PITFALLS IN A DISCOVERY: THE CHRONICLE OF CHLOROQUINE*

G. ROBERT COATNEY

Laboratory of Parasite Chemotherapy, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

It is traditional in this Society that the President deliver an address at the annual banquet. In line with that tradition, I have chosen to discuss one facet of that patriarch of human disease—malaria. The facet I have selected is the chronicle of the antimalarial drug, chloroquine—a true story tinged with an element midway between romance and intrigue. In view of the recent public interest in drugs for human consumption, this story is timely; it has not been recounted before.

Practically all of the world's regular supply of quinine was denied to the Allies following the Japanese invasion of Pearl Harbor in December 1941. This was a most serious loss for it was apparent that a long war lay ahead and that much of it would have to be fought in highly malarious areas.

This country moved immediately to meet the emergency. The War Production Board (on April 4, 1942) issued Conservation Order M-131 which took quinine off the market and restricted its use almost completely to the treatment of malaria. At the same time, an appeal was made to those who held supplies of the alkaloid to deposit them with the War Production Board. The response was excellent and a large supply of cinchona alkaloids was acquired for purely military needs.

The National Research Council was apprised of the fact that a usable mixture of the total alkaloids of quinine, known as totaquine, could be prepared. After an investigation, that body recommended the use of totaquine as a quinine substitute.

In another move, the War Production Board undertook to stimulate production of Atabrine† (quinacrine), the only synthetic antimalarial of promise at the time. As a consequence of that action, there were always sufficient supplies for military use.

Concurrently, the National Research Council stimulated extensive research on the pharmacologic aspects and clinical use of Atabrine. This culminated in the highly successful loading dose technique of J. A. Shannon and the Recommendation of Confidence in the drug.

The Board of Economic Warfare expedited shipment of cinchona bark from South America and attempts were made to encourage the planting of cinchona in Costa Rica, Peru, Ecuador and several other places.

Later events showed that synthetic drugs were equal to the task but at the time the effort to build up supplies of quinine, to stimulate the use of totaquine, and to develop new areas of cinchona culture seemed most important.

The most significant step for this country was the organization of an extensive program of research in antimalarial drugs. A group at the National Institute of Health under the leadership of the late Lyndon Small had initiated a program on synthesis of new antimalarial drugs as early as 1939. To them goes the credit for the first coordinated American approach to the problem of synthetic antimalarial drugs. On that foundation, the Committee on Medical Research of the Office of Scientific Research and Development, National Research Council, later organized the war program. That effort involved scientists from the universities and industry, private individuals, the U. S. Army, the Navy and the Public Health Service, plus appropriate liaison with Great Britain and Australia. In the beginning, the program was coordinated by a group of conferences, subcommittees, and, from November 1943, by the Board for the Coordination of Malarial Studies[1] (hereafter referred to as the Board) using the facilities and help of the National Research Council.

The overall search for new antimalarial agents involved the screening of some 16,000 compounds,

* Presidential address before the American Society of Tropical Medicine and Hygiene at its annual meeting, November 2, 1961, in Atlanta, Georgia.

† Ordinarily this drug would be referred to under its American pharmacopoeia name of quinacrine. In this discussion, however, the trade name, Atabrine, will be used because it was the first name given to it and was used almost universally during the period covered by this report.

most of them for both suppressive and prophylactic activity against several avian malarias, plus a thorough study of the toxicology and pharmacology of many of the preparations in lower animals. Finally, the appraisal was undertaken of some 80 compounds against the malarias of man. These latter studies turned up antimalarial activity in compounds of several structural types, along with new data on the biology of the disease itself. The cooperative wartime effort produced four important advances:

1. New and important data on the general biology of the disease;
2. Reliable methods for appraisal of antimalarial activity;
3. A better understanding of Atabrine, *i.e.*, its worth, and its limitations;
4. Discovery of synthetic compounds better than Atabrine.

The most important of these new compounds was SN-7618 (SN = Survey Number) later known as chloroquine. The Germans had synthesized this compound before the war but, incredible as it may seem now, they discarded it. I will explain later how this happened. Chloroquine received its first U. S. trial in man in early 1944,[2] and by early 1946 over 5000 individuals had been studied and every symptom observed was recorded in an effort to uncover even minimal toxic manifestations. In every respect, SN-7618 surpassed Atabrine. A short course, or even single doses, produced excellent therapeutic response. One dose weekly gave complete suppression. It did not color the skin and eyes, it was less apt to produce gastrointestinal disturbances and it could be produced at moderate cost. Subsequent use marked it as the drug of choice for suppression (prophylaxis) and therapy of malaria the world over. As evidence of the confidence now placed in this drug, the International Cooperation Administration (now the Administration for International Development) purchased, during Fiscal Year 1960, a total of 88,240,000 chloroquine diphosphate tablets and for the medicated salt program in Brazil, 184,500 pounds of the powder; in F.Y. 1961, 75,500,000 tablets; and in F.Y. 1962, 137,250,000 tablets. At this point, I am getting ahead of the real story of chloroquine. Let us now turn back and see how this remarkable drug, now the keystone of malaria therapy, was discovered.

The story begins in 1934 at the Elberfeld laboratories of the Bayer I.G. Farbenindustrie A.G. where H. Andersag synthesized a 4-aminoquinoline.[3] According to available records, Andersag made only two salts of the base. His favorite was the 2.4-dihydroxybenzoic acid. This salt received the name Resochin, being the *RESO*rcinate of a 4-amino*CHIN*olin, using the German designation. The same compound is now known as chloroquine. It was 1945, however, before this startling fact became known to malariologists and even today, it is known only to a few outside the "inner circle." W. Kikuth, of the Elberfeld laboratories, tested Resochin against bird malaria (1935) and found it to be as effective as Atabrine but slightly more toxic. On the basis of the Kikuth tests, the compound was given to F. Sioli who tested it (1935 or 1936) against blood-induced vivax malaria in four paretics at the psychiatric clinic in Düsseldorf. There are no actual records of these tests but he is credited with reporting it, 1) as equally effective as Atabrine, and 2) as saying that it was "too toxic for practical use in humans."[4] Whatever his conclusions might have been, the report of its slightly greater toxicity over Atabrine in lower animals seems to have been the factor which brought the decision to abandon it. This decision by Bayer . . . may have had merit in terms of the times although later it became known by the Germans as the "Resochin error."

Atabrine, the first synthetic antimalarial for the treatment of acute attacks and for suppression of malaria, was placed on the market by the Germans in 1932. They were having a hard time gaining its acceptance against the powerful quinine interests of the Dutch, so they had to decide whether to bring out in 1934–5 another synthetic compound which, apart from imparting no stain to the skin and eyes,—a real deterrent to the use of Atabrine—did not appear decidedly better than Atabrine but even more toxic.

With the decision to discard Resochin, Andersag was asked to attempt the synthesis of a less toxic compound. To speed his efforts he was given two able assistants, S. Breitner and H. Jung. This team produced the methylated Resochin, later known as Sontochin, in 1936. Investigation by the chemotherapeutic and toxicological laboratories at Elberfeld showed this compound to be equally active with Atabrine but less toxic. It was now four years after the introduction of Atabrine and during this time

experience had shown that a synthetic, *i.e.*, Atabrine, could do better than hold its own with quinine, so the Germans decided on an extensive exploration of the new compound.

It is interesting in this connection that when the 5-man task force, Military Intelligence Division, Supreme Headquarters Allied Expeditionary Forces (SHAEF), discussed antimalarials with Kikuth at Elberfeld, 21 to 27 April 1945, as Germany was collapsing, he mentioned having tested Resochin. He gave its formula and said that Sioli had tested it in patients but he had no records of the human trials. Kikuth was enthusiastic about Sontochin and the SHAEF report, appendix 5, carries a 7-page report on it which was prepared by Kikuth.[5] A British intelligence team of 7 members visited Elberfeld, 7 to 23 August 1945, and also discussed new antimalarials with Kikuth. In this instance, he failed to mention Resochin but spoke highly of Sontochin. He presented the team with the same 7-page report, as given to the SHAEF group earlier, which they included in their report as appendix 4.[6]

Kikuth's trials in lower animals, begun in May of 1937, showed Sontochin to be an effective compound and less toxic than Resochin. That data gave impetus to human trials which were begun in November 1937 and ran until May 1938. In those trials, Sioli treated 16 cases of blood-induced vivax malaria. The results were so encouraging that a second series of tests was run at the Institute for Tropical Diseases in Hamburg in 1938 by P. Muhlens, W. Menk and W. Mohr. These tests were against natural infections of all four species including 28 falciparum cases, 19 vivax, 2 ovale and 1 malariae. In 1939, Menk treated 65 cases, including children, infected with *Plasmodium falciparum* in the Cameroons. In the same year (1939), there was a 4th series of trials in a mental hospital in Dresden so that by the end of 1939 the German investigators had treated over 1100 cases of malaria with Sontochin and were, therefore, well aware of its toxicity and efficacy against the human malarias.[7] The Germans patented each of these drugs, Resochin and Sontochin, along with other 4-aminoquinoline derivatives in November 1939[8] and, through the cartel system, the same patents were taken out in this country in favor of the Winthrop Chemical Company in March 1941.[9]

There was no patent system in France which protected the method of production of a chemical substance used for medicinal purposes, so to gain some protection in that country, Bayer . . . , in July 1941, forwarded samples of Sontochin, complete data on its synthesis and on testing trials to the French firm of Rhône-Poulenc whose pharmaceutical branch is known as Specia (Société Parasiene d'Expansion Chemique). The French, in return for such 'a favor' had a working arrangement with Bayer . . . whereby they agreed to confine their promotion of Bayer . . . products to the so-called French Empire alone. This "marriage of convenience" had worked well for Atabrine and, therefore, the Germans saw no reason to withhold Sontochin from Specia even though World War II was already underway.

As a consequence of these arrangements, P. Decourt, a clinical consultant to Specia, was made aware of the drug and the clinical results obtained in the German trials. Decourt, although skeptical of the German claims, took the drug to Tunisia for human trials. By July 1942, Decourt had obtained good therapeutic results against *Plasmodium vivax*, without adverse side effects. In order to carry out more extensive trials, he invited J. Schneider[10] to join him at Tunis. In August of that year, these two investigators set up two types of trials in Tunisia: 1) treatment of acute cases testing Sontochin against Atabrine and quinine, and 2) suppressive trials in the field testing Sontochin against Atabrine in West Tunisia. Decourt returned to France in September and Schneider carried on the trials until the Allied invasion of North Africa on 9 November, 1942, after which he had to stay in Tunis when that city was occupied by the Germans. Schneider was well pleased with the treatment results and so reported to Decourt in November.

The Allied Forces arrived at Tunis in May of 1943 and Schneider, impressed with the results of his suppressive trials with Sontochin, decided to offer the remaining supplies of the drug and his data to the U. S. Army. On 25 May 1943, he was flown to Algiers in an American plane where, on 30–31 May, he turned over 5,000 tablets of Sontochin and the clinical data collected at the Hospital Ernest Conseil in Tunis to Colonel L. D. Moore. Schneider's report to Colonel Moore contains the following sentence on page 6: "Through the United States Consulate I have kept in contact with Major Michael Furcolow, M.D. of the United States Public

Health Service who has asked me to come to Algiers to confer with the competent authorities. It is to Colonel Moore, named above, that I submit, this day, all of the facts in my possession." As evidence of Schneider's cooperation with the Allied Effort, he was given a certificate signed by the Deputy Surgeon, Colonel E. Standlee.[11]

The next chapter in the story opens in New York City. The Winthrop Chemical Company, through their cartel arrangement with Bayer ..., received the manufacturing directions for Sontochin in a letter on 10 May 1939 (the U. S. Patent was not issued to Winthrop until 4 March 1941). In October 1940, J. T. Sheehan synthesized a small amount of the compound. Shortly thereafter, the Director of Medical Research, J. B. Rice, presented the compound to L. T. Coggeshall and J. Maier of the Rockefeller Foundation for tests in lower animals. In January 1941, Maier reported to Rice that the compound was active against *Plasmodium cathemerium* in canaries.[12] Winthrop did not exploit the lead nor did they release the Maier data until almost two years later. In retrospect, the delay in releasing the Maier data was tragic but it could hardly have been avoided as we will see later.

The need for synthetic antimalarials was well recognized by the Services and the Division of Medical Sciences, National Research Council in 1941, but many problems presented themselves in carrying out a systematic search for such agents. Among these problems were choice of lower animal hosts, choice of test parasite(s), development of reliable screening procedures and source of drugs for the tests. Some compounds were received by the testing groups from individual chemists in colleges and universities, but such sources could not supply the number required for large-scale testing; those had to come from the pharmaceutical and chemical firms whose commercial interests had to be protected.

Confronted with this situation, the Subcommittee on the Coordination of Malarial Studies found itself in a quandary by the spring of 1942. This was solved in November 1942 when all the commercial firms accepted the terms of reference set down for their protection in establishing the Office for the Survey of Antimalarial Drugs at Johns Hopkins University in July, under F. Y. Wiselogle. The Winthrop Company transmitted the Maier data on Sontochin to the Survey Office within one month following the agreement, and here occurred another SNAFU.

On 20 January 1943, at a meeting of the Panel on Pharmacology, W. H. Taliaferro called attention to a report from Maier, via Winthrop, to Wiselogle dealing with tests on a new derivative of 4-aminoquinoline, SN-183, against *P. cathemerium* (Maier's original report of January 1941 dealt only with trials against *P. cathemerium*) and *P. gallinaceum* which, in comparison with Atabrine, stood up well. It was the consensus of the group that further work ought to be done on the compound. Sometime following the Panel meeting, the Chairman reviewed the data and stated, in a letter to the Survey Office, that there was no need for the study of additional derivatives of 8-aminoquinoline. He had mistaken the structure; it was a 4-aminoquinoline and *not* an 8-aminoquinoline. For some reason, now obscure, that decision was allowed to stand and from then until well after the invasion of North Africa, the data on the Winthrop compound (a smoldering fire) was kept in the open files of the Survey Office.

It will be recalled that Schneider released Sontochin and his clinical records to the Allies on 30 May 1943. The material was forwarded to the Surgeon General, U. S. Army, Washington, by Brig. Gen. Fred Blésse, Commanding General, North African Theatre Operations U. S. Army, on 8 July 1943; the delay was probably occasioned by the fact that Schneider's report (in French) was translated by HEADQUARTERS NORTH AFRICA. This material was received promptly and the drug made available to W. M. Clark, then Chairman, Division of Chemistry and Chemical Technology, National Research Council. At a meeting of the Subcommittee on the Coordination of Malarial Studies on 2 September 1943, Clark made a brief report on the drug. Information was to the effect that it had been "captured from the enemy in North Africa" and there was uncertainty whether it was Italian or German in origin. He mentioned, too, that the chemical structure probably had been established by W. A. Jacobs but he was not prepared to make a final report.

Evidently, the confusion regarding "capture" and origin of the drug can be explained by the fact that the drug and the accompanying

report got separated in the Surgeon General's office. It was not until 9 September, after Clark's original report, that the late Lt. Col. Roger G. Prentiss, Jr. sent a letter of transfer to Capt. E. H. Cushing (M.C.) U.S.N., Division of Medical Sciences, National Research Council. The complete report and the letter are in the archives of the Council.

During the same month, Jacobs and L. C. Craig of the Rockefeller Institute, determined the structure of Sontochin and found it to be identical to the compound synthesized at the Winthrop Chemical Company by Sheehan in 1940, in other words, SN-183.

The disclosure to the Subcommittee for Coordination of Malarial Studies in November of 1943 that the two compounds (SN-183 and Sontochin) were identical created havoc bordering on hysteria. We had "dropped the ball" and in so doing had lost valuable time in the search for a reliable synthetic antimalarial. The number, SN-183, under which the Winthrop Sontochin had been catalogued in the Survey Office, was declared dead and a new number, SN-6911, assigned to it. All the biological data were declared secret under the Espionage Act, U.S.C. 50, 31–32.

With the large amount of clinical data from Schneider showing it to be less toxic than Atabrine, plus the Maier data against *P. cathemerium* and *P. gallinaceum*, plus new data from M. K. Geiling showing it to be four to eight times as active as quinine against *Plasmodium lophurae*, it was felt reasonably safe to undertake preliminary tests in man with a full toxicological workup to proceed simultaneously.

On 4 May 1944, protocols for human trials by the Navy, the Army and the Public Health Service were approved by the Board and were carried out to show the effectiveness of the compound was no greater than that of Atabrine,[13] but by the time the data were collected other American investigators had discovered that another compound was even more effective than SN-6911; that compound was SN-7618.

We now turn the clock back again in unraveling the history of SN-7618. The record shows that K. Blanchard, at an early meeting of the Board's Panel on Synthesis, had advocated an investigation of derivatives of 4-aminoquinoline. His consideration of the acridine nucleus had led him to think that less complex basic nuclei might exhibit high antimalarial activity. He favored the 7-chloro compound because it was roughly ⅔ of the Atabrine molecule. No one was interested! Finally, in the spring of 1943, about the time Schneider presented Sontochin to the American Army in North Africa, Blanchard, R. C. Elderfield and Wiselogle met in Baltimore. During their meeting, Blanchard called attention to a U.S. Patent No. 2,233,970, assigned to the Winthrop Chemical Company which described 23 final products of 4-aminoquinoline said to have effect against malaria. (Two are important to this discussion because they later carried Survey numbers SN-6911 and SN-7618). He further stated that there was fragmentary information on this group of compounds as antimalarials in the Russian literature.[14, 15] On this basis, he again proposed the idea of synthesizing 7-chloro derivatives of 4-aminoquinoline. This time his proposal was accepted and because of the Winthrop Chemical Company's basic interest in this group of compounds, it was agreed that they would be asked to make them. One wonders now why, up to that time, Winthrop had made only one 4-aminoquinoline, *i.e.*, Sontochin in 1940. The answer may be that the Germans, in the case of Resochin at least, thought the process of synthesis too costly to be profitable and this thought was accepted by Winthrop. Whatever the cause, the Winthrop laboratories did not synthesize SN-7618 until they were asked to do so during a conference in Washington, D. C. which Blanchard and Clark had with Rice of Winthrop in November 1943. This request was confirmed in a letter from Rice to Clark and later, during a second conference in Baltimore in early December 1943, between Clark, Marshall and Blanchard.

The record of the Board, 29 April 1944, shows that Blanchard and Elderfield were to see if they could expedite the synthesis of *four* compounds, one without the methyl group but with chlorine in the 7 position (*i.e.*, SN-7618), and get 250 grams of it as soon as possible. This was accomplished and by late May, L. H. Schmidt was able to report on its acute toxicity in dogs showing that it was nine times as toxic orally as SN-6911, and chronic toxicity studies in monkeys showed that it was four times less toxic than SN-6911.

By 29 June, the Board had sufficient interest in SN-7618 to recommend that the Patent Division of the Office of Scientific Research and Development be alerted for any action they

deemed necessary to protect the National interest. This action by the Board was based on studies which showed it to be eight to thirty-two times superior to quinine and two to twelve times as active as Atabrine in three avian infections. There was also evidence that the wide spread between therapeutic and toxic doses carried over to human malarias, plus the fact that, like SN-6911, it was devoid of certain undesirable side reactions common to Atabrine, *i.e.*, gastro-intestinal irritation and the staining of the skin and eyes.

By the fall of 1944, twenty-five derivatives of 4-aminoquinoline, including SN-6911, had been made and tested against avian malaria. The most active was SN-7618 and human trials were so favorable, based on toxicity and overall antimalarial activity, that the Board recommended extensive clinical trials in Army and Navy installations both here and abroad.

At this point, hopes were high that the American effort had yielded the "magic bullet" and that it could be patented in favor of the government of the United States. Blanchard and others, aware of the Winthrop patent, did not share the view that SN-7618 was patentable. In this they were right for word soon came to the Board that there were blanket patents covering virtually all the 4-aminoquinolines then under test. On the basis of that information, it was thought best not to raise the question of patents for fear of alienating the drug companies whose cooperation was needed to produce new compounds. The Office of Scientific Research and Development took cognizance of the latter situation but, even so, they placed responsibility on the Board for notifying it of special instances of sufficient importance to warrant protection of the government. "Sufficient importance" was defined as an effectiveness in man equal to or better than Atabrine. The Board accepted that responsibility.

About the end of November 1944, the Board was informed IN CONFIDENCE through the Office of Scientific Research and Development lawyers, "that SN-7618 is not subject to further patents in the United States either as a new composition of matter or as a therapeutic agent for the treatment of malaria, and that it is covered by the claims of at least two issued patents owned by the Winthrop Chemical Company (Nos. 486079[16] and 2,233,970). This settled the patent rights. Now the Board could give its full attention to evaluating SN-7618 and related compounds.

Immediately, the Panel on Clinical Testing established protocols for investigating the usefulness of SN-7618 in civilian and military installations both here and abroad, with the result that more comprehensive investigations soon got underway with gratifying results.

During the next several months, groups cooperating with the Office of Scientific Research and Development carried out pharmacological and clinical studies against vivax malaria employing various dosage regimens of 4-aminoquinolines.[17-20] The rapid exchange of information between the cooperating groups permitted quick analysis of the data so that by June it was felt that certain 4-aminoquinolines should be superior to Atabrine for the routine management of malaria. In terms of oral dosage necessary for a generally useful drug, the choice would be between SN-7618 and SN-8137. The tendency for SN-7618 to persist for longer periods of time than SN-8137 should enhance its value as a suppressant. It was well recognized that SN-7618 produced toxicity when given at high dosage but since those dosages were well above, 10 times or more, that required either for therapy or for suppression it appeared that work should be directed toward establishing dosage schedules of SN-7618 adequate for suppression and therapy for comparison with similar data on Atabrine.

The human pharmacological studies of R. W. Berliner and collaborators had produced data to show that a single weekly dose of 0.3 grams (base) of SN-7618 should maintain a plasma drug level sufficient for complete suppression of malaria and by mid-summer (1945) this had been confirmed by H. Most and collaborators and by Coggeshall and others against vivax malaria. At about the same time, Most's group showed that a dosage of 1.5 grams (base) given in three days was highly effective against acute attacks of vivax. The effectiveness of these dosages against falciparum malaria was soon established by the 20th Hospital Group of the India-Burma Theatre and by others.

The data just referred to above, which are presented only as the main highlights of the human trials, plus collaborative data collected over the past two years from trials in avian infections, and the study of the pharmacology and toxicology in lower animals and in man, led the Board, in December 1945 (published in 1946[21])

to approve a statement setting forth the principal data on SN-7618 as related to absorption, excretion, tissue distribution and degradation, toxicity, antimalarial activity and recommended dosage regimens.

The Board thereby decided that among the known drugs, SN-7618 was the drug of choice for the management of malaria. But the drug did not have a name. To take care of this, the Board, in February 1946, recommended to the Council on Pharmacy of the American Medical Association that SN-7618 be hereafter designated chloroquine, a name suggested by E. K. Marshall in November 1945. This was accomplished in March.[22] Later, as one of its final actions before the Board was dissolved on 30 June 1946, it recommended to the Surgeon Generals of the Army and the Navy that chloroquine be added to the supply table and this was done officially on 7 July 1947.

The main story of chloroquine, 1934 to 1946, involves investigators of six countries on five continents and embraces its initial discovery, rejection, re-discovery, evaluation, and acceptance. Results since 1946 have made it the drug of choice for malaria the world over. It was the only antimalarial used by our Armed Forces and most of the Allied Forces in Korea. It has since been employed by most of the Free World Forces when deployed in malarious areas and is the drug of choice in the world-wide malaria eradication program under the World Health Organization.

It is gratifying in this connection to be able to state that the benefits from this remarkable drug are not limited to malaria alone. It is now frequently employed for the treatment of collagen diseases, especially rheumatoid arthritis and discoid lupus erythematosis and, in addition, enjoys a good record in the treatment of extra-intestinal amoebiasis, clonorchis infection and several other parasitic diseases.

The cooperative effort necessary to develop chloroquine brought together the greatest concentration of scientific talent ever assembled for solving a single medical problem. As a member of the Board and its panel on pharmacology and as an active investigator, I had a ringside seat.

REFERENCES

1. This group, under the Division of Medical Sciences, NRC, was first known as the Conference on Chemotherapy of Malaria, 8 July 1941, then the Subcommittee on Coordination of Malarial Studies, 20 January 1943, and, finally, the Board for Coordination of Malarial Studies, 10 November 1943 to 30 June 1946. The members of the Board were:
   R. F. Loeb, Chairman
   G. A. Carden, Jr., Exec. Secretary
   W. M. Clark
   G. R. Coatney
   L. T. Coggeshall
   F. R. Dieuaide
   A. R. Dochez
   E. G. Hakansson
   E. K. Marshall
   C. S. Marvel
   O. R. McCoy
   F. T. Norris
   W. H. Sebrell
   J. A. Shannon
2. Much of the material for this chronicle is from the Bulletin on Malaria Research, Vol. 1 & 2 and from Malaria Reports, Vol. 1 to 7, Board for Coord. of Mal. Studies. Where that is not the case or where supplemental data are included, appropriate references are given.
3. For most of the material dealing with contributions by staff members of Bayer I.G. Farbenindustrie A.G. and for that Company's arrangement with the French firm of Rhône-Poulenc, I am indebted to Dr. Karl Koenig, Farbenfabriken Bayer A.G., Leverkusen, with whom I had discussions in Geneva, Switzerland in November 1960 followed by detailed letters on 2 December 1960, 9 and 24 January 1961 and 1 September 1962. Also, Dr. Walter Kikuth, of the same organization, in a letter dated 1 September 1962, gave me valuable information on actual drug tests.
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6. British Intelligence Objectives Sub-Committee, 1945. Pharmaceuticals: Research and Manufacture at I.G. Farben-Industrie. [Reported by H. Hepworth, H. J. Barber, B. A. Hems, W. P. Kennedy, H. J. Parish, H. W. Thompson and A. C. White] BIOS Final Report 116, Item 24, 280 pp.
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9. U.S. Patent Office, U.S. Pat. No. 2,233,970. Quinoline compound and process for making the same. H. Andersage, S. Breitner, and H. Jung, Wuppertal-Elberfeld, Germany, assignors to Winthrop Chemical Company, Inc., New York, N. Y. 4 pp.

10. The details of Dr. Decourt's connection with Specia and the studies under his direction in N. Africa were given to me by Dr. Jean Schneider, now Professeur agrégé, Faculté de Médecine de Paris with whom I had conversations in Lisbon, Portugal in September 1958, and in Paris early in 1960, plus a letter dated 16 September 1962.
11. The document, dated 30 May 1943, contains four typed paragraphs and is signed by E. Standlee, Col., MC, Deputy Surgeon, NATO. There is a short handwritten addition on 31 May 1943 which was signed by L. D. Moore, Col., MC. A photocopy of that document and B. B. Siner's translation into English of Schneider's full report are in my possession.
12. Dr. C. M. Suter, Director Research, Sterling-Winthrop Research Institute, Rensselaer, N. Y., searched the old Winthrop files and supplied me with material transmitted in two letters dated 16 and 28 August 1962.
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