in English). Though it offers no new insights, it is to be recommended as a first-rate primer to the period before penicillin; for an earlier work which provided similar, and equally valuable, fare see BRUNEL, Jules (1951). Antibiosis from Pasteur to Fleming, *J. Hist. Med., 6,* 287-301.

(34) DUMONT, Allan E. (1985). An Observation of Penicillin by a New York Surgeon in 1885. *Surg., Gyn., Obstet., 161,* 394-396.

(35) FLETCHER, Charles (1984). First Clinical Use of Penicillin. *Brit. Med. J., 289,* 1721-1723. This publication is immediately followed (p. 1.724 ff) in the *Journal* by another article on early war uses and a letter to the editor, both of which are reminiscences, but, since they provide minor addenda to the greater history of penicillin, they are not cited here.

year old woman with disseminated breast cancer» as a subject. There was, of course, no expectation that the cancer might be responsive to penicillin, but there remained the very real question of whether penicillin itself might be toxic. The antibiotic was duly injected with neither positive nor negative, the more important aspect, effects. It remains a fact that much of the secondary literature on penicillin continues to put forth an Oxford bobby (Albert Alexander) as the first case. It was, admittedly, the first one where a bacterial infection was treated by Florey's penicillin — and the case had considerable dramatic appeal. It was not, however, the first case ever, nor, for that matter, was the above-noted breast cancer case. It has for some years been known that yet another New York physician, Martin Henry Dawson, some 55 years after Frederick Dennis, tried Fleming's «mould juice» on an endocarditis patient, without success however (36).

In what is one of the more important of the recent original contributions to the penicillin historiographic literature, it has been demonstrated that

> «Three claims that penicillin had been used effectively on patients around that time 'i.e., 1930? have arisen from work by Fleming himself, C. G. Paine, and A. Dickson Wright...but until now no claim has been substantiated by documented clinical notes» (37).

Paine had been a student at St. Mary's Hospital Medical School (London) where Fleming spent his entire adult career and also lectured in bacteriology. While Paine's interest in penicillin was gained there (1928/9), he was not to experiment with penicillin until some limited research at Sheffield University somewhat later (1930/31). Over a six month period he used crude filtrates of the antibiotic on several different patients, one (a neonate's gonorrheal eye infection), that with the clearest written record of evidence, was treated with great success. The actual case history notes have been preserved and have now been reproduced by Wainwright and Swan (38). These authors have been able to clear up errors in earlier published histories, inclu-

(36) CLARK, Ronald W. (1985). *The Life of Ernst Chain: Penicillin and Beyond,* New York, St. Martin's Press, is only one of several recent sources in which the Dawson attempt is mentioned; see p. 64 of Clark's work.

(37) WAINWRIGHT, Milton; SWAN, Harold T. (1986). C. G. Paine and the Earliest Surviving Clinical Records of Penicillin Therapy. *Med. Hist., 30,* 42-56.

(38) *Ibid.,* p. 45.

ding that of Macfarlane, otherwise writer of the best works on both Fleming and Florey, as noted above (39).

Wainwright and Swan have considered another matter beyond 'first use,' and that is: Why wasn't penicillin developed after Fleming's 1929 announcement paper? Their answer is that given by so many others who have written upon the penicillin story — the state of technological development in chemical isolation, purification, characterization and preservation of molecular activity was not then sufficient. Gladys Hobby, among others, recognized this great 1930's lacuna of technological development (40). What remains of interest, however, is that, to date, no critical history of the development of the relevant technologies exists which focuses primarily upon the 1930's and technology's role in the retarding (i.e., from 1929 to 1940) of the onset of the discovery era (41).

But it was Ronald Hare, who had worked in Fleming's laboratory during the relevant period, who most clearly addressed the question of why the latter failed to pursue penicillin. Privy to some theretofore (i.e., prior to 1982) unavailable laboratory notebook pages, Hare was able to reconstruct the tenor of the times and provide firm evidence of why penicillin languished for more than a decade. Hare's close consideration of the technical obstacles and other, quite inexplicable intellectual lapses, on the part of both Fleming and his aids Craddock and Ridley, demonstrates better than any other historical research why penicillin was dropped in Fleming's now famous Praed Street laboratory (42).

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(39) *Ibid.*, p. 49. These authors also point out the same error made by BALDRY, P. (1976). *The Battle Against Bacteria,* Cambridge, University Press, p. 106, to the effect that Florey had watched Paine at work applying penicillin to a wound. This, Wainwright and Swan assert, «is no more than imaginative writing». For a review of Baldry see the article cited in fn 14 above.

(40) HOBBY (1985), *op. cit.* (fn. 20), p. 44. Similar recognition by other authors, such as Hare, Williams, Macfarlane, etc., restate this same point.

(41) In an opinion piece by HOWIE, James (1986). Penicillin: 1929-1940, *Brit. Med. J., 293,* 158-159, citing Wainwright and Swan and others, Howie bemoaned the lack of the kind of financial support that might have possibly led to a greater technological development during the 1930's, vis-a-vis antibiotics-like compounds, with the words: «Politicians and Treasure mandarins should be reminded of the vast and unforeseen benefits that may accrue from allowing intelligent scientists to play themselves by exercising their skills on what they find interesting» (p. 159).

(42) HARE (1982), *op. cit.* (fn 3). See also Hare's other enlightening publication of the period: (1983). The Scientific Activities of Alexander Fleming, Other than the Discovery of Peni-

Finally, of the three men who shared the Nobel Prize for penicillin —Fleming, Florey, and Chain— the latter, Ernst Boris Chain, was without a critical biography until recently. Ronald Clark provided the last link in the chain of needed biographical studies of this triumvirate (fn 35). The work is, however, most frustrating, for, while it uses many and valuable direct quotations from both published and archival sources, it provides no citations and only a limited and unremarkable bibliography. While nothing new, once again, is offered in the (mined-out?) penicillin story, Chain's later career (especially as major domo to the antibiotics industry of Europe) is documented; thus, we are provided with much previously unavailable information. (Lady Chain provided Clark *carte blanche* to the «extensive correspondence and papers of Sir Ernst».) Several other recent articles have emphasized Chain's crucial role in the penicillin story (43).

IV. *BEYOND PENICILLIN*

If the penicillin literature of the past two decades suggests strongly that the contention of the mined-out phenomenon is accurate, what other evidence exists in support of such a claim? Is it just the penicillin story which seems recently to have been coming in salami slices, or are there other reasons to believe that the sameness of discovery and development of discovery era antibiotics, as posited above, makes for a depauperate historiographic resource?

The streptomycin history is a logical place to turn to test the argument. Julius Comroe has recently published a two-part article that stresses the point that Selman Waksman had had a number of opportunities for early

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cillin. *Med. Hist., 27,* 347-372, which, contrary to its title, does include some discussion on penicillin.

(43) See especially, SHEPPARD, Julia (1982). Illustrations from the Wellcome Institute Library: The Chain Papers. *Med. Hist., 27,* 434-435; Editor. (1979). Obituary: Sir Ernst Chain. *Brit. Med. J.,* Aug. 25, p. 505; ABRAHAM, E. P. (1980). Ernst Chain and Paul Garrod. *J. Antimicrob. Chemother., 6,* 423-433; and Sir Ernst B. CHAIN (1978). The Penicillin Discovery: Past and Present. *Japanese J. Antibiot., 31,* 493(29)-507(43) (in Japanese; no English summary). Sheppard also, parenthetically, mentions that papers relating to penicillin history from both Ronald Hare and Norman Heatley were recently (ca. 1982) given to the Wellcome Library. Heatley, interviewed in the NOVA video history (see fn 29 above), remains a major figure in the whole penicillin story and for whom there is no biography.

(i.e., both before and after 1929) discovery of antibiosis presented to him during various stages in his research career (44). It is implied that these moments could have functioned in the same serendipitous manner that did obtain for Fleming, but Waksman in some cases either did not see, or, in other cases, did not seize these opportunities. Comroe goes on (in Part II) to reassess the role of several other workers in the streptomycin story and argues, convincingly, that the distribution of credit for certain aspects of the recognition of streptomycin's use and, especially, value in treating tuberculosis was inaccurate and unfair. This is not dissimilar to the penicillin story in which Florey's and Chain's roles were long unsung.

Comroe gained his insights, which represent a valuable contribution to the sociological aspects of antibiotics historiography, from the published literature; nothing, however, is offered on the history of science or of technology regarding streptomycin, nor did Comroe make any use of primary sources. There have been others, as well, who have considered the problem of the inequity of the dispensing of kudos in the streptomycin story (45). These sociological features clearly represent possibilities for some level of further, more critical research. Only a few other minor recent publications exist concerning streptomycin (46).

Chemically somewhat similar to the penicillins, the cephalosporin family of antibiotics has enjoyed considerable success in medical application. The discovery of the producing fungus (*Cephalosporium acremonium*; now reclassified, by some, as *Acremonium chrysogenum*) in a sewage outfall off the coast of Cagliari, Sardinia (1945) has been told a number of times. Of the many who have considered the technical aspects of this group of agents, which continues to expand as semisythetics, Edward P. Abraham remains central. Abra-

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(44) COMROE, Julius H., Jr. (1978). Pay Dirt: The Story of Streptomycin. *Amer. Rev. Resp. Dis.* Part I: From Waksman to Waksman, *117,* 773-781; Part II: Feldman and Hinshaw; Lehman, *117,* 957-968.

(45) SAKULA, Alex (1988). Selman Waksman (1888-1973): Discoverer of Streptomycin: A Centenary Review. *Brit. J. Dis. Chest, 82,* 23-31. See especially p. 29 and the discussion of Albert Schatz.

(46) See DANIEL, Thomas M. (1988). Selman A. Waksman and the First Use of Streptomycin. *J. Lab. Clin. Med., 111,* 133-134; and BREATHNACH, C. S. (1987). Waksman. *Irish Med. J., 80,* 436; see also the short, but interesting biographical sketch by WALKER, J. C. (1982). Pioneer Leaders in Plant Pathology: Benjamin Minge Duggar. *Ann. Rev. Phytopathol., 20,* 33-39, which contains some minor new information on Duggar's role in both the development of streptomycin and that of aureomycin.

ham was a young member of Florey's «Oxford team» during the penicillin development period and went on to a successful career in development of the cephalosoprins. He has, in recent years, written a number of review articles on these antibiotics (47). Not an historian of science, Abraham's articles are of the reminiscence genre, but do represent much of what has been published on the history of the cephalosporins.

In so saying, once again the spectre of mining out an historiographic resource seems not an unjust argument. The chemistry of the cephalosporins and the penicillins is similar, the rise of the semisynthetic versions of each has much in common, and the medical testing and eventual applications are not dissimilar between the two groups. Because of these similarities, it is not surprising that they are often considered together in any of a number of different, and different types of, publications. As with other historical studies (above), Sydney Selwyn provides an outstanding short introductory history of the beta lactam antibiotics, i.e., the penicillins and cephalosporins, that is highly recommended and cannot be over-estimated (48). But, and this is the crucial point with regard to the present argument, nothing new is offered in Selwyn's otherwise fine book.

Some thinly sliced salami may be called for in the case of one aspect of the cephalosporin story, however. The chemistry of the molecular nucleus of the cephalosporins (7-ACA, or 7-aminocephalosporanic acid), while not terribly dissimilar to that of the penicillins (6-APA, or 6-aminopenicillanic acid), proved extremely difficult to cleave. Cleavage is a necessary step in the production of semisynthetic versions of the basic moeity. The solution to the problem was finally forthcoming in the laboratories of Eli Lilly and Company where some very elegant techniques were pioneered (49). A critical his-

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(47) See especially three publications by ABRAHAM, E. P. (1979). A Glimpse of the Early History of the Cephalosporins. *Rev. Inf. Dis., 1,* 99-105; (1981). The Beta Lactam Antibiotics. *Sci. Amer., 244,* 76-86; and (1987). Cephalosporins: 1945-1986. *Drugs, 34* (Suppl.2), 1-14. While not history, a technical review article by Barbara MURRAY and Robert MOELLERING (1981). Cephalosporins. *Ann. Rev. Med., 32,* 559-581, provides an excellent entrepot to the technical literature of the cephalosporins.

(48) SELWYN, Sydney (1980). *The Beta-Lactam Antibiotics: Penicillins and Cephalosporins in Perspective.* London, Hodder and Stoughton. See Chapter 1 (of 55 pages), a history with the best collection of relevant illustrations available in one place; the coverage is from «prescientific» times to the present.

(49) See *Profile of an Antibiotic: Keflin (sodium cephalothin, Lilly).* Indianapolis, Eli Lilly and Company, 1966, p. 10 ff. Also from Lilly is *Healers from the Sea: The Story of the Cephalosporins.* 2nd ed. (1971). It may be of some value to offer here, albeit a personal aside, a caveat to

tory would be of considerable value here, especially as the reaction method finally developed was unique in the history of chemical techniques.

Full histories, as has been stated, remain lacking for any antibiotic save those on penicillin and vancomycin. Nystatin, an antifungal antibiotic, suffered in a recent historical study (touted as being the «whole story») in that no, or very little, mention was made of the science, technology or medical testing associated with the agent (50). The study further failed to place the two women scientists who pioneered nystatin into perspective. Sociologists of science, though, may profit by the author's discussion of the activity of the private granting agency involved in the support of the nystatin studies.

Hubert Lechevalier, long associated with the Waksman Institute at Rutgers University, and well-known co-author of a leading work in the history of bacteriology (*Three Centuries of Microbiology,* New York, 1965), had been involved in the discovery and early development of neomycin. His quarter century review of the sucesses of that agent provided a short reminiscence style introduction (51). Similar review articles for chlortetracycline, aztreonam, and even vancomycin have of late been published, all lacking new insights (52).

A series of publications which are not histories of specific antibiotics, but

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graduate students in search of a dissertation topic. Since the principal venue of primary source materials in much of the history of antibiotics lies in the vaults of pharmaceutical houses, one must make sure that the sources are available for study when needed. The present author was within a few days of beginning research, having just moved the family 1,500 miles to do so, on the history of the cephalosporins at the Lilly archives, when a sudden legal action sealed all the relevant files on this antibiotic group!

(50) BALDWIN, Richard S. (1981). *The Fungus Fighters: Two Women Scientists and Their Discovery.* Ithaca, Cornell University Press; a review of this work has been published: McGRAW, Donald J., (1983). *Isis, 74,* 116-117.

(51) LECHEVALIER, Hubert A. (1975). The 25 Years of Neomycin. *CRC Critical Reviews in Microbiology,* May issue, pp. 359-397.

(52) See JUKES, Thomas H. (1985). Some Historical Notes on Chlortetracycline. *Rev. Inf. Dis., 7,* 702-707; SYKES, Richard B., *et al.* (1968). Aztreonam: Discovery and Development of the Monobactams. *NJ Med.,* Special Issue, January, pp. 8-15; GRIFFITH, Richard S. (1984). Vancomycin Use — An Historical Review. *J. Antimicrob. Chemother., 14*(Suppl. D), 1-5. While Conover stated in 1971 that every important class of antibiotic agent had been discovered prior to about 1960, the monobactams (including aztreonam) were discovered about the time he was writing. The correctness of Conover's statement is not challenged by this discovery, however, as the monobactams are only monocyclic variants of the larger beta lactam agents and cannot be said to truly represent a new class of antibiotics.

consider the discovery era (and later), offer a melange of repetition and some new information. Though nothing new is present in D. Perlman's brief history of the antibiotics industry, a useful table showing dates of initial reports of new agents (from before 1945 to 1974) is present. Others have reviewed the overall history of chemotherapy, including the sulfa drugs. The growth of an antibiotic screening (soil sampling) program has, as well, been discussed (53).

The discovery era was not without its warts, and, in the revealing of one of these, Richard McFadyen offers a fine nugget drawn from the otherwise over-worked mine of antibiotics historiography. Again, appealing to the sociologists of science, rather than to its internalist historians, McFadyen details the story of a scandal involving no less a personage than Henry Welch and no less a federal agency than the Food and Drug Administration. Signal service is done by the telling of this intriguing tale (54).

V. *INSPECTING THE MINE*

It is, of course, quite impossible to prove the correctness of the argument that the mine of primary resources of antibiotics history is exhausted merely by the state of the secondary literature. Nevertheless, it is obvious that the majority of the publications appearing over the past two decades suggest

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(53) See PERLMAN, D. (1974). Evolution of the Antibiotics Industry, 1940-1975. *Amer. Soc. Microbiol. News, 40,* 910-916; surveys also include: SPRING, Maxwell (1975). A Brief Survey of the History of the Antimicrobial Agents. *Bull. NY Acad. Med., 51,* 113-116; HIRSCH, James G. (1980). The Greatest Success Story in the History of Medicine. *Med. Times, 108,* 36-43; RHOADES, Everett R. (1980). A Seminar on Antibiotics. *OK State Med. Assoc., 73,* 176-179, offers an «annotated chronology» of discoveries, but introduces more errors in the business of repeated tellings (e.g., he gives the wrong year for the coining of the word antibiotic; p. 179). Finally, see WOODRUFF, H. Boyd, *et al.* (1979). Evolution of an Antibiotic Screening Programme: A Tribute to Justo Martinez Mata. *Hindustan Antibiot. Bull., 21,* 71-84, which is very much an original offering. Woodruff, a pioneer in his field, later published his reminiscences as: (1981). A Soil Microbiologist's Odyssey. *Ann. Rev. Microbiol., 35,* 1-28, which contain several sections on antibiotics. Some personal experiences Woodruff recounts help to fill in a few, otherwise small, gaps in the discovery era history; for instance, he states that Waksman coined the term antibiotic over a lunchtime conversation at which he (Woodruff) was present (p. 7).

(54) MCFADYEN, Richard (1979). The FDA's Regulation and Control of Antibiotics in the 1950's: The Henry Welch Scandal, Felix Marti-Ibañez, and Charles Pfizer & Co. *Bull. Hist. Med., 53,* 159-169.

that, where the primary sources are being carefully examined, little new is being discovered, at least with regard to penicillin. The sameness of discovery and development of agents appearing during the period of 1940 to 1960 further seems to limit how much interpretive value can be extracted from the resource if one wishes to focus primarily on internalist features of the science and technology of any of the other agents. In fine, that is not to say that sociologists of science might not well strike rich veins, but if all other aspects of the recent literature are any indications, deep digging will be required.