J. Parasitol., 94(4), 2008, pp. 934–945

HISTORY OF THE DISCOVERY OF SULFAQUINOXALINE AS A COCCIDIOSTAT

William C. Campbell
Research Institute for Scientists Emeriti and Department of Biology, Drew University, Madison, New Jersey 07901.
e-mail: wcampbel@drew.edu

ABSTRACT: Sulfaquinoxaline played an important part in the demotion of roast chicken from vaunted Sunday-dinner status to an unrespected position on the everyday menu of the Western world. It had its origins in the chemical synthetic program that sprang from the introduction of sulfonamide drugs into human medicine in the 1930s. The program was sustained through the years of World War II despite declining clinical use of that chemical class. Several sulfa drugs were known to be active against the sporozoan parasite (*Plasmodium* spp.) that causes malaria, but were not satisfactory in clinical practice. A sulfonamide that had a long plasma half-life would ipso facto be considered promising as an antimalarial drug. Sulfaquinoxaline, synthesized during the war, was such a compound. It proved too toxic to be used in human malaria, but was found to be a superior agent against another sporozoan parasite, *Eimeria* spp., the causative agent of coccidiosis in domestic chickens. In 1948 sulfaquinoxaline was introduced commercially as a poultry coccidiostat. It was not the first sulfonamide found active against *Eimeria* spp. in poultry, but its practical success in disease control firmly established the routine incorporation of anticoccidial drugs in poultry feed. In this way, the drug exerted a major impact on the worldwide production of poultry meat. Although it has long been eclipsed by other drugs in poultry management, it continues to be used in other host species. This article describes the discovery of sulfaquinoxaline as a practical therapeutic agent, and examines the way in which the discovery arose from a partnership between industry and academia.

Sulfaquinoxaline (SQ) has faded from its glory days as a pioneer feed additive for controlling disease in chickens; yet by virtue of its continuing use as a coccidiostat in special circumstances, it continues to bring medical and financial benefit to its ingesters and investors, respectively. Patented in 1946, its efficacy in poultry coccidiosis and its value as a dietary prophylactic were reported soon afterward. Its subsequent field success was so great that it affected management practices in the poultry industry, and contributed to a marked reduction in the price of poultry meat. In so doing, it initiated an era of routine use of dietary chemicals to achieve efficiency in meat production.

The sulfonamide drugs (''sulfas'') had been discovered as antibacterial agents in the 1930s, and before the decade was out their efficacy had been shown to extend to protozoan parasites. Susceptible eukaryotes included 2 rather closely related parasites, *Plasmodium* sp., the agent of human malaria, and *Eimeria* sp., the agent of poultry coccidiosis. Nevertheless, by the close of World War II in 1945 no sulfonamide was known to be satisfactory in either disease. Soon after the war, however, the superior attributes of SQ in coccidiosis were described, and by 1948 its triumph in the marketplace had begun. This had become possible because of a collaboration between scientists at a state-run experiment station and scientists at the industrial laboratory where it had been synthesized.

In the context of time and place, the idea of testing SQ against coccidia in chickens was not a matter of intellectual virtuosity. Yet, because of the enormous consequence of such an experiment, the question of how it came about acquires considerable historical significance. It will be argued here that although it may not be possible to say precisely who first proposed this line of experimentation, much can be said about the people and the circumstances responsible for it. It will be suggested that discovery of the drug's efficacy in avian coccidiosis can be traced to wartime concern about human malaria as well as to everyday concern about a disease in chickens. The underlying collaboration between public and private research institutions will be given particular attention.

Received 17 July 2007; revised 20 September 2007; accepted 6 February 2008.

DISCOVERY AND DEVELOPMENT

During World War II the search for new antimalarial drugs was intense, and Merck & Co., Inc. (hereafter ''Merck'') was among the companies engaged in that endeavor. The multicompany nature of the program reflected the high priority given to malaria research by the War Production Board under the auspices of the National Research Council's Office of Scientific Research and Development (D. F. Green, unpubl. obs.; Coatney, 1963). In the field of medicinal chemistry the sulfonamide molecule was all the rage, and more than 5,000 structural derivatives would be made by the end of the war (Bryskier, 2005). One objective of the program was to find a sulfonamide derivative that would be effective against the malaria parasite and would not need to be given repeatedly during the course of a day. At Merck, chemist Max Tishler (Fig. 1) and his associate, John Weijlard (Fig. 2), synthesized the molecule 2-(4-aminobenzene-sulfonamide)-quinoxaline (alternatively designated 2-sulfanilamido-quinoxaline). A patent application was filed on their behalf on 8 January 1944. The compound became known generically as sulfaquinoxaline, and SQ became both a trademark and a handy everyday diminutive.

Max Tishler was then at the beginning of his rise to eminence as a leader in pharmaceutical research and development. He had been an outstanding graduate student in the chemistry department of Harvard University, earning a Ph.D. in 1934 and staying on as a junior faculty member. At that time, Merck was seeking to expand its objectives beyond the manufacture of fine chemicals. In 1937, as part of its strategy of placing high priority on research, the company recruited Tishler. He would go on to become President of the Merck Sharp and Dohme Research Laboratories (a Division of Merck & Co., Inc.), a member of the National Inventor's Hall of Fame, and a member of the National Academy of Sciences (Sarett and Roche, 1995). In 1987, the National Medal of Science was conferred on him by the President of the United States (Ronald Reagan) at a ceremony in the White House. An application for a patent on SQ was filed on 8 January 1944. The patent, assigned by Weijlard and Tishler (1946) to Merck & Co. Inc., was issued on 16 July 1946 (U.S. Patent No. 2,404,199). As would be expected, it dealt almost entirely with the chemical structure of SQ and

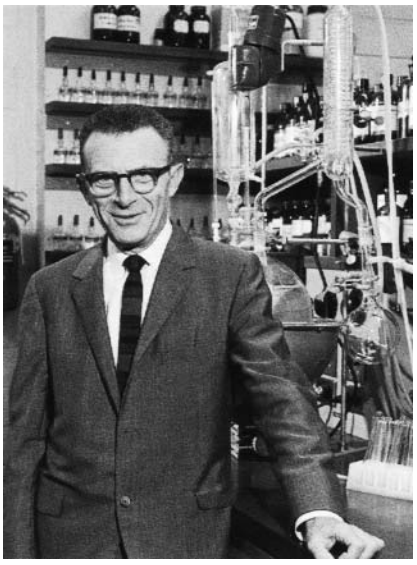


FIGURE 1. M. Tishler. Merck & Co. Inc. photograph.

FIGURE 2. J. Wiejlard. Merck & Co. Inc. photograph.

synthetic processes for making it. It did note, however, that the new compound was slowly excreted in treated animals, making it possible to maintain antibacterial plasma levels with low dosage. Long before the patent was issued, the basic chemical and biological properties of the compound had been reported in the scientific literature.

The chemical synthesis was reported in a paper in which Weijlard and Tishler, now joined by their colleague Erickson, noted that the compound was slowly eliminated from treated animals and was highly effective against pneumococcal infections in mice when administered only once a day (Weijlard et al., 1944). Underlying the brief mention of SQ's biological properties in that chemical report, and acknowledged by the authors, was an intense study carried out by scientists in the biological arm of the company (the Merck Institute for Therapeutic Research, then under the direction of Hans Molitor).

The antibacterial efficacy of SQ was studied in vitro and in vivo; and it was shown that daily doses of SQ (given orally over a 5-day treatment period) were as effective against lethal *Diplococcus pneumoniae* infections in mice as sulfadiazine or sulfathiazole in divided doses given 4 times a day (Smith and Robinson, 1944). The compound thus acquired distinction among the early sulfa drugs, most of which would become known as ''short-acting sulfonamides.''

Although malaria was the prime focus of the early Merck studies, little mention was made of it in the published reports—probably because much of the wartime information on antimalarial testing was officially declared secret (Coatney, 1963). Seeler et al. (1944) recorded that SQ suppressed ''certain avian malaria infections'' when administered in single doses at 48 hour intervals'' whereas sulfadiazine and sulfapyrazine had to be given 3 times daily or incorporated in the diet. The authors referred to ''*P. lophurae* and another species of avian malaria'' without mention of host species, suggesting deliberate caution on their part. Once the war was over, and SQ had been employed for other purposes, there would have been little incentive for the investigators to prepare technical reports for publication. There are passing postwar statements to the effect that SQ had been tested against malaria in chickens and ducks, and had been found very effective (Seeler et al., 1944; Green, 1947; Anonymous, 1949). According to the anonymous report of 1949, the tests were done in late 1942 or early 1943. Presumably they were carried out against *Plasmodium gallinaceum* in chickens and *Plasmodium lophurae* in ducks, these being standard malaria models at that time (before nonprimate mammalian models had become available). The present writer has found only 1 reference to antimalarial testing of SQ in the human. It occurs in unattributed articles in a Merck magazine (Anonymous, 1952a) and a poultry magazine (Anonymous, 1952b). Both are about the success that SQ was having in the control of coccidiosis in poultry, and the latter article was based in part on promotional material provided by Merck (Craig, 1952). The poultry magazine text states (by way of background on SQ): ''Preliminary studies in man indicated that it had some effect on human malaria . . . ''. The Merck Review text is identical except that the words ''in man'' are absent. These articles would have been written by and for nonscientists, some 7–9 yr after any such trial in humans had taken place. It is possible that they reflect some confusion between tests against malaria in humans and tests done in systems used as models of human malaria.

The early biological data showed that SQ met the objective of finding an antimalarial sulfonamide with a long plasma half-life, and it seemed possible that such a drug could fill an important medical and strategic need. In both World War I and World War II the movement of quinine from the East to the West was disrupted, stimulating several nations to set up research programs aimed at finding a synthetic replacement for the natural alkaloid. The urgent search for antimalarials in the United States during World War II was 1 such program (Coatney, 1963; Black et al., 1981; Campbell, 1986; Sneader, 2005). On the basis of the tests against avian malaria, it seemed possible that SQ could become the desired long-acting sulfonamide for preventing and treating malaria in military personnel. That

FIGURE 3. D. F. Green. Merck & Co. Inc. photograph.

would change when the Merck team investigated the toxicity, excretion rates, and urinary excretion products of SQ. The studies were done in rats, dogs, rabbits, and monkeys (*Maccacus rhesus*), and at least urine analysis seems to have been done in humans (Scudi and Silber, 1944; Seeler et al., 1944; Stevens et al., 1946). Toxic effects observed at high dosage included hypothrombinemia in rats, with resultant internal bleeding (Mushett and Seeler, 1947). The most significant finding was that the relatively insoluble 3-hydroxy derivative of the compound precipitated in the kidneys of rat and monkey, but not dog or rabbit (Seeler et al., 1944). A later report would show that SQ was very well tolerated in poultry (Cuckler and Ott, 1955). In the meantime, however, the renal precipitation and kidney damage in monkeys put an end to any further consideration of SQ as an antimalarial drug for humans.

Prospects for the sulfonamides in the malaria arena no longer looked good. The 1 sulfonamide with a long plasma life was out of the picture, and the short plasma life of the other sulfonamides was 1 of the reasons for shelving the whole class (Black et al., 1981). Another reason was that the 4-amino-quinolines were rising to the forefront as antimalarials. They had been studied as antimalarials for a decade (Coatney, 1963), and the leading candidate, which was to become famous as chloroquine, had its first American trial in humans in the year that the SQ patent was filed. With the collapse of SQ as a contender,

FIGURE 4. P. Delaplane. RIAES photograph.

the amino-quinolines quickly eclipsed the sulfonamides as potential agents for the control of malaria. (Interest in the sulfonamides would be revived decades later when resistance to chloroquine emerged and synergism between sulfas and dihydrofolate reductase inhibitors was appreciated.)

With human application thwarted, Merck sought outside help in assessing the potential value of SQ in veterinary medicine. This was done through the agency of 1 of its scientists, David F. Green (Fig. 3). In the 1930s, Green had worked half-time at Merck while pursuing his Ph.D. degree at Rutgers University. An important fact (which seems to have been overlooked in the present context) is that Green, several years before the synthesis of SQ, had been senior author of a paper on the pharmacology of sulfa drugs (Green et al., 1938). That paper reported data obtained at Rutgers University on sulfonilamides provided by Merck (the research being financially supported by Merck). Moreover, Green's report dealt with the renal clearance of sulfonilamides. Sulfa drugs were a hot topic at the time and Green had attended at least 1 scientific meeting at which they had been debated. By the time SQ was synthesized, Green was working full-time at Merck and would have been very familiar with its research on new sulfa-drug candidates. He was thus well positioned to initiate efforts to exploit SQ for animal health, and that responsibility was assigned to him as Manager of Merck's Veterinary Department (Anonymous, 1949).

In 1944 or early 1945 Merck provided a sample of SQ to poultry pathologist John Paul Delaplane (Fig. 4) of Texas A&M. Presumably the initial Merck approach to Delaplane was made by Green, but it has not been possible to confirm this. By July 1945, Delaplane had not only tested the Merck compound in chickens, but had published his finding that SQ had prophylactic activity against the bacterium *Pasteurella avicida* (agent of enzootic fowl cholera; Delaplane, 1945). Soon thereafter (1 January 1946) Delaplane returned to the Rhode Island Agricultural Experiment Station (RIAES) whence he had come, and in quick succession he and his associates found SQ highly effective against *Eimeria tenella* (1 of the agents of cecal coccidiosis) and against *Eimeria necatrix* (an agent of intestinal coccidiosis) in chickens (Delaplane et al., 1947).

The role actually played by each of the associates is not evident from the scientific literature. A quarter-century after these events, a newspaper reporter described Thomas C. Higgins as the 1 who discovered the efficacy of SQ against coccidiosis (Sawtelle, 1971). Higgins (Fig. 5) was 1 of 2 coauthors on Delaplane's first (1947) publication on the subject, and the newspaper article was apparently based on an interview with Higgins made 25 yr after his initial contribution to the discovery. The reporter added that Higgins ''was joined in the dis-

FIGURE 5. T. C. Higgins and D. F. Green, at dedication of Delaplane Memorial Laboratory, University of Rhode Island, Kingston, Rhode Island. From undated newspaper clipping in University of Rhode Island Library.

covery'' by Delaplane. Higgins himself, in a letter written to his son 41 yr after the event, recalled how he ''had hounded John [Delaplane] for weeks to test the drug'' but that he ''was always too busy'' (Higgins, 1987). Delaplane, on his return from Texas, had become Chairman of Pathology at RIAES. Higgins was agricultural extension poultryman and presumably had neither the drug nor the authority to initiate a trial in Delaplane's department. As he recalled it, he then hit upon a plan to get things moving. He needed, at that time, to come up with a project for a student who had been assigned to work with him. He says in his letter that he had the idea of having the student test SQ against coccidiosis under the direction of Delaplane and himself, and that he ''persuaded John to cooperate with me in setting up the trial.'' He goes on to describe the proposed ''very simple . . . and probably crude'' trial as consisting of 2 groups of chickens that would be inoculated with coccidial oocysts, with 1 group then being given SQ in the drinking water. In writing that personal letter, Higgins takes it as understood that the experiment was carried out, for he goes on to say that ''the results were astounding''—all untreated chickens died whereas all treated chickens survived and were free of infection. It is clear that a student assistant did indeed carry some responsibility for the conduct of the trial. The paper mount of a photographic projection slide in the archives of the University of Rhode Island, bears the following hand-written notations: ''First coccidiosis work with sulfaquinoxaline'' and ''Chas Chong Chinese student with T C Higgins.'' Despite its historical significance, this first trial is not mentioned in the initial publication; nor, indeed, has the present writer been able to find any public documentation of it. It may have provided the impulse for a more complex and ''publishable'' trial and have been considered unworthy of or unnecessary for inclusion in the paper that announced the breakthrough discovery.

The Higgins letter does not say when the first trial was made. Nor does the Delaplane report of 1947 give dates for the experiments described therein. In that Delaplane report, however, a passing reference is made to the weather in Rhode Island in the summer of 1946, when at least some of the work was being carried out. Further evidence as to when the essential discovery was made is to be found in the projection slide mentioned above. The image (Fig. 8) shows the severely damaged cecum of a chicken infected with *E. tenella* lying next to the cecum of a chicken successfully protected by administration of SQ. The inscription, probably made by Higgins, includes ''Spring 1946'' as well as the words ''First coccidiosis work with sulfaquinoxaline.'' The slide thus clearly refers to the very first trial, and indicates that the discovery was made in 1946, the year in which the patent was issued. That conclusion is in accord with an unsigned article in a Merck magazine (Anonymous, 1949).

Apparently Delaplane recalled the discovery somewhat differently. An obituary article on Delaplane appeared in a newspaper within days of his death, and its tone makes it likely that he had himself been the direct or indirect source of the information in it. (The article, entitled ''Dr. Delaplane, 50, Dead in Texas'' was unsigned. A photocopy is in the archives of the University of Rhode Island, but it does not reveal the date of the newspaper or the place of publication. It was probably published in Rhode Island in 1956.) The writer noted that in 1941, Delaplane found that sulfathiazole would prevent infectious Coryza in poultry, and added that he ''had been screening sulfa drugs for the control of the respiratory form of fowl cholera'' when 1 of them, SQ, ''turned out to be highly effective.'' The writer of the article further added ''On impulse, he suggested to a foreign trainee working in the department that he feed the drug to some birds infected with coccidiosis. The results were startling and further testing proved the effectiveness of treatment. Out of these tests came the principle of low-level, continuous medication as a practical means of poultry disease control.'' The 2 accounts, given many years after the event, are at variance in regard to the impetus driving the crucially important first experiment. We will probably never know the truth of this matter, or be able to applaud 1 party or another for historical inerrancy. Those who spend a lifetime in science sometimes find that modestly divergent perceptions may be driven further apart, quite unconsciously, by the frailty of memory.

The contribution made by Delaplane and his colleagues at RIAES was not confined to matters of therapeutic efficacy. Particularly important was their finding that SQ treatment did not interfere with development of immunity (at least in the case of *E. tenella*). They described the histopathological characteristics of a toxic reaction that seemed to be associated with SQ treatment under certain conditions (Delaplane and Milliff, 1948). From their various studies they concluded that SQ provided safe and effective control of coccidiosis in chickens when the drug

FIGURE 6. L. C. Grumbles. Photo by Bob Dooman.

was incorporated in feed and administered continuously throughout the growth of the birds. Strongly supporting that conclusion was a second efficacy paper published by the RIAES group (Grumbles et al., 1948). The first author of that important contribution was Leland C. Grumbles, DVM (Fig. 6) who had graduated from the veterinary college of Texas A&M in 1945, just as Delaplane was finishing his first stint at that institution. He then joined Delaplane at RIAES and participated in the SQ work before returning to Texas A&M for the remainder of his long academic career. The paper dealt with coccidiosis under field conditions, with only natural exposure to infection. Almost 20,000 chickens (many of them on litter on which other flocks had been raised) were fed a diet containing 0.0125% SQ, while at the same time more than 3,000 control birds (all on clean litter) were raised on unmedicated feed. The mortality rate was 1% in the treated birds and 17% in the controls. Outbreaks of such severity were by no means uncommon under the intensive production methods then being employed.

While these encouraging results were being obtained at RIAES, a program of developmental research was underway at Merck & Co., Inc. Parasitologist Ashton Cuckler was hired by Merck in 1947 to work on the malaria project, but soon focused his attention on the chemotherapy of coccidiosis, a field in which he was to become a notable leader (Campbell, 2001). In discussion with the present writer, he disclaimed any significant role in evaluating SQ as a coccidiostat, but that may be unduly modest. With the assistance of Ms. Christine Malanga, Cuckler demonstrated resistance in 1 strain of *Eimeria acervulina* and 2 strains of *E. tenella* after exposure to suboptimal dosages of SQ for 15 successive passages in chickens (Cuckler and Malanga, 1955). With his friend and colleague, poultry physiologist Walther Ott, he carried out a series of elaborate safety trials that showed that in-feed administration of SQ was very well tolerated by chickens, turkeys, and ducks (Cuckler and Ott, 1955). They also demonstrated that SQ was lethal to the sporozoite and schizont stages of the life cycle, but did not fully suppress their development (Cuckler and Ott, 1947, cited by Chapman, 2003). As pointed out by Chapman, that observation was helpful in explaining the acquisition of immunity by chickens in which clinical coccidiosis had been averted by SQ prophylaxis. Most of these studies were published after SQ was introduced to the marketplace. It is not known how much of the information was on hand when Merck sought approval from the Food and Drug Administration (FDA) to market SQ, but Cuckler's firsthand knowledge of the drug must have contributed to the success of the application. In January 1985 Cuckler told the present writer that he and Green had traveled by train together from Rahway, New Jersey, to Washington, D.C., to submit the application for FDA approval. When they left the FDA for their return journey on the same day, they had already been given informal approval of the application. Formal confirmation arrived by mail soon afterwards. One wonders if this is a speed record, and what feelings it might conjure up in those currently responsible for applying for regulatory approval of new drugs. Lest the timing seem truly incredible to a modern reader, it may be pointed out that in the 1940s there was no federal (FDA) requirement for evidence that a drug actually worked. Safety was all, and it was not until the 1962 passage of the Kefauver–Harris Amendment to the Food, Drug, and Cosmetic Act that proof of efficacy was demanded. According to Tishler (1988), Merck established that SQ was depleted from poultry tissues before the birds went to slaughter. It is worth remembering, however, that although ''additives'' in the food of meat animals have been regulated under the Act since its inception in 1938, it was not until the 1950s (and the creation of a Veterinary Medicine Branch within the FDA's Bureau of Medicine) that serious attention was given to ''tissue residues'' in meat. Thus the preparation of a ''New Drug Application'' was much less formidable in 1948 than it has since become.

In 1948 SQ was introduced as a commercial product. Feed manufacturers bought the drug from Merck and incorporated it into a feed premix for sale to poultry producers. When properly mixed with feed to give a final concentration of 0.0125%, it provided chickens with a daily intake of SQ sufficient to prevent outbreaks of coccidiosis. The drug also had the advantage of being usable therapeutically in drinking water (the compound itself is insoluble in water, but its sodium salt is soluble). Early reports of toxic reactions under field conditions were not easy to confirm or explain (Delaplane and Milliff, 1948; Davies and Kendall, 1953; Cuckler and Ott, 1955; Joyner and Davies, 1956; Spoo and Riviere, 2001). Because Merck sold SQ only to the manufacturers of commercial feeds and the producers of veterinary therapeutic products, the use of the drug was well

controlled and poultry producers found that the benefits of treatment far outweighed the risk of toxic reactions.

Because of the importance of sulfas as antibacterial agents in humans, their mode of action had been elucidated soon after they were introduced—before SQ had even been synthesized. Their essential role as inhibitors of folate synthesis had been discovered in 1940 and was confirmed and amplified by others in subsequent decades (Woods, 1940; Northey, 1948; Petri, 2006). It was natural that studies would be undertaken to see if the action against protozoa would be similar. As early as 1946 it was observed that anticoccidial efficacy was reversed when *p*-aminobenzoic acid (PABA) was fed to chickens that were receiving sulfonamide treatment (Horton-Smith and Boyland, 1946). From this and subsequent studies, it became clear that the antiprotozoal activity of sulfonamides, like their antibacterial activity, resides in the blockade of folate biosynthesis, and that this blockade results from the structural similarity of the drugs to PABA, 1 of the intermediates required for the synthesis of dihydrofolic acid (Adams, 2001). Competitive inhibition of folate biosynthesis in the coccidial parasite blocks the series of metabolic steps leading to conversion of uracil to thymine, thus depriving the parasite of the DNA needed for the production of proteins (Looker et al., 1986). The Therapeutic Index (safety margin) of the drug derives from the fact that mammals and birds ingest folic acid in their diet and are also the beneficiaries of the folic acid produced by enteric bacteria (Zhu et al., 2005). Chickens therefore can make DNA without having to synthesize folic acid intracellularly. To put these events in a broader historical context, it may be noted that SQ was brought to market at a time when the chemical composition of DNA was known but its physical structure was not, and at a time when it was unusual to understand the biochemical mechanism of a drug when first introduced.

The use of sulfonamides against bacterial infections in humans was limited by drug resistance in the pathogens and incomplete spectrum of efficacy against significant pathogen species. The same proved true for SQ in the control of coccidiosis in poultry (Geary et al., 1986; McDougald, 1986). In the second half of the 20th century, many other drugs were brought to market to control coccidiosis, especially in the increasingly large, sophisticated, and lucrative production of 'broiler'' chickens (McDougald, 1990). More than a dozen distinct chemical entities had been brought to market by 1984. Their trade names, characteristics, and introduction dates were tabulated by McDougald (1986), and their chemical structures were itemized by Chabala and Miller (1986). Under the ''selection pressure'' of dietary medication and intensive production, drug resistance invariably emerged; but a spirited competition among chemical and pharmaceutical companies resulted in a more-or-less steady supply of effective new drugs. The competition also resulted in a raising of the acceptable standard for efficacy, with a new candidate being expected to be effective against 7 or 8 species of avian coccidia. Synthetic chemicals were used more or less exclusively until an ionophorous metabolite of a filamentous bacterium was found active against coccidia (Shumard and Callendar, 1967) and by the 1980s antibiotic ionophores had come to dominate the market. Throughout these years of competition the use of SQ declined, and in the United States it had been relegated to use only in cattle, sheep, and rabbits by the end of the century (Lindsay and Blagburn, 2001).

From the middle of the century, vaccination was used to a limited degree (Shirley and Long, 1990), but the vaccines contained live coccidian oocysts, and under practical conditions it was difficult to formulate them and administer them in a way that would allow infection to reach immunogenic but not pathogenic proportion. By the end of the century, the introduction of new drugs had almost ceased, but nonliving ''subunit'' vaccines had been developed (Danforth and Augustine, 1990). They may prove economically and environmentally (as well as biologically) attractive, in which case they may come to replace the drugs that have been central to successful poultry production since the heyday of SQ.

THE LINKAGE OF PRIVATE AND PUBLIC LINEAGES

No one would suggest that the testing of SQ for efficacy in chickens was an imaginative scientific idea. Yet it was an important idea—important because of both the practical outcome and because of the blending of governmental and industrial interests. The trials conducted by Delaplane and his associates demonstrated not only the efficacy of SQ in preventing outbreaks of disease caused by *E. tenella* (Delaplane et al., 1947) but also the practical control of multiple coccidial species by means of feeding low levels of the drug in the diet (Grumbles et al., 1948). This is rightly lauded as an outstanding example of the research accomplishments of the experiment stations in general and of the Rhode Island station in particular (Chapman, 2003). It would be misleading, however, to characterize that achievement only in reference to academia or academic extensions such as governmental experiment stations. The case of SQ stands as an early example of successful collaboration between American industry and state governments as represented by agricultural experiment stations. More specifically, the discovery and development of this important agricultural tool can be said to be a joint effort on the part of Merck and RIAES. The customary recital of authorship and titles of papers published in the scientific literature tends to give a deficient picture of this partnership. The same can be said (with the imbalance being in the other direction) for the promotional literature issued in support of the marketing of the compound. The advertising of commercial compounds, however, recedes from historical view as the products themselves disappear from the shelves. The scientific literature enjoys the advantage of being more weighty and more enduring than the commercial ephemera. The collaboration between the parties might be described, to borrow a term from biology, as mutualism. The actual contribution of each of the 2 parties deserves some consideration.

The discovery of SQ as a coccidiostat can be seen as an outgrowth of the discovery that earlier sulfonamides were active against coccidia in chickens. The first sulfonamide report, in this context, was Levine's (1939) article on the efficacy of sulfanilamide against *E. tenella*. It had been preceded by awareness that sulfur was coccidiostatic (Herrick and Holmes, 1936), but this is not mentioned by Levine and was evidently not a factor in his decision to test sulfanilamide. He may have become aware of the efficacy of sulfur at about this time, because he described his own studies with sulfur at a meeting in 1941 (Chapman, 2003). Levine wrote that he was unaware of any ''well substantiated reports'' on the effect of sulfonamides on ''intestinal protozoa.'' He makes no reference to blood-borne

protozoa. Had his work been prompted by reports of the efficacy of sulfonamides on malarial parasites he probably would (and certainly should) have said so. Instead, he records that he was 1 of a number of scientists trying to extend the successful use of sulfas in human (bacterial) infections into utility in animal health. This is supported by the fact that Levine's publication was soon followed by reports on the efficacy of other sulfas (reviewed in Chapman, 2003). In any case, the RIAES studies do not seem to have arisen from an awareness of Levine's report on sulfanilamide. Delaplane does not cite Levine's work, but cites Seeger's informal 1945 report (Seeger, 1946) on the efficacy of sulfaguanidine against *E. tenella* and his 1946 report on the efficacy of sulfamethazine against the same species (Delaplane et al., 1947). It is possible that Delaplane's work was prompted, at least in part, by awareness of Seeger's work.

Alternatively, the testing of SQ as coccidiostat can be seen as an extension of earlier reports of the efficacy of sulfonamides against bacterial infections, not in humans, but in poultry. The earlier studies, however, had been distinctly unpromising (see for example, Wernicoff and Goldhaf, 1944). The exceptional promise of the slow-clearance SQ molecule had been shown by Delaplane himself. Before testing SQ against coccidia, he had found it prophylactically effective against *P. avicida* (agent of endemic fowl cholera) in chickens (Delaplane, 1945).

Yet again, the discovery can be seen as an extension of work in the 1930s that showed sulfonamides to have antimalarial activity. Both the *Plasmodium* spp. of malaria and the *Eimeria* spp. of coccidiosis are members of the Apicomplexa. Within that phylum, both pathogens belong to the class Conoidasida, although belonging to different orders, namely, the Haemosporidora and Eucoccidiorida, respectively (Roberts and Janovy, 2005). The 2 pathogens would be expected to share some chemotherapeutic sensitivities, and if a drug showed even marginal efficacy against malaria, it would be sensible to test it in coccidiosis. The activity of the sulfonamide molecule against *Plasmodium* was more than merely marginal. Between 1938 and 1945 sulfanilamide proved to be potent but species-specific against *P. knowlesi* in monkeys; and sulfadiazine and sulfapyridine were effective to a greater or lesser extent against various stages of *P. gallinaceum* in chickens and *P. vivax*, *P. falciparum*, *P. malariae* in humans. The results of those studies were summarized by Northey (1948). Delaplane and his colleagues make no reference to the reported tests of sulfas against malaria. This is not surprising in view of the comparative rarity and obscurity of such tests, accentuated by wartime constraints on publication. However, the Merck scientists, because of their own wartime research on malaria (and perhaps the permissible sharing of unpublished data between laboratories), were certainly aware of the efficacy of sulfonamides in malaria when they gave SQ to Delaplane.

The intellectual lineage of SQ at the Rhode Island field station is thus open to interpretation, but there is no doubt of the importance of the work, and no doubt that it was made possible by the synthesis at Merck of the molecule known as sulfaquinoxaline. Had the compound not been synthesized, it could not have been tested. Had it not been chemically novel, and thus patentable as new ''composition of matter,'' it probably would not have been developed as a commercial product. (Compounds such as sulfuric ether, DDT, and sulfanilamide were made years, or even centuries, before their medicinal value was realized, and they could be exploited commercially only through use-patents of limited geographical availability, or through molecular modification, specialized formulation, marketing expertise, and the like.)

In his publications, Delaplane acknowledged Merck as provider of the compound, and as provider of the funding that made his initial studies on SQ possible. What we may never know is whether Merck gave the drug (and the funding) to Delaplane for the express purpose of having it tested against coccidia. Both Green and Delaplane were fully qualified to arrive independently at the conclusion that SQ should be tested against coccidia in chickens. In giving this particular new sulfonamide to Delaplane, Green clearly intended that it be tested in chickens; Delaplane, after all, was a poultry specialist and even had sulfa-drug experience (apparently finding sulfamerazine and sulfathiazole active but not useful against the *Pasteurella* of fowl cholera; Delaplane, 1945). Indeed, Delaplane specifically acknowledged that SQ had been called to his attention ''through the courtesy of Merck and Company . . . as having possible use in poultry'' (Delaplane, 1945). Green was very much attuned to research on sulfa drugs and, as mentioned, had studied the pharmacokinetics of sulfanilamide as early as 1938. It would be natural for him to suggest a therapeutic target for Delaplane's studies on the new compound, and it would be equally natural for him to propose a target of importance in poultry husbandry (why else offer the drug?). The target, because what he was offering was a new sulfa drug, would surely have been a bacterium such as *Pasteurella avicida*, or a coccidial pathogen such as *E. tenella*, or both. Delaplane and his colleagues in fact tested the new drug against both.

In a Memorandum of Agreement between Merck and RIAES, dated 27 November 1946 (Anonymous, 1946), Merck pledged a grant of $5,000 to RIAES ''for the purpose of developing knowledge on the therapeutic activities of Sulfaquinoxaline in controlling diseases of poultry.'' Specific diseases were not mentioned. The research was to be planned ''in consultation with Dr. D.F. Green of the Veterinary Medical Department of Merck.'' The date of the Memorandum is curious because, as mentioned, there is some evidence that the first work with SQ in coccidiosis was done in the spring or summer of 1946. Delaplane had been hired by RIAES (for the second time) as of 1 January 1946. He would have brought from Texas A&M his unique knowledge of SQ's antibacterial efficacy in poultry, and perhaps his sample of the drug. The November 1946 memorandum may thus have been a regularization and extension of an ongoing project. Writing informally 41 yr later, Higgins, as mentioned above, recalled the first trial as having been done in the spring of 1946, after he had ''hounded'' Delaplane for weeks to get him to test SQ in coccidiosis. The collaboration between Merck and RIAES seems to have been mutually satisfactory, as evidenced by its continuation in subsequent years. A further agreement between the 2 parties was signed in May 1948; RIAES director Mason H. Campbell wrote to Green expressing his ''appreciation to you and your Company for the help and interest which you have shown in our research program'' (Anonymous, 1948).

Delaplane did not include Green as a co-author, nor did his acknowledgments indicate whether he was indebted to Green for any scientific idea. In introducing their first report on SQ

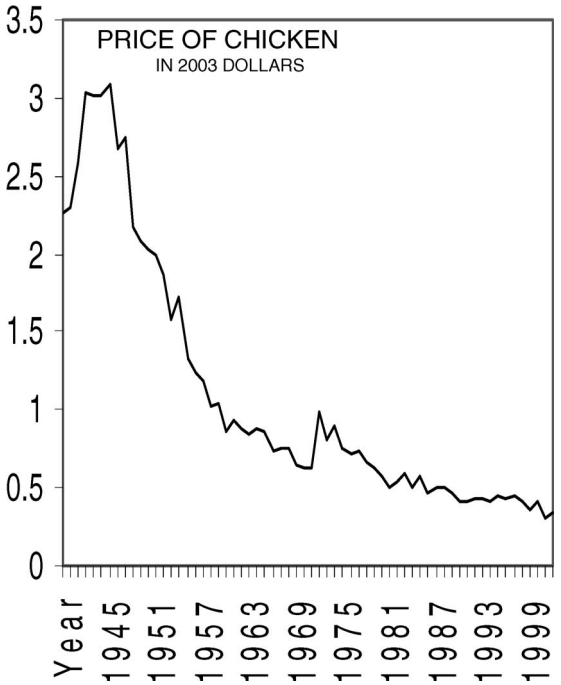


FIGURE 7. Decline in price of poultry meat following introduction of coccidiostats in 1948. Annual average of monthly live-weight price of chicken per pound received by farmers (expressed in 2003 dollars calculated from data of the Federal Reserve Bank of Minneapolis, Minnesota, 2006). The decline reflects an increase in the use of intensive production methods, which were made practicable by the introduction of the drugs. No attempt is made to disentangle the causative contributions of the methods and the drugs.

and coccidiosis, authors Delaplane, Batchelder, and Higgins pointed out that SQ was effective against *bacterial* respiratory infections of poultry at levels lower than those required for other sulfas (Delaplane et al., 1947). Then, turning to the subject of coccidiosis, they added that ''it was logical to expect that sulfaquinoxaline would possess a similar activity at the low levels mentioned,'' referring to the low levels of SQ that Delaplane had used against the bacterium *P. avicida*. Considering that the protozoon, like the bacterium, was already known to be susceptible to sulfonamides, and that the prolonged plasma levels of SQ could be expected to permit the use of low dosages, the logic of the idea would be evident to anyone familiar with the situation, including David Green. Any new sulfa, especially 1 known to have slow renal clearance, should be tested against coccidia (and bacteria) in poultry. (The utility of the sulfas previously tested in poultry had been limited by the need to administer intermittent bouts of treatment at maximal dosage.) There seems to be nothing in the record to suggest that Delaplane sought new sulfas from Merck. Indeed, his first article makes it clear that the initial contact was made by a Merck representative (unnamed by Delaplane). We know from Delaplane's words that the representative (Green) conveyed not only a material sample, but also knowledge that the material had particular promise for use in poultry. SQ held that promise by virtue of being a sulfonamide with slow renal clearance and with proven efficacy against a protozoan pathogen in chickens and ducks. It seems likely that Green would have presented that rationale to Delaplane when seeking his collaboration. No record has been found to support that idea, nor would it find support in the later personal recollections of Delaplane and Higgins (above). The record does indicate that Merck provided Delaplane with data on the correlation between dietary concentrations of SQ and subsequent concentrations of the drug in the blood of treated chickens (Delaplane, 1945). Depending on the details of the actual exchange between the 2 parties, it might or might not have been appropriate for Delaplane to include Green among the authors of the article announcing the efficacy of SQ against coccidia. There was a hint of disappointment on this score in a 1988 communication from Green to the present writer, in which Green surmised that his absence from the list of authors reflected a then-common attitude of academic scientists toward industrial research (D. F. Green, unpubl. obs.).

The student who worked with Higgins was not accorded authorship; nor was he even mentioned in published accounts of the work. Any surprise that this might evoke today may be attributed to a shift in attitude toward authorship over the past 60 yr. We have, however, no way of knowing how much Mr. Chong actually contributed. In the personal letter that Higgins wrote long after the event, he made it clear that he and Delaplane did not share with their student their own sense that the first trial of SQ in coccidiosis had yielded an important discovery. It would seem that Chong was treated as technician rather than as junior collaborator. He may indeed have been hired as a student laborer, but the tone of Higgins' letter suggests that some degree of research training would have been an objective, and this is supported by reference to a ''foreign trainee'' in the obituary article on Delaplane (above). The remaining author of the key 1947 article was veterinarian R. M. Batchelder. The record appears to be silent on his contribution to the discovery of the efficacy of SQ in the prevention of poultry coccidiosis.

Eight months before he died at 82 yr of age, Tishler reminisced about the invention of SQ (Tishler, 1988). He and Weijlard had made the original synthesis of SQ as early as 1942 (Anonymous, 1949) and more efficient industrial syntheses were devised soon afterward (Stevens et al., 1946), so Tishler was remembering events of more than 40 yr in the past. He recalled that following the abandonment of SQ as an antimalarial, he and Green had independently become interested in looking for other uses for the compound. Tishler's group of chemists provided the compound to Green, who then ''found that it was active as a coccidiostat.'' Apparently Tishler (in old age, and perhaps all along) regarded the SQ research at Texas A&M and RIAES as a contracted service. In that view, Merck had simply given grant monies to outside workers to enable them to find another kind of biological activity and then to evaluate practical prophylactic and therapeutic regimens for it. The company was simply outsourcing work that it did not (yet) have the capacity to do in-house. The success of the venture was valuable to both sides; and evidently each side viewed the accomplishment through the lens of its own contribution.

REFLECTIONS AND CONCLUSIONS

Following the commercial introduction of SQ in 1948, the price of broiler chickens in the United States declined sharply, and continued to decline over many years, during which SQ was succeeded by other coccidiostats (Fig. 7). Over the same time period, the raising of chickens became more intensive (Na-

Convenient 8.3 oz. "Pocket-Bottle" size medicates 50 gallons of water without the fuss and bother of measuring!

NEW 19.2% S.Q.®

Also available HANDY 1 QT. SIZE
Medicates 200 gallons of water.

S.Q. is the only coccidiostat effective against *all* 7 of the most damaging species of coccidia in chickens *and* turkeys. This extra protection against "coxy" losses is another example of THE MERCK MARGIN OF SURETY!

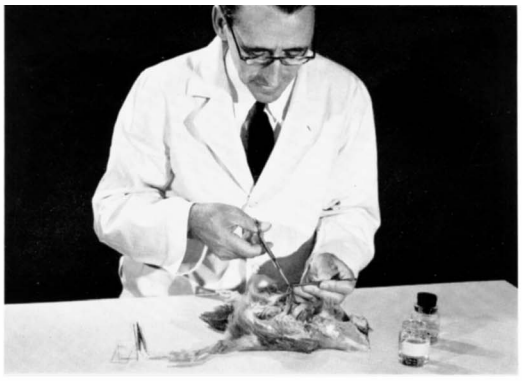
And...S.Q. controls death losses – Reduces severity of Fowl Cholera outbreaks.

S.Q. 19.2%, at recommended levels, is completely soluble in all types of water—will not clog automatic drinking fountains.

Be sure to ask for 19.2% S.Q. Solution wherever Poultry Health Products with THE MERCK MARGIN OF SURETY are sold, or write to Merck & Co., Inc., Chemical Division, Rahway, New Jersey, for information.

MERCK WITH THE MERCK MARGIN OF SURETY
POULTRY HEALTH PRODUCTS

8



Building a Poultry Practice

Veterinarians can develop, easily and rapidly, a substantial practice among poultry raisers. By investing a little time in diagnostic work, they can educate growers to the value of professional supervision of flock health.

Your position with the poultryman is strengthened when, through prompt application of modern drugs such as SULFAQUINOXALINE, you guard him against severe economic loss. You can prescribe SQ with confidence for the *prevention* and *control* of coccidiosis outbreaks, because it is effective against all economically significant species of coccidia that attack chickens and turkeys.

WRITE FOR LITERATURE

The following publications are available on request:

Sulfaquinoxaline Veterinary—detailed information on the use of SULFAQUINOXALINE in the *prevention* and *control* of coccidiosis in poultry and rabbits.

Annotated Bibliography on Sulfaquinoxaline—summaries of scientific publications on the chemistry, pharmacology, and clinical value of this drug.

Annotated Bibliography on Coccidiosis—A digest of the recent literature on this disease in all species of domestic animals.

SULFAQUINOXALINE

Research and Production for Better Poultry and Animal Health

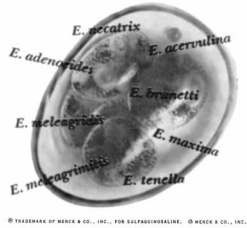
MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY

9

Journal of the American Veterinary Medical Association—December, 1953
North American Veterinarian—November, 1953

When other drugs fail against coxy breaks...ask for feeds containing

SQ



THE ONLY COCCIDIOSTAT EFFECTIVE AGAINST ALL IMPORTANT COCCIDIAL SPECIES

No other drug can match the effectiveness, safety, and economy of S.Q. in treating outbreaks of coccidiosis in chicks, poults, pullets—*and* birds in production. Unlike other drugs, S.Q. works best during the all-important 72- to 96-hour period after infection, when coccidia are most vulnerable to medication.

S.Q.—used promptly at therapeutic levels—will check coxy outbreaks . . . cut losses by holding mortality and stunting to a minimum . . . keep flocks on feed until the outbreak is under control.
Merck Chemical Division, Merck & Co., Inc., Rahway, N. J.

S.Q.® with THE MERCK MARGIN OF SURETY

10

SCIENCE REPORT

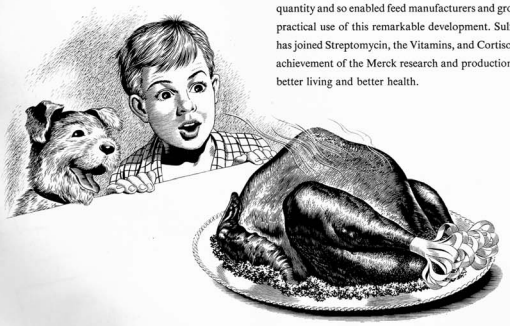
Science—and Thanksgiving dinner

Research helps bring more turkeys to American tables

TURKEY for Thanksgiving dinner is an American birthright. But the quality and number of birds that reach dinner tables depends on protection provided against the costly poultry destroyer—coccidiosis.

Today, Sulfaquinoxaline—a product of Merck research—has brought poultry growers simple, low-cost ways to *prevent* and *control* outbreaks of coccidiosis in chickens as well as turkeys. Countless millions of birds now have been successfully treated with this new poultry life-saver.

Six years of research were required to perfect Sulfaquinoxaline. Then, Merck solved the complicated problem of producing it in quantity and so enabled feed manufacturers and growers to make practical use of this remarkable development. Sulfaquinoxaline has joined Streptomycin, the Vitamins, and Cortisone as another achievement of the Merck research and production program for better living and better health.



Research and Production for the Nation's Health

MERCK & CO., INC.
Manufacturing Chemists
RAHWAY, NEW JERSEY
In Canada: MERCK & CO. Limited — Montreal

11

via, 2000) and therefore more vulnerable to the ravages of infectious disease. It is unlikely that the raising of chickens in densely populated ''broiler houses'' would have been successful if coccidiosis had not been controlled. In this context Navia (2000) states that ''sulfaquinoxaline enabled a revolution in the practice of poultry production.'' It was a revolution that would spread throughout much of the world. It was a revolution that was by no means inevitable, for the drugs were expensive and their widespread use in a veterinary context depended on postwar reductions in chemical costs (McDougald, 1982). On the other hand, once the economic problems were solved there was no going back. Chapman (2003) cites a statement made by the veterinary parasitologist Philip Hawkins as early as 1949: ''In sulfaquinoxaline, we now have the most satisfactory sulfonamide for the prevention of coccidiosis in poultry. Whether we like the idea of medicated feed or not, we have no choice in the matter; it is here to stay. Although we may object to the adulteration of feedstuffs with medicine, we must remember that our unnatural methods of livestock and poultry production have forced us to this extreme.'' Godley and Williams (2007) have recently provided a detailed comparison of the industrialization of poultry production in Britain and the United States.

In recent years, further doubts have been raised about the ethical and ecological rectitude of intensive livestock production and its associated chemical dependency. Use of the same or similar antimicrobial agents in the treatment of human disease and in the enhancement of livestock production has been much criticized. The associated hazard has been stated by Drews (2000b), who postulated that the use of sulfonamides in coccidiosis control may have accelerated the emergence of drug resistance in certain strains of bacteria in humans. Important as these issues are, they are beyond the scope of this historical examination. In the middle of the 20th century those engaged in the development of SQ were caught up in the euphoria of doing well (scientifically, medically, economically) while at the same time doing good (improving agricultural productivity).

Drews (2000a) has noted that structural derivatization of the sulfonamide molecule led to the development of new diuretic, antidiabetic, and antihypertensive medicines for human use. Nevertheless, the triumph of SQ in animal husbandry is of importance in its own right. Navia (2000) refers to the benefits that SQ conferred on humankind in the form of plentiful and inexpensive dietary protein, and suggests that these benefits may even have exceeded the benefits brought by the sulfa drugs through successful treatment of bacterial diseases.

It was the toxicity of the sulfonamides in humans, together with the emergence of resistant pathogens, that limited the utility of that chemical class in controlling human diseases—and it was the toxicity of a quinoxaline derivative in monkeys that led to a new era in the production of poultry meat. The importance of the sulfas in human medicine gradually faded from public awareness as their clinical deployment diminished and they were superseded by antibiotic drugs. The present writer was among the many children whose lives were almost certainly saved by the efficacy of the sulfonamides against bacterial infections. Fortunately, there are written accounts, popular as well as scholarly, in which the story of the sulfa drugs in human medicine is told (see, for example, Silverman, 1942; Ryan, 1992; Sneader, 2005; Hagar, 2006). The history of SQ in chickens, in contrast, has been neglected (Campbell, 2001).

Considering the speed with which the Food and Drug Administration (FDA) approved the use of SQ in poultry, there is some irony in the fact that the FDA had been strengthened by a great scandal in which a sulfonamide was involved. In 1937 about 100 patients, mostly children, died after ingesting a commercial preparation of sulfanilamide (Hager, 2006). But it was the excipient diethylene glycol, not the drug, that was lethal. Spurred by the tragedy, the Food and Drug Act of 1906 was replaced by the much more demanding Federal Food, Drug and Cosmetic Act of 1938. A decade later the safely data required for a veterinary drug were apparently so limited in scope that they could be evaluated in only a few hours. Still, a new era in the regulatory control of medicines had begun.

As a proprietary product (Figs. 8–11) SQ was a commercial success and a trendsetter, to be followed by many other coccidiostats over the succeeding decades. For better and for worse, it helped turn poultry raising into a poultry industry. It was added to chicken feed but, commercially and metaphorically speaking, it was not mere chicken feed. The scientific literature would lead one to believe that the phenomenon that was SQ was the achievement of researchers at the Rhode Island Agricultural Experiment Station. To read the literature of commerce is to conclude that the credit belongs instead to researchers at Merck. For once, the truth does not lie somewhere in between. It is to be found, rather, by adding the 2 together.

ACKNOWLEDGMENTS

For locating and providing access to relevant documents, the author is particularly indebted to Emily Brown of the Archives and Special Collections Department, University of Rhode Island Library, Kingston, Rhode Island; to Joseph Ciccone of the archives of Merck; and to Catherine Ryan, of the Drew University Library. The author is also grateful to Dr. Michael A. Rice, University of Rhode Island; Susan Vath of Merck Research Laboratories; Dr. Jeffrey L. Sturchio, Merck; and Dr. Thomas Craig, Texas A&M University, for valuable assistance.

LITERATURE CITED

ADAMS, H. R. 2001. Veterinary pharmacology and therapeutics. Blackwell, Ames, Iowa, 1,201 p.

ANONYMOUS. 1946. Document in the Archives and Special Collections Department of the University of Rhode Island Library, Kingston, Rhode Island. (Cited by permission.)

———. 1948. Document in the Archives and Special Collections Department of the University of Rhode Island Library, Kingston, Rhode Island. (Cited by permission.)

———. 1949. Chick-saver: New Merck sulfa-drug means healthier chickens, more eggs. Merck Review 10(1).

———. 1952a. Protecting poultry profits. Merck Review 14(7).

———. 1952b. Coccidiosis—Ex poultry enemy number one. American Egg and Poultry Review (June): 30–33.

BLACK, R. H., C. J. CANFIELD, D. F. CLYDE, AND W. PETERS. 1981. General. *In* Chemotherapy of malaria, 2nd ed., L. J. Bruce-Chwatt (ed.). World Health Organization, Geneva, Switzerland, 261 p.

←

FIGURES 8–11. Advertisements from the 1950s for Merck's first poultry product. Parasitologist Dr. A. C. Cuckler appears in the photograph in Figure 9. Archives, Merck & Co., Inc.

BRYSKIER, A. 2005. Historical review of antibacterial chemotherapy. *In* Antimicrobial agents, A. Bryskier (ed.). ASM Press, Washington, D.C., pp. 1–12.

CAMPBELL, W. C. 2001. In memoriam: Ashton C. Cuckler. Journal of Parasitology **87:** 466–467.

———. 1986. Historical introduction. *In* Chemotherapy of parasitic diseases, W. C. Campbell and R. S. Rew (eds.). Plenum Press, New York, p. 3–21.

CHABALA, J. C., AND M. W. MILLER. 1986. Chemistry of antiprotozoal agents. *In* Chemotherapy of parasitic diseases, W. C. Campbell and R. S. Rew (eds.). Plenum Press, New York, p. 25–85.

CHAPMAN, H. D. 2003. Origins of coccidiosis research in the fowl—the first fifty years. Avian Diseases **47:** 1–20.

COATNEY, G. R. 1963. Pitfalls in a discovery: the chronicle of chloroquine. American Journal of Tropical Medicine and Hygiene **12:** 121–128.

CRAIG, D. W. 1952. Letter to Stephen Urner, American Egg and Poultry Review, 92 Warren St., New York, New York. Archives, Merck & Co., Inc.

CUCKLER, A. C., AND C. M. MALANGA. 1955. Studies on drug resistance in coccidian. Journal of Parasitology **41:** 302–311.

———, AND W. H. OTT. 1947. The effect of sulfaquinoxaline on the development stages of *Eimeria tenella*. Journal of Parasitology **33:** 10–11.

———, AND ———. 1955. Tolerance studies on sulfaquinoxaline in poultry. Poultry Science **34:** 867–879.

DANFORTH, H. D., AND P. C. AUGUSTINE. 1990. Control of coccidiosis: Prospects for subunit vaccines. *In* Coccidiosis of man and domestic animals, P. L. Long (ed.). CRC Press, Boca Raton, Florida, p. 343–348.

DAVIES, S. F. M., AND S. B. KENDALL. 1953. Toxicity of suphaquinoxaline (2-sulphanilamidoquinoxaline) for chickens. Veterinary Record **65:** 85–88.

DELAPLANE, J. P. 1945. Sulfaquinoxaline in preventing upper respiratory infection of chickens inoculated with infective field material containing *Pasteruella avicida*. American Journal of Veterinary Research **6:** 207–208.

———, R. M. BATCHELDER, AND T. C. HIGGINS. 1947. Sulfaquinoxaline in the prevention of *Eimeria tenella* infections in chickens. North American Veterinarian **28:** 19–24.

———, AND J. H. MILLIFF. 1948. The gross and micropathology of sulfaquinoxaline poisoning in chickens. American Journal of Veterinary Research **9:** 92–96.

DREWS, J. 2000a. Drug discovery: A historical perspective. Science **287:** 1960–1964.

———. 2000b. Response [to Navia, 2000]. Science **288:** 2133.

GEARY, T. G., S. A. EDGAR, AND J. B. JENSEN. 1986. Drug resistance in protozoa. *In:* Chemotherapy of parasitic diseases, W. C. Campbell and R. S. Rew (eds.). Plenum Press, New York, New York, p. 209–236.

GODLEY, A., AND B. WILLIAMS. 2007. The chicken, the factory farm and the supermarket: The emergence of the modern poultry industry in Britain. Working Paper No. 50. Working Paper Series, University of Reading. http:// www.rdg.ac.uk/business/Research/bus-discussion-papers.asp

GREEN, D. F. 1947. Draft statement alerting poultry industry to Merck's investigation of sulfaquinoxaline as a potential coccidiostat. Archives, Merck & Co., Inc. (Cited by permission).

———, J. B. ALLISON, AND M. L. MORRIS. 1938. The renal excretion of sulfanilamide in dogs. Journal of Pharmacological and Experimental Therapeutics **64:** 263–270.

GRUMBLES, L. C., J. P. DELAPLANE, AND T. C. HIGGINS. 1948. Continuous feeding of low concentrations of sulfaquinoxaline for the control of coccidiosis in poultry. Poultry Science **27:** 605–608.

HAGER, T. 2006. The demon under the microscope. Harmony Books, New York, New York, 340 p.

HERRICK, C. A., AND C. E. HOLMES. 1936. Effects of sulphur on coccidiosis in chickens. Veterinary Medicine **31:** 390–391.

HIGGINS, T. C. 1987. Letter to Lawrence Higgins. Archives and Special Collections Department of the University of Rhode Island Library, Kingston, Rhode Island. (Cited by permission).

HORTON-SMITH, C., AND E. BOYLAND. 1946. Sulphonamides in the treatment of caecal coccidiosis of chickens. British Journal of Pharmacology **1:** 139–152. (Cited in Looker et al., 1986.)

JOYNER, L. P., AND S. F. M. DAVIES. 1957. Sulfaquinoxaline poisoning in chickens. Journal of Comparative Pathology **66:** 39–48.

LEVINE, P. P. 1939. The effect of sulfanilamide on the course of experimental avian coccidiosis. Cornell Veterinarian **29:** 309–320.

LINDSAY, D. S., AND B. L. BLAGBURN. 2001. Antiprotozoal drugs. *In* Veterinary pharmacology and therapeutics, H. R. Adams (ed.). Blackwell, Ames, Iowa, p. 992–1016.

LOOKER, D. L., J. J. MARR, AND R. L STOTISH. 1986. Modes of action of antiprotozoal agents. *In* Chemotherapy of parasitic diseases, W. C. Campbell and R. S. Rew (eds.). Plenum Press, New York, New York, p. 193–207.

MCDOUGALD, L. R. 1982. Chemotherapy of coccidiosis. *In* The biology of the coccidian, P. L. Long (ed.). University Park Press, Baltimore, Maryland, p. 375–428.

———. 1986. Coccidian and related infections. *In* Chemotherapy of parasitic diseases, W. C. Campbell and R. S. Rew (eds.). Plenum Press, New York, New York, p. 159–170.

———. 1990. Coccidian and related parasites. *In* Coccidiosis of man and domestic animals, P. L. Long (ed.). CRC Press, Boca Raton, Florida, p. 307–320.

MUSHETT, C. W., AND A. O. SEELER. 1947. Hypothrombinemia resulting from the administration of sulfaquinoxaline. Journal of Pharmacology and Experimental Therapeutics **91:** 84–91.

NAVIA, M. A. 2000. A chicken in every pot, thanks to sulfonamide drugs. Science **288:** 2132–2133.

NORTHEY, E. H. 1948. The sulfonamides and allied compounds. Reinhold, New York, New York, p. 660.

PETRI, W. A. 2006. Sulfonamides, trimethoprim–sulfamethoxazole, quinolines, and agents for urinary tract infection. *In* Goodman and Gilman's The pharmacological basis of therapeutics, 11th ed., L. L. Brunton, J. S. Lazlo, and K. L. Parker (eds.). McGraw-Hill, New York, New York, p. 1111–1126.

ROBERTS, L. S., AND J. JANOVY, JR. 2005. Foundations of parasitology. McGraw Hill, Boston, Massachusetts, 670 p.

RYAN, F. 1992. The forgotten plague. Little, Brown, Boston, Massachusetts, p. 460.

SARETT, L. H., AND C. ROCHE. 1995. Max Tishler. Biographical memoirs. National Academy of Sciences, National Academies Press **66:** 352–366.

SAWTELLE, S. 1971. R.I. man's research assured ''chicken in every pot.'' Providence Evening Bulletin, 16 November 1971, p. 28.

SCUDI, J. V., AND R. H. SILBER. 1944. Urinary excretion products of sulfaquinoxaline. Journal of Biological Chemistry **156:** 343–348.

SEEGER, K. C. 1946. Sulfamethazine in the treatment of induced and natural *Eimeria tenella* infections. Poultry Science **25:** 411.

SEELER, A. O., C. W. MUSHETT, O. GRAESSLE, AND R. H. SILBER. 1944. Pharmacological studies on sulfaquinoxaline. Journal of Pharmacology, and Therapeutics **82:** 357–377.

SHIRLEY, M., AND P. L. LONG. 1990. Control of coccidiosis in chickens: Immunization with live vaccines. *In* Coccidiosis of man and domestic animals, P. L. Long (ed.). CRC Press, Boca Raton, Florida, p. 321–341.

SHUMARD, R. F., AND M. E. CALLENDER. 1967. Monensin, a new biologically active compound. VI. Anticoccidial activity. Antimicrobial Agents and Chemotherapy (Bethesda) **7:** 369–377.

SMITH, D. G., AND H. J. ROBINSON. 1944. Some chemotherapeutic properties of sulfaquinoxaline. Proceedings of the Society for Experimental Biology and Medicine **57:** 292–295.

SNEADER, W. 2005. Drug discovery: A history. Wiley, Chichester, England, p. 468.

SPOO, J. W., AND J. E. RIVIERE. 2001. Sulfonamides. *In* Veterinary pharmacology and therapeutics, H. R. Adams (ed.). Blackwell, Ames, Iowa, p. 796–817.

STEVENS, J. R., K. PFISTER, AND F. J. WOLF. 1946. Substituted sulfaquinoxalines. I. The isolation and synthesis of 3-hydroxy-2-sulfanilamidoquinoxaline and related quinolines. Journal of Biological Chemistry **68:** 1035–1039.

TISHLER, M. 1988. Interview of Max Tishler conducted by Leon Gortler, July 13, 1988. Archives, Merck & Co., Inc.

WEIJLARD, J., AND M. TISHLER. 1946 2-sulphanilamido-quinoxaline. Patent 2,404,199. United States Patent Office, Washington, D.C., 16 July 1946.

———, ———, AND A. E. ERICKSON. 1944. Sulfaquinoxaline and some related compounds. Journal of the American Chemical Society **66:** 1957–1959.

WERNICOFF, N. E., AND T. M. GOLDHAF. 1944. The field use of sulfathiazole in some diseases of poultry. Cornell Veterinarian **34:** 199–213.

WOODS, D. O. 1940. The relationship of p-aminobenzoic acid to the mechanism of action of sulfanilamide. British Journal of Experimental Pathology **21:** 74–90.

ZHU, T., Z. PAN, N. DOMAGALSKI, R. KOEPSEL, M. M. ATAAI, AND M. M. DOMACH. 2005. Engineering of *Bacillus subtilis* for enhanced total synthesis of folic acid. Applied and Environmental Microbiology **71:** 7122–7129.

J. Parasitol., 94(4), 2008, p. 945

Book Review:

Outwitting College Professors: A Practical Guide to Secrets of the System, John Janovy, Jr. Pearson Custom Publishing, Boston, Massachusetts. 149 p. ISBN 0536418500.

Over the years, I have enjoyed reading John Janovy's popular books. *Outwitting College Professors* was no different! This book was written for beginning students. It is a primer designed to serve as a guide for students through the ''minefield'' created by professors and administrators in our system of higher education. But it is more than that, too. As I read it, all of my ''long ago'' experiences in the classrooms of Colorado College emerged. For me, this means that the book rates as a good read for the new/old professor as well as the new/old student.

There are 11 chapters and an appendix (the latter entitled ''How to Be a Good College Student If You Really Want To''). In the first chapter, John explains why one needs to outwit the ''prof'' and then how to do it. In the second chapter, he attempts to distinguish between what he calls a normal prof and those he calls ''terminally insecure, or the feminist female/lecherous male, or the really incompetent prof with no interpersonal skills (and burnt out cases).'' He then provides a checklist, which he describes as his ''Outwittability Profile,'' that is recommended to the new student as a way to categorize the prof and create what is called an ''outwitting plan.'' Since most profs are normal, the plan should work. For the abnormal types, he has written a special chapter called ''Advanced Outwitting.'' I think the advice he gives in the last paragraph of this chapter is about as good as you can get when it comes to advanced outwitting. He says, ''Academia serves as a home for some really dangerous types, profs that can have a major negative impact on your entire college career and perhaps even your chances of a good job afterwards. Learn to recognize these types and avoid them if possible. Academia also provides a haven for some truly wonderful profs who are happy, intelligent, and excited about their jobs and interactions with students. Learn to recognize these kinds, too, and cultivate them.''

Throughout the book, John describes techniques by which the student can present herself/himself to the prof as a way of playing by the unwritten rules of learning in the academy. These rules refer to the dress code, how to verbally interact with the prof without making a fool of yourself, what to expect from tests, and how, and how not, to complete a good project and write a good paper. He even has a chapter dealing with letters of recommendation and how to be sure that the student has a good idea about what to expect in the given prof's letter.

Whether you are a ''wet behind the ears'' freshman, a beginning graduate student, a junior professor, or a seasoned teaching veteran, this is an interesting read, make no mistake about it. Considering the combination of John's enthusiasm for teaching and his forty years of experience, I can see why he would/could write such a book. I heartily recommend it.

Gerald W. Esch, Department of Biology, Wake Forest University, Winston-Salem, North Carolina 27109.