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PROFESSOR DOCTOR WERNER
SCHULEMANN
MALARIIOLOGIST

COMBINED INTELLIGENCE OBJECTIVES
SUB-COMMITTEE
CONFIDENTIAL

INTERVIEWS WITH PROFESSOR DOCTOR WERNER SCHULEMANN
MALARIOLOGIST
FORMERLY OF BONN UNIVERSITY

Reported By

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CICOS Target Number 24/17 d
Medical

COMBINED INTELLIGENCE OBJECTIVES SUB-COMMITTEE
G-2 Division, SMAEF (Rear) APO 413

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Composition of teams: as shown on page I
Introduction:

This report consists of two separate interviews with Professor Doctor Werner Schuleman. The first was conducted on 9 and 10 May 1945 by Major Monroe E. Freeman, Sn.C., A.U.S. and Commander Charles L. McCarthy (M.C.) U.S.N.R. and the second on 25 May 1945 by Doctor Hamilton Southworth U.S.P.H.S. The two interviews cover essentially the same material but, since they differ materially in detail and presentation, both are being included in the report.

Section I

Interview by Commander McCarthy and Major Freeman.

General Information:

Prof. Dr. Werner Schuleman is 57 years of age and speaks fluent English. From 1918 to 1936 he was head of the Pharmaceutical Department of the I.G. Farbenindustrie Plant at Elberfeld. He left that company for personal reasons and went to Bonn University as Prof. of Pharmacology and Director of the Institute of Pharmacology. In 1924, together with Fritz Schönhöfer and August Wintger, he discovered Plasmochin, the first synthetic antimalarial. For this he received the Emil Fischer Medal from the German Chemical Society in 1928. Schulemann is also the discoverer of Phanodom and many other new chemical compounds which are now widely used as local anesthetics. He received the Mary Kingsley Medal from the Liverpool School of Tropical Medicine in 1938. In 1939 he gave a series of lectures sponsored by the University of London, at The Wellcome Research Institution.

Since leaving the employ of the I.G. Farbenindustrie, he has continued to work on synthetic antimalarials, particularly on a new group of compounds designated the 'S' group and comprising seventeen related substances. Compounds of this group were synthesized in 1928 and patents taken out by the I.G. Farbenindustrie Company. They were tested by Dr. Roehl and found to have no chemotherapeutic value. Since termination of his contract with the I.G. Company in 1941, Prof. Schuleman has been connected with and partially subsidized by the Schering Chemical Co. of Berlin. This firm now makes S-11, the most important member of this group, and holds the patent rights to it. S-11 has never been placed on the market and only enough has been made to supply Prof. Schulemann for his experiments.

Schulemann is a graduate in medicine as well as a chemist, and for the past five years has been civilian consultant on anti-malarials to the German National Research Council (Reichsforschungsrat).
On 18 October 1944 his Institute at Bonn was completely destroyed by bombing. He sent his three chemical assistants mentioned below to Berlin to work in the Pharmacological Institute under Prof. Heubner. Work on the 'S' Group had scarcely started there when they were bombed out in January, 1945. No further chemical investigation has been done since October 1944.

A number of experimental animals and mosquitoes infected with Plasmodium gallinum and P. cathemerium were rescued at Bonn and used as a nucleus to set up a temporary laboratory in the three top floors of the Cwynhausem Reserve Hospital. This hospital of 450 beds received a large number of chronic malaria cases and the laboratory was able to carry out blood studies on the toxicity of atabrin, quinine hydrochloride and plasmochin.

Organization of Institute at University of Bonn and at Bad Osynhausen.

Upon affiliation with the University of Bonn, Prof. Schulemann began the organization of an institute for research on malaria, trypanosomiasis, and other transmissible diseases. This organization was fairly well established and all divisions outlined below were operating when the laboratories were destroyed in October 1944. Divisions and Professional Staff at the University of Bonn were as follows:

**Director:** Prof. Schulemann.

- **Investigations on Protozoa, Malaria, and Trypanosomiasis:**
  - Dr. Hermann Wurmbach, Fräulein Luise Kratz.

- **Investigations on Bacterial Infections:**
  - Dr. Oesterlein, Dr. Kreiser, Dr. Ching (now dead)

- **Pharmacology and Toxicology:**
  - Prof. Schulemann, Dr. Lopf.

- **Synthetic Chemistry:**
  - Dr. Oesterlein, Dr. Saure, Dr. Zirfas.

- **Animals:**
  - Herr Dohm.

The additional laboratory assistants and cleaners are not listed.

Funds supporting this work came from the following sources:

**a) For equipment and supplies:**

1. University of Bonn 22,000 RM
2. Deutsche Forschungsgemeinschaft 25,000 "
3. Special Fund, Ministry of Education 5,000 "
4. Special Fund, Ministry of Education (Approx) 50,000 " per yr.

4) Additional funds were provided (if needed) by Schering Pharmaceutical Co., Berlin.
b) Salaries were paid by:
1) University of Bonn.
2) Deutsche Forschungsgemeinschaft
3) Schering Pharmaceutical Co.

All of these sources of income have stopped since the laboratory of the University of Bonn were abandoned.

Conversations with Prof. Schulemann indicated that the chief activity at Bonn was research in malaria. Work on the bactericidal effects of some barbiturate compounds had been under way, but had not progressed far. The Division of Pharmacology and the Division of Toxicology, and Synthetic Chemistry were functioning mostly in support of the malarial investigations. The Chemistry division had synthesized a series of drugs for possible use as antimalarials and the Division of Pharmacology and Toxicology had studied their toxicity. Most of the data and the records of these investigations were lost when the laboratories were destroyed in October 1944.

Schulemann moved to Bad Oeynhausen in October 1944 and set up a small laboratory of about 10 to 15 rooms on the upper floors of the Koenighof Reserve Hospital. Owing to limitations of equipment, space, and staff, activities were cut to a minimum. No facilities for chemical work were available, so the chemists, Dr. Oesterlein, Dr. Saure, and Dr. Zirfas, went to Berlin in November 1944 to work under Dr. Heubner at the laboratories of the Pharmacological Institute. Bomb damage to the laboratories in Berlin stopped all chemical work in January 1945.

At the Bad Oeynhausen laboratory, Dr. Schulemann, Dr. Wurmbach, and Fräulein Kratz continued the mosquito breeding work, maintained the selected strains of malaria, and were able to continue some of the histopathological studies on infected canaries.

**Personnel**

1) Prof. Schulemann.
2) Prof. Wurmbach, zoologist and parasitologist, a "Sonderführer" in Wehrmacht uniform but not an Army medical officer. His status is that of a specialist for scientific research.
3) Fräulein Luise Kratz, civilian assistant.
4) Herr Dohm, civilian assistant, care and breeding of experimental animals.
5) Dr. Oesterlein) All civilians, last known whereabouts - Berlin, January 1945.
   Dr. Saure. 
   Dr. Zirfas
6) Other personnel at University of Bonn, whereabouts not known at present.

According to Prof. Schulemann, the studies on 3-11 can be continued without serious delay if the following faculties can be obtained:
a) New laboratory quarters.
b) Transport of equipment, animals, mosquitoes, and birds from Bad Oeynhausen.
c) Maintenance of present personnel:
   Dr. Schulemann, Dr. Wunabach, Fräulein Kratz, Herr Dohm
d) Chemical laboratory, equipment and supplies for synthesis of S-ll.
e) Chemists: Dr. Saure, Dr. Zirfas to carry on chemical work.

Report on use of atabrin and of chinoplasmin in 257 soldiers with benign tertian malaria.

In order to get some data on the problem of treatment of relapses in benign tertian malaria, Prof. Schulemann and his assistant treated a large group of soldiers at Godesberg with atabrin alone and another group with chinoplasmin. The plan of treatment was as follows:

**Group I**: Atabrin - one intravenous injection daily for two days with dosage of 0.03 grams - then three injections daily for 3 days with dosage of 0.01 grams. Relapses occurred at rate of 27% to 40%. (Only an estimate as there was not a long time follow up).

**Group II**: Chinoplasmin (Quinine hydrochloride 0.10 grams plus plasmochin 0.03 grams). One tablet t.i.d. for 14 days. In severe cases - 21 days. Relapses occurred at rate of 8% to 10%.

Tablets of sodium salixylate were given at the same time as the chinoplasmin and the urine was treated with FeCl₃, and tested with a colorimeter for a purple color. Actual taking of the medicaments could be controlled in this way. From these experiments Schulemann concluded that atabrin was far from the ideal drug for treatment of malaria because of the large percentage of relapses. Although the combined use of quinine and plasmochin gave excellent results in the treatment of relapses, a new drug for the treatment of the original attack and for causal prophylaxis of malaria was needed. He began chemical studies and animal (canary) experiments with a group of compounds which had been synthesized in 1928 at I.G. Farbenindustrie at Elberfeld. There were seventeen of these which were known as the 'S' Group. After seven years of pharmaceutical trial he found only one compound known as S-ll (S-eleven) to have value as an antimalarial in non-toxic doses. A description of his methods of research and results follows.

Experimental research on antimalarials.
Description of methods used.

A) The Roehl method in which canaries were injected with blood containing malaria parasites in which treatment of the disease was begun shortly (2 to 6 hours) after infection and continued for 6 consecutive days. This will be designated as the "old test method" in the description below.
B) The Schulemann method in which canaries were injected with sporozoites taken directly from the salivary gland of an infected mosquito. The injection is made with a fine glass canula into a pea-sized, sharply demarcated deposit of fat on the anterior chest wall just external to the outer border of the pectoralis major muscle. This fatty area can be easily and constantly found by moistening and brushing aside the feathers over the breast area. This site is chosen rather than a wing because its immobility permits injected material to remain localized for a sufficient time to allow a good development of parasites before dissemination through the tissues.

In this method treatment is not begun until the 4th day after injection - a sufficient interval to allow development of tissue types of parasites. Treatment was continued daily for 6 days. This method will be called the "new test method" here. All medication was introduced directly into the stomach of the canary with a flexible hollow tube (Roehl) seven and one-half centimeters long.

C) A group of 5 infected canaries was used as untreated controls and each antimalarial drug was given to 5 canaries. Two strains of plasmodia were used, i.e., P. gallinaciura and P. catheemerium. Experiments were carried out with natural quinine, its four optically active derivatives, atabrin, plasmochin and the new antimalarial known as S-ll. After death of the canaries, or at stated intervals, sections of tissues were stained with a new modification of Giemsa's stain. In this way the tissue phase (exo-erythrocytic phase) of the development of the life cycle of the parasite was worked out and the pathological effects produced by the toxins liberated by the parasite were studied in the brain, liver, lung, spleen, etc. Schulemann's modified Giemsa staining technique is given in Appendix II.

D) These studies proved definitely that some of the parasites develop inside the endothelial cells while others develop outside these cells. Prof. Schulemann believed that he was the first person to prove this point, but he was informed that this had also been done in the United States about three years ago. His work, which was demonstrated to us in slides and beautiful colored drawings, is ready for publication.

A summary of his experiments follows:

1. Old test method of Roehl:

   a) Comparison of synthetic quinine (Rabe) and natural quinine.

   Racinat (1 1) (- -)  
   Optically active (11)  
   Optically active (--))  
   The same effect as natural quinine.

   Racinat (1-)
   Optically active (1-)  
   Optically active (-1)  
   No effect at all.

   - 9 -
b) New antimalarials S-9, S-10, S-11 compared with quinine.

S-9  -No effect at all.
S-10 -Only trace of activity.
S-11 -In dilution of 1:200 about the same effect as quinine hydrochloride in dilution of 1 to 500.

By this method it was found that S-11 shows only one-half the efficacy of quinine; it is not useful in the treatment of new actue malaria infections.

2. New Test Method (Schulemann) (Infection with sporozoites and waiting four days before beginning treatment).

a) Controls and all infected canaries treated daily for six days with 0.5 ccm. per 20 grams of bird of:
   1) Quinine hydrochloride in a dilution of 1 to 500.
   2) Atabrin " " " 1 to 300.

All canaries died on the ninth or tenth day after infection. From these observation Schulemann believes that quinine and atabrin by this method have no effect at all, that is to say, no effect in treating relapses. (By waiting four days and allowing the development of the tissue phase of the parasites a stage of infection simulating a relapse in produced).

b) Controls and all infected canaries treated daily for six days with 0.5 ccm. per 20 grams of bird of:
   1) Plasmochin in a dilution of 1 to 5000.
   2) S-11 " " " 1 to 200.

The infection was attenuated and death of the birds did not occur until as late as the twentieth day, or not at all. It was concluded that S-11 in a dilution of 1 to 200 was of the same value as plasmochin in a dilution of 1:5000 but that S-11 was much less toxic since no cyanosis was produced by S-11. Prof. Schulemann felt that the first step had been accomplished in finding a substance which effects the exo-erythrocytic form of malaria. He hoped that by continuation of this work a new remedy effective for (1) causal prophylaxis, and (2) treatment of relapses, could be found. Because the records were lost in the bombing at Bonn on 18 October 1944, no exact figures on the lethal dose of S-11 in birds were available. The approximate figures are as follows:

1/2 c.c. of a dilution of 1-200 per 20 grams of bird is the safe dose for experiments.
1/2 c.c. of a dilution of 1-100 is the border-line dose.
1/2 c.c. of a dilution of 1-50 is the lethal dose.

S-11 has never been used in human malaria. During these experiments with plasmochin he came to the conclusion that
the toxic effects (cyanosis, etc.) of the drug were due to embarrassment of the circulation resulting from the drug's action on the myocardium rather than production of toxic substances in the bloodstream.

In his pathological studies Schulemann was assisted by Prof. Wurmbach. They found all stages of destruction of the liver, lung, spleen and lymph glands due to toxins produced by the parasites, and believed that the vague symptoms of pain in various parts of the body in latent malaria could be thus accounted for. The lymph spaces in brain were filled with plasmodia. He made use of the liver puncture technique of Prof. Gützeit. (Professor of Medicine at Breslau University) in living birds to follow the course of the infection, and considers this technique a distinct aid in the diagnosis of latent malaria in humans. The Henry flocculation test was of no diagnostic value in the diagnosis of latent malaria of birds.

Chemical Formula and Synthesis of S-ll.

Synthetic organic compounds, described in detail in Appendix 1, were synthesized by Prof. Schulemann and his associates about 1928 for I.G. Farben (D.R.P. 499826) at Elberfeld. According to Prof. Schulemann, Dr. Roehl concluded that these compounds had no value in malaria therapy, although laboratory reports subsequently obtained from Prof. Schulemann indicate some chemotherapeutic activity. Nothing was done with these compounds until Prof. Schulemann revived his interest in them at the University of Bonn in 1941. At this time a series of seventeen closely related compounds were synthesized by Dr. Saure and his assistants and some preliminary estimates of their antimalarial activity were made. One of these compounds, S-ll, was selected for further study.

Prof. Schulemann described, as S-ll the original compound synthesized in 1928. This compound was 4 N bis (diethyl amino ethyl) amino diethyl catecholate. It was synthesized by nitrating the diethyl amino ether of catechol in the 4 position, reducing with tin and hydrochloric acid, and heating the amine for 5 hours at 135° C with an excess (3-4 mols.) of chloro ethyl diethyl amine. This last step gave yields of about 30%.

Subsequent study of the laboratory reports (Appendix 1) obtained from Prof. Schulemann indicate that Dr. Saure synthesized 17 derivatives of N (diethyl amino ethyl) aniline (or N bis diethyl amino ethyl aniline) which had one or two methyl, methoxy, ethoxy, or chlorine groups substituted in the ring in various combinations and positions. These products were designated S-1, S-2, S-3, etc; and from this S-ll appears to be 4 N is (diethylaminooethyl) amino, 2 chloro, ethyl phenolate. It was prepared by chlorinating phenacetin, removing the acetyl group by hydrolysis, and condensing the amine with chloro ethyl diethyl amine as described above. The product was a yellow oil in 13% yield.

The compounds were synthesized by Dr. Saure, and according to Prof. Schulemann, were obtained as hydrochloric salts, made up as a
10% solution in 1% NaHSO₃, solution sealed in glass ampoules by Schering Co., Berlin. The compound is said to decompose slowly when exposed to air, but in sealed ampoules remains stable for several years.

Miscellaneous Information secured from Prof. Schulemann.

A description of a new lens and condensor for the use with the ordinary microscope. This is called a Phasenkrontrast Einrichtung (Phase-contrast apparatus) and permits the observation of tissue differentiation in fresh unstained specimens in a manner considered superior to anything we have had at our disposal to date. The appearance of the tissue cells strands is that secured by reflected light and that seen in the darkfield. It was stated that only twelve of these apparatuses have been manufactured to date by Carl Zeiss (Jena), and that Prof. Schulemann secured his exemplar from the German Research Council. For three years previous to his departure Prof. Schulemann and a large number of assistants, particularly Dr. A. Zipp (whereabouts unknown at present) had been working on a new idea in chemotherapy, i.e., the action of a new group of phenobarbital compounds on bacterial infections such as those caused by the pathogenic streptococci. Although no definite report on this field of investigation could be secured because of destruction of all records, Prof. Schulemann stated that the progress made was so satisfactory that the work would be continued at the earliest possible moment.

Prof. Gützeit, Professor of Medicine at Breslau and consultant in medicine to the National Research Council of Germany, has developed a new method of liver puncture used in the study of known malaria in birds and humans and also used for diagnosis of latent malaria in humans. He was able to make a positive diagnosis by stained smears obtained by liver puncture and start treatment with Plasmochin long before symptoms of relapse appeared.

The following list of doctors to contact for knowledge of advances in medicine made during the war in Germany was given us by Prof. Schulemann.

Prof. Dr. Handloser - General Oberstarzt - Chief of all medical services of Army, Navy, and Air Force.
Prof. Dr. Schreiber - Adviser in hygiene to Nat. Research Council. Prof. Dr. Gützeit - Consulting Internist to Prof. Handloser and member of Nat. Res. Council - also Prof. of Medicine at Univ. of Breslau.
Dr. Sergius Breuer - General Secretary of Nat. Res. Council, A man who is well informed of all its activities.
Prof. Dr. Spatz - Head of Brain Research Institute at Kaiser Wilhelm Institute, Berlin - Buch.
Prof. Dr. Heubner - Director of Pharmacological Institute at Univ. of Berlin; has made extensive studies of toxicology of blood malaria.
Prof. Dr. Herzberg - Specialist in Virus diseases (Influenza and Epidemic Hepatitis) was at Greifswald on the Baltic Sea.
Recent work of Professor Werner Schulemann.

Schulemann was picked up by the 9th Army at Bad Oeynhausen. Schulemann stated that after moving to Bonn in 1936 he was paid by I.G. for 5 years not to associate himself with another commercial firm. About 3 years ago, however, he made an agreement with Schering and started work with Dr. Oesterlein developing a series of potential antimalarials originally patented by I.G. in 1927 but rejected by Roehl as of little promise. When Schulemann was bombed out of Bonn on October 18, 1944, he salvaged 200 of his canaries, his four mosquito strains, and enough equipment to set up anew on the top floor of the Koenighof Reserve Hospital at Bad Oeynhausen. This British have now swept him out, in order to make room for a headquarters, but he has been taken under U.S. custody.

Series of Compounds.

The original I.G. compounds were the Dimeplasmin series made by Kropp and Schulemann. The new series has been made by Schulemann’s associate Saure, and the "S" nomenclature results from his name. Eighteen of them have been synthesized (see Appendix I), but the exact numerical order was lost when the records were burned at Bonn. The most promising, however, is S11, which has the structure:

\[
\begin{align*}
\text{OC}_2\text{H}_5 & \quad \text{OC}_2\text{H}_5 \\
\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2 & \quad \text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2
\end{align*}
\]

and is estimated by Schulemann to have 1/3 to 1/2 the activity of Quinine by the old Roehl test.

Schulemann uses cathemerium in his canaries, and practically all his testing has been by the Roehl technique. He has devised, however, a "New Test", wherein sporozoites from infected mosquitoes are injected into the peassized fat-pad which lies lateral to the canary's pectoral muscle. The salivary glands are dissected out, mixed with canary serum, and the glands of one mosquito injected
into each bird by means of a capillary pipette. About twenty birds are used for each experiment, including 4-5 controls and 5 treated with quinine. So as to compensate for the inevitable delay before the last birds are injected, the series of 20 are given a second series of injections in reverse order a few hours later into the contralateral fat pad. Thus each gets the salivary sporozoites of 2 mosquitoes. Treatment is not begun until the 4th day and is then continued for 6 days. Schulemann boasts of the fact that he always uses groups of 5 birds for each dosage in his tests, while Kikuth may use but 1 or 2. In both tests he also uses only 0.5 cc daily per 20 gm. of bird, so that his results with a 1/100 solution correspond to kikuth's with 1/200.

By the old Roehl test, about 13 S compounds have been tested, and only S10 and S11 have shown any activity. With S10 this was but a trace, but S11 at 1/200 had about the same activity as Quinine at 1/500. When, therefore, the New Test was devised, S11 was chosen for comparative trial. The initial test was interrupted by the destruction of Schulemann's laboratory, and no subsequent ones have been possible. Its protocol shows that all 4 control birds died on the 9th and 10th days. 5 birds treated with Quinine HCl 1/500 also died on the 9th-10th days, and 5 dosed with Atebrin 1/300 died on the 8th-11th days. All these birds showed a high degree of parasitemia, and the compounds appeared to be of no benefit. 5 birds, however, were treated with Plasmochin 1/5000. They all began to show parasites at the same time as the control birds (about day 6), but the number of these remained low and only 2 birds died (days 11 and 13). One bird was killed on day 10 for pathological studies, and the subsequent records of the surviving 2 were lost after the 15th day by the destruction of the laboratory.

The last group of 5 birds was treated with S11 at 1/200. 1 died on day 12 but with only a slight parasitemia. Another was killed on day 11 for pathological studies. 3 were still alive when all records were lost on day 15, and one of these seemed to be on its way towards a cure. The general course of these birds was very similar to those treated with plasmochin. Pathologically, the one killed on day 11 was about identical with the plasmochin treated bird autopsied on the previous day. In contrast to the controls and to those dosed with Quinine or Atebrin, there was little hepatic or splenic enlargement and relatively few E-forms.

By canary tests, S11 is much less toxic than Plasmochin. A 1/100 solution approximates the MLD, and 1/50 is generally lethal. 1/200 is therefore the maximum tolerated dose. No animal toxicity studies have been made.

S11 is a yellow oil with a B.P. of 205-207° at 3mm pressure. It oxidizes readily and is therefore made up by Schering in sterile ampoules of 1 cc volume containing 0.1 gm of S11 in water with 0.01 gm of NaHSO₃. The dihydrochloride salt is used. Schulemann adds 19 cc of tap water to the contents of 1 ampoule to get his 1/200
Synthesis of Sll is accomplished as follows, according to Saure, whom I tracked down at his home near Huckeswagen:

\[
\text{OH} \quad \rightarrow \quad \text{OC}_2\text{H}_5 \quad \rightarrow \quad \text{OC}_2\text{H}_5 \quad \text{NO}_3 \quad \rightarrow \quad \text{OC}_2\text{H}_5 \quad \text{NH}_2
\]

Yield 60-70% in last strip

No human tests have been made with Sll, and Schulemann makes no definite claims for it. He points out that only 1 side-chain has been tried, because the chloroethylidethylamine required in its production was easily available as an intermediary for novocaine. He also suspects that the dimethoxy derivative would be more active than the diethoxy derivative. Saure made some of this but lost it. Schulemann believes he has a group of compounds which needs further study and development and which promises to have a Plasmochin-like action. He has made no test of Sll for causal prophylactic action. He believes his work is unknown to Elberfeld, but I wonder if Kikuth's revival of interest in related compounds of the Diapromin and Dimeplasmin series may not have resulted from rumors as to Schulemann's work.

Schulemann maintains his strain of gull\n\text{Snaceum} in roosters but has used it very little during the way. Sll has never been tested against it.

General comments on Antimalarials.

Schulemann was sceptical about Sontochin, stating that its only advantage over Atebrin was its lack of skin staining. He agreed with Kikuth that Chinoplasmin was more effective than Atebrin in preventing
recurrences of vivax malaria. One of his students named Rinck searched the War Office records last summer for follow-ups on 257 cases of B.T. malaria treated for 2-3 weeks with Chinoplasmin at the Tropenlazarett, Bad Godesberg, between July 1942 and January 1943. 23 relapses were uncovered, and allowing for lost records, a relapse rate of about 10% was estimated. Comparable cases were treated with atabrin but no follow-up had been made when their names and records were lost in the destruction of Schulemann's laboratory. Nearly all the B.T. strains were of Mediterranean origin. Schulemann believes in the efficacy of Plasmochin combined with Atebrin and continues his interest in Atepe, which is Atebrin 0.1 gm and Plasmochin 0.005 gm. He recommended Atebrin 0.05 gm and Plasmochin 0.0005 gm daily as the suppressive for the German army, but it was turned down. While admitting that large doses of Plasmochin cause methemoglobinemia, he feels that there is another cause for the cyanosis occasionally shown by patients on 0.01 gm tid. In a survey of 100 cases on this dosage at Bad Godesberg he never found over 25% methemoglobin. He suspects that Plasmochin has a direct effect on myocardial conduction.

Schulemann states that he has worked out the life history of the cathemerium tissue-phases in histological preparations made following his method of fat-pad injection. His original slides were destroyed at Bonn, and what he has left seem to be EEF in various various stages of development. He believes that sporozoites may penetrate histiocytes or any undergo an initial extracellular division. He agrees with Missiroli that the number of chromatin granules they contain may determine their development and fate. There are generally about 4 days of tissue-phase development before erythrocytic forms appear. But on one occasion after 48 hours and once after 72 hours, he has transmitted the infection by means of blood to clean birds. He attributes his success in tracing the development of the E-form to a modification of the Giemsa staining technique in which mercury bichloride is used in the clearing of the slide (see Appendix II). Schulemann is also interested in the histopathology of cathemerium malaria. The number of E-form to be found in the liver and spleen of untreated birds makes him wonder if these locations have been sufficiently searched (if necessary after liver puncture) in cases of human malaria.

By injecting colloidal palladium, Schulemann has stirred up the reticuloendothelial system to give a monocytosis in roosters and then has tried blood-induction of gallinaceum infection. In 10 birds this technique led to an unusual course of the infection. E-forms developed more rapidly than normal, and the birds died of cerebral or pulmonary symptoms. Meanwhile the usual blood infection was reduced by a marked phagocytosis of the erythrocytic forms.

Other Drugs.

While at Bonn, Schulemann also worked with Oesterlein in an attempt to find a new class of antibacterial agents. He steered clear of the sulfonamides but sought for other groups of compounds which would resemble \(-S-\tilde{O}-\text{NH}_2\) in having an amino group contiguous
to two \( =O \) groups. For testing he used the culture of hemolytic in
streptococci in whole blood by the rotating tube method of Field
and Green, as he felt it was the in vitro technique which most
closely approximated in vivo conditions. He tried

\[
\begin{align*}
\text{O} & \text{C} \text{C} \text{NH}_2 \\
\text{C} & \text{C} \text{O}
\end{align*}
\]

and also this compound with amino substitutions on the phenyl ring,
but without success. When, however, one of the nuclear \( \text{NH}_2 \)s was
acetylated, he found a trace of activity. Next he tried barbiturates,
and with a para-amino-phenyl substitution again found a trace of
activity. He hopes to continue this work. Before taking up the
S compounds, he also worked for a while with thiazoles of the type
\[
\begin{align*}
\text{N} & \text{O}_2 \text{H}_5 \\
\text{N} & \text{C}_2 \text{H}_5
\end{align*}
\]

in the hope of find antimalarial activity. He had no
success and abandoned the field because synthesis was so difficult.

Conclusion

In his S compounds Schulemann is just reworking the Dimeplasmin-
Diapromin series which has been pretty well shown to be useless in
terminating attacks of human malaria. Schulemann, however, is hoping
these compounds may lead the way to a radical cure. He seems to be
unaware of the fact that Diapromin, which has the structure

\[
\begin{align*}
\text{OC}_2 \text{H}_5 & \text{OC}_2 \text{H}_5 \\
\text{CH}_2 \text{CH}_2 \text{N(C}_2 \text{H}_5)_2 & \text{CH}_2 \text{CH}_2 \text{N(C}_2 \text{H}_5)_2
\end{align*}
\]

was tried by Sioli in 1936-7 as a causal prophy-
lactic and found without activity (see Appendix III). It seems doubt-
ful if his lead is a good one, but it is very interesting that his
New Test shows a similarity of action between Plasmodchin and Sll.
APPENDIX I

Structural Formulae of S series of Compounds.

\[
\begin{align*}
\text{S10} & : R = \text{CH}_2\text{CH}_2\text{N}\text{C}_2\text{H}_5 \\
\text{S11} & : R = \text{CH}_2\text{CH}_2\text{N}\text{C}_2\text{H}_5 \\
\end{align*}
\]

Von den in obigem Patent aufgeführten Verbindungen wurden dargestellt der 4-N- Diäthylaminoäthyl-amino-benzocatechindioäthyläther (Beisp. 13) und der 4-N-Bis(diäthylaminoäthyl)-amino-benzocatechindioäthyläther (Beisp. 14). Während das Mono-aminoalkylierungsprodukt im therapeutischen Versuch nur eine angedeutete, schwache Wirkung bei der Infektion des Kanarienvogels mit Malaria-Plasmodien zeigte, brachte das Di-aminoalkylierungsprodukt eine Verzögerung des Angehens der Infektion von einigen Tagen. (Genaueres über die Wirkungsprüfung unten!)

Im Anschluß an diese beiden direkt dem D.R.P. entnommenen Verbindungen wurde eine Anzahl weiterer Substanzen dargestellt, bei denen die Substituenten und die Stellung der Substituenten zueinander und zu der zu aminoalkylierenden Aminogruppe variiert wurden.

Wege das 2-N-Diäthylaminoäthyl-amino-4-chloranisol und das 2-N-Bis(diäthylaminoäthyl)-amino-4-chloranisol dargestellt werden. Aus p-Toluclidin erhielten wir schließlich durch Nitrierung, Diazitierung und Verkochung mit Säure das 4-Oxy-3-nitrotoluol, das methyliert, reduziert und dann in das 2-N-Diäthylaminolaminoäthyl-amino-4-methylanisol und das 2-N-Bis(diäthyl-aminoäthyl)-amino-4-methylanisol übergeführt werden konnte.

Die 4 zuletzt angeführten Produkte wurden noch nicht im therapeutischen Versuch geprüft.
**Therapeutische Wirkungsprüfung.**

Die therapeutische Wirkungsprüfung der beschriebenen Produkte wurde so vergeben, daß die im chronischen Toxversuch (6 Tage nacheinander je 20 g Kanarienvogel, 0,5 cm² der wäßrigen Lösung des salzauren Salzes peroral) ermittelte symptomlos vertragene maximale Dosis 6 Tage lang nacheinander - wieder 0,5 cm pro 20 g Vogel - peroral gegeben und das Blut des am selben Tag mit der ersten therapeutischen Dosis infizierten Vogels vom 2. Tage an untersucht wurde.

**Ergebnisse.**

<table>
<thead>
<tr>
<th>Produkt:</th>
<th>Dosis:</th>
<th>Verzögerungstage:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I) 4-N-Diethylaminoethylamino-benzocatechindimethyläther</td>
<td>1:200</td>
<td>abgeschwächter Verlauf der Inf.</td>
</tr>
<tr>
<td>(II) N-Bis(diethylaminoethyl)-amino-benzocatechindimethyläther</td>
<td>1:200</td>
<td>3 - 8</td>
</tr>
<tr>
<td>(III) N-Bis(diethylaminoethyl)-p-phenylenediamin</td>
<td>1:100</td>
<td>ø</td>
</tr>
<tr>
<td>(IV) N-Diethylaminoethyl-p-phenetidin</td>
<td>1:50</td>
<td>ø</td>
</tr>
<tr>
<td>(V) N-Bis(diethylaminoethyl)-p-phenetidin</td>
<td>1:50</td>
<td>ø</td>
</tr>
<tr>
<td>(VI) 4-N-Diethylaminoethyl-amino-2-äthoxytoluol</td>
<td>1:200</td>
<td>ø</td>
</tr>
<tr>
<td>(VII) 4-N-Bis(diethylaminoethyl)-amino-2-äthoxytoluol</td>
<td>1:200</td>
<td>ø</td>
</tr>
<tr>
<td>(VIII) 3-N-Diethylaminoethyl-amino-4-chlorphenetol</td>
<td>1:200</td>
<td>ø</td>
</tr>
<tr>
<td>(IX) 3-N-Bis(diethylaminoethyl)-amino-4-chlorphenetol</td>
<td>1:200</td>
<td>ø</td>
</tr>
<tr>
<td>(X) 4-N-Diethylaminoethyl-amino-2-chlorphenetol</td>
<td>1:200</td>
<td>ø</td>
</tr>
<tr>
<td>(XI) 4-N-Bis(diethylaminoethyl)-amino-2-chlorphenetol</td>
<td>1:200</td>
<td>ø</td>
</tr>
<tr>
<td>(XII) 5-N-Diethylaminoethyl-amino-2-chloranisol</td>
<td>1:50</td>
<td>ø</td>
</tr>
<tr>
<td>(XIII) 5-N-Bis(diethylaminoethyl)-amino-2-chloranisol</td>
<td>1:50</td>
<td>ø</td>
</tr>
</tbody>
</table>


Von den Benzthiazolderivaten wurden bisher dargestellt:

- 2-Amino-6-methoxybenzthiazol
- 4-Amino-6-methoxybenzthiazol
- 7-Amino-6-methoxybenzthiazol
- 6-Aminobenzthiazol.

Das 5-Aminobenzthiazol ist synthetisch am schwersten zugänglich und konnte bisher nicht erhalten werden.

Die Monoalkylierungsprodukte von 4- und 7- Amino-6-methoxybenzthiazol wurden - wie auch schon früher berichtet - bereits im therapeutischen Versuch geprüft. Sie zeigten neben hoher Toxizität keine Spur von Wirksamkeit. Das 2-Amino-6-methoxybenzthiazol läßt sich nur sehr schwer alkylieren, da die 2-Aminogruppe nur schwach basisch ist. Über diese Reihe von Produkten, die von Herrn Dr. SAURE bearbeitet wird, soll nach Abschluß Untersuchungen genauer berichtet werden.
Experimenteller Teil

I. 4-N-Diäthylaminoäthyl-brenz catechindiäthyläther. (Dr. SAURE)

1) 4-Nitrobenz catechindiäthyläther: cf. Beilste.VI, 789

- Fp: 73-75°
- Ausbeute: 98%.

2) 4-Aminobenz catechindiäthyläther: (cf. Beilste.XIII, (306)

- Reduktion von 1) mit Sn und HCl, Ausäthern, Vakuumdestill.
- Kp: 135°/5mm; farbloses Öl.
- Fp: 47-48°
- Ausbeute: 70%.

3) 4-N-Diäthylaminoäthyl-brenz catechindiäthyläther:

- (D.R.P. 499 826, Frdl.17, 2548)
- 2) mit 1 Mol Chloräthyldiäthylamin 3 Std. auf 100° erwärmen, Reaktionsprodukt in Wasser lösen, Basengemisch mit Pottasche aussalzen, ausäthern, Vakuumdestillation.
- Kp: 187-190°/3mm; gelbliches Öl.
- Ausbeute: 30%.

II. 4-N-Bis(diäthylaminoäthyl)-aminobenz catechindiäthyläther. (Dr. S.)

- (D.R.P. 499 826, Frdl.17, 2548)
- Monocalkylierungsprodukt mit 3-4 Mol Chloräthyldiäthylamin umsetzen (5 Std. 135°). Aufarbeitung wie oben.
- Kp: 213°/5mm; gelbliches Öl.
- Ausbeute: 35%.

III. N-Bis(diäthylemoathy1)-p-pheny lendiamin: (Dr. SAURE)

1) N-Bis-(Diäthylaminoäthyl)anilin: (C.1930, 1697)

- Anilin mit 3-4 Mol Chloräthyldiäthylamin 6 Std. auf 125° erwärmen. Aufarbeitung wie üblich.
- Kp: 160°/4mm; gelbliches Öl.
- Ausbeute: 76%.

2) N-Eis(Diäthylaminoäthyl)-p-pheny lendiamin:

- 1) in 5n-HCl mit wässr. NaNO₂, nitrosieren, Lösung auf 50° erwärmen und mit Zn-Staub reduzieren, Alkalisieren, mit Pottasche aussalzen, weitere Aufarbeitung wie üblich.
- Kp: 193-195°/3mm; gelbes Öl.
- Ausbeute: 45%.
IV. **N-Diethylaminoethyl-p-phenetidin:** (Dr. SAURE)

p-Phenetidin wird mit 1 Mol Diethylaminoethylchlorid in Benzol 1 Std. auf dem siedenden Wasserbad erhitzt. Kristallbrei in Wasser lösen, vom Benzol trennen, Aufarbeitung wie üblich.
Kp. 147-148°/3mm; farbloses Öl.
Ausbeute: 60%.

V. **N-Bis(diethylaminoethyl)-p-phenetidin:** (Dr. SAURE)

(IV wird mit 3-4 Mol aminooalkylchlorid 5 Std. auf 125° erhitzt. Aufarbeitung wie üblich.
Kp. 188-190°/3mm; gelbes Öl.
Ausbeute: 45%.

VI. **4-N-Diethylaminoethyl-amino-2-ethoxytoluol:** (Dr. SAURE)

(1) **4-Nitro-2-aminotoluol:** (cf. Beilst. XII, 844)

- o-Toluidin wird in konz. Schwefelsäure bei 0° mit Nitriersäuregemisch (HNO₃ d: 1,4) nitriert. Das abgeschiedene Sulfat wird mit NaOH zersetzt.
  Fp. 107°, gelbe Kristalle.
  Ausbeute: 70%.

2) **4-Nitro-2-oxytoluol:** (cf. Beilst. VI, 365)

  Fp. 118°, gelbe Nadeln.
  Ausbeute: 86%.

3) **4-Nitro-2-ethoxytoluol:** (cf. Beilst. VI, 366)

- 2) in alkoholischer KOH mit Jodethyläthylieren.
  Fp. 61°.
  Ausbeute: 85%.

4) **4-Amino-2-ethoxytoluol:** (cf. Beilst. XIII, 574)

- 3) mit Sn und HCl reduzieren, alkalisieren und die Base mit Wasserdampf abtrieben.
  Kp. 143-146°/17mm.
  Ausbeute: 70%.

5) **4-N-Diethylaminoethyl-amino-2-ethoxytoluol:**

- 4) mit 1 Mol Chloräthyläthylamin 3 Std. auf 100° erhitzten, Aufarbeitung wie üblich.
  Kp. 175-177°/3mm; gelbliches Öl.
  Ausbeute: 50%.
VII. 3-N-Diethyldiaminoethyl-amino-4-chlorphenetol: (Dr. SAURE)

1) 3-Nitro-4-acetaminophenetol: (Ar. 229:457)
Phenazetin wird mit 65%iger HNO₃ nitriert. Unkristallisieren aus Alkohol.
Fp: 103°
Ausbeute: 82%

2) 3-Nitro-4-Aminophenetol: (Ar. 229:460)
1) mit alkoholisch-wässeriger KOH verseifen.
Fp: 113°: rote Nadeln.
Ausbeute: 94%

3) 3-Nitro-4-chlorphenetol: (Ber. 32.157)
2) wird in 25%iger HCl bei 0° diazotiert und hierauf unter Rühren Cu-Bronze zugegeben. Abfiltrieren, Rückstand mit Alkohol auskochen.
Fp: 47°, aus Alkohol.
Ausbeute: 53%

4) 3-Amino-4-chlorphenetol: (Ber. 32.157)
3) wird in 25%iger HCl mit Sn reduziert. Mit rauchender HCl Hydrochlorid fallen, alkalisieren, mit Wasserdampf abtreiben.
Kp: 122-123°/3mm; farbloses Öl.
Ausbeute: 71%

5) 3-N-Diethyldiaminoethyl-amino-4-chlorphenetol:
4) wird mit 1 Mol Chloräthyldiäthylamin 5 Std. auf 100° erhitzt, Aufarbeitung wie üblich.
Kp: 170-173/3mm; gelbes Öl.
Ausbeute: 30%

IX. 3-N-Bis(diethylaminoethyl)-amino-4-chlorphenetol: (Dr. SAURE)
3-Amino-4-chlorphenetol wird mit 3-4 Mol Chloräthyldiäthylamin 6 Std. auf 130° erhitzt. Aufarbeitung wie "üblich,
Kp: 191-194°/3mm; gelbes Öl.
Ausbeute: 25%.
X. 4-N-Diethylaminoethylamino-2-chlorphenetol: (Dr. ZIRFAS)

1) 2-Chlor-4-aminophenetol: (Ber.32,156)

Ausbeute: 69%.
Verseifen der Acetamino-Gruppe mit HCl und Abtrennen der Base mit Wasserdampf.
Fp: 66°; Weisse Nadeln.
Ausbeute: 80%.

2) 4-N-(diethylaminoethyl)-amino-2-chlorphenetol: (Dr.ZIRFAS)

2-Chlor-4-aminophenetol wird mit 1 Mol Chloräthyldiäthy-amin in Xylol 12 Std. gekocht. Aufarbeitung wie üblich.
Kp: 164-1870/3mm; gelbliches Öl.
Ausbeute: 37%.

XI. 4-N-Bis(diethylaminoethyl)-amino-2-chlorphenetol: (Dr.ZIRFAS)

2-Chlor-4-aminophenetol wird mit 3-4 Mol Chloräthyldiäthy-amin 12 Std. auf 130° erhitzt. Aufarbeitung wie üblich.
Kp: 205-207°/3mm; gelbes Öl.
Ausbeute: 13,5%.

XII. 5-N-Diethylaminoethylamino-2-chloranisol: (Dr.ZIRFAS)

1) 5-Nitro-2-aminooanisol: (D.R.P. 98 637, Frdl.V, 67)

Acet-o-anisidid wird in 65%iger HNO3 nitriert, das entfallende Gemisch mit 50%iger Schwefelsäure verseift und das hierbei entstehende Gemisch in heisser, 25%iger Schwefelsäure gelöst. Beim Erkalten fällt das 5-Nitro-2-aminooanisol aus.
Fp: 139-140°.
Ausbeute: 38%.

2) 5-Nitro-2-chloranisol:

1) wird in salzsaurer Lösung diazotiert und anschliessend mit Cu-Bronze behandelt. Das 2-Chlorprodukt fällt aus und wird mit Wasserdampf abgetrieben.
Fp: 83°; gelblich-weisse Nadeln.
Ausbeute: 71%.

3) 2-Chlor-5-aminooanisol:

Reduktion von 2) mit Sn und HCl, alkalisieren, ausäthern, Äther verdampfen
Fp: 77°.
Ausbeute: 90%.
4) **5-N-Diethylaminoethyl-amino-2-chloranisol:**

3) wird mit 1 Mol Chloräthyldiäthyamin 6 Std. auf 100° erhitzt. Aufarbeitung wie üblich.
Kp: 186-189°/4mm; gelbes Oel.
Ausbeute: 27%.

XIII. **5-N-Bis(diethylaminoethyl)-amino-2-chloranisol: (Dr. ZTRFAS)**

(XII) wird mit 3-4 Mol Chloräthyldiäthyamin 8 Std. auf 130° erhitzt. Aufarbeitung wie üblich.
Kp: 203-206°/3mm; gelbes Oel.
Ausbeute: 33%.

XIV. **2-N-Diethylaminoethyl-amino-4-chloranisol: (Dr. ZTRFAS)**

1) **p-Chloranisol (Ar.233,31)**

Chlorierung von Anisol mit PCl₅ bei 70-100°: fraktionierte Destillation.
Ausbeute: 62%

2) **4-Chlor-2-nitroanisol: (Ber.29.2599)**

1) wird mit Salpetersäure (d:1,4) nitriert, die Nitroverbindung scheidet sich kristallin ab. Umkristallisieren aus Alkohol.
Fp: 98,5°: gelbliche Nadeln.
Ausbeute: 57%.

3) **4-Chlor-2-aminoanisol:**

Reduktion von 2) mit Sn und Salzsäure, Alkalisieren und Abreiben des Amins mit Wasserdampf.
Fp: 82°
Ausbeute: 90%.

4) **2-N-Diethylaminoethyl-amino-4-chloranisol:**

3) wird mit 1 Mol Chloräthyldiäthyamin 6 Stdn. auf 130° erhitzt. Aufarbeitung wie üblich.
Kp: 169-173°/2mm" schwach gelbliches Oel.
Ausbeute: 47%.

XV. **2-N-Bis(diethylaminoethyl)-amino-4-chloranisol: (Dr. ZTRFAS)**

(XIV) wird mit 3-4 Mol Chloräthyldiäthyamin 6 Stdn. auf 130° erhitzt. Aufarbeitung wie üblich.
Kp: 183-187°/2mm; gelbes Oel.
Ausbeute: 43%
XVI. 2-N-Diethylaminoethyl-amino-4-methylanisol: (Dr. ZIRFAS)

1) 3-Nitro-4-cyctolool: (Ber. 24, 1960)

p-Toluidin wird in der Wärme in etwa 25%iger HNO₃ nitriert, die Nitrierlösung auf 0° abgekühlt und durch Zulaufenlassen von NaNO₂-Lösung diazotiert. Man läßt einige Zeit stehen und erwärmt dann zur vollen Zersetzung versichtig. Das entstandene 3-Nitro-4-cyctolool wird mit Wasserdampf abge-trieben.
Fp: 32°
Ausbeute: 58%.

2) 3-Nitro-4-methoxytoluol: (P. 28, 287)

Methylierung von 1) in wässriger NaOH mit Dimethylsulfat, ausäthern, Destillation im Vakuum.
Kp: 155-157°/13mm
Ausbeute: 59%.

3) 3-Amino-4-methoxytoluol: (P. 28, 288)

Fp: 51, 5°; weiße Blättchen.
Ausbeute: 87,5%.

4) 2-N-Diethylaminoethyl-amino-4-methylanisol:

3) wird mit 1 Mol Chloräthyldiamin 8 Std. auf 100° erwärmt. Aufarbeitung wie üblich.
Kp: 139-143°/1mm
Ausbeute: 51%.

XVII. 2-N-Bis(diethylaminoethyl)-amino-4-methylanisol: (Dr. ZIRFAS)

(XVI) wird mit 3-4 Mol Chloräthyldiamin 24 Std. auf 100° erhitzt. Aufarbeitung wie üblich.
Kp: 154-157°/1mm
Ausbeute: 43%.

- 26 -
gez.: Dr. S. Saure.
Schulemann's Modified Giemsa Staining Technique

1. Tissue is fixed in Susa solution, embedded in paraffin, and cut in 5 μm sections. Excess \( \text{HgCl}_2 \) is removed with dilute \( \text{Kl} \), and the section passed through dilute \( \text{Na thiosulfite} \) and into water buffered according to the method of Professor Weise of Hamburg.

2. Staining is accomplished by soaking for 24 hours (12 hours for spleen and bone-marrow) in a solution freshly prepared as follows:
   a. Make up Solution A
   - Azure I 2.0
   - Methylene Blue 1.0
   - Water to 250.0
   b. Make up Solution B
   - Eosin W.G. 1.0
   - Water 100.0
   c. Mix 0.6 cc of Solution A with 50 cc of Weise buffered water.
   d. Mix 0.6 cc of Solution B with 50 cc of Weise buffered water.
   e. Mix these two dilute solutions together and use fresh. In the staining bowl the slides are placed obliquely with the section side downwards to avoid precipitation.

3. Decolorizing is accomplished by dipping:
   a. For 30 seconds into a mixture of saturated solution of \( \text{HgCl}_2 \) 25 cc and water 75 cc.
   b. Then into distilled water (at least 72 hours old so that some \( \text{CO}_2 \) is present) till clear.

4. The slide is then passed fairly rapidly through the following solutions:
   a. Acetone 70 cc and Xylol 30 cc.
   b. Acetone 30 cc and Xylol 70 cc.
   c. Acetone 5 cc and Xylol 95 cc.
   d. Pure Xylol.
   e. Pure Xylol.

and finally embedded in Gaedax, a synthetic resin of I. G. manufacture (a polychlornaphthalene) that has no traces of acid.
Diapromin-prophylaxis tests in malaria infection by mosquito and blood transmission. - F. Sioli, 1936-1937.

Diapromin was first administered to patient No. 62/III. She had been infected by means of 10 anopheles. Diapromin was administered from the 8th to the 12th day after the infection, 0.1 gm daily, i.e., a total of 0.5 gm. The first febrile attack occurred on the 15th day after the infection, i.e., 4 days after the last dose of Diapromin; plasmodia were found already 2 days before. The period if incubation and the development of the plasmodia were not influenced by Diapromin.

After a discussion with Dr. Kikuth, the author applied a dosage of 3 times 0.1 gm Diapromin on the day before the infection, 3 times 0.1 gm on the day of infection, and 3 times 0.1 gm on the following 4 successive days. This treatment was administered to patients 3/IV after mosquito infection and 4/IV after blood infection.

For a control, patient 2/IV was inoculated on the same day with the same anopheles, and patient 5/IV with the same blood. The time of incubation and the development of the plasmodia were not influenced by the Diapromin medication, neither in the case of the mosquito infection nor in the case of blood infection. The development of the mosquito infection and of the blood infection went through an exactly parallel course in those treated with Diapromin and in the untreated patients.

Individual enumeration:

Case 2/IV without Diapromin infected on 8 June with 18 anopheles. 1st febrile attack 21 June.
Case 3/IV with Diapromin infected on 8 June with 15 anopheles. 1st febrile attack 21 June.
Abundant plasmodia findings in both cases on 21 June.
Case 5/IV blood inoculation on 10 June without Diapromin, 1st febrile attack 17 June.
Case 4/IV blood inoculation on 10 June with Diapromin, 1st febrile attack 23 June.

In both cases sufficient plasmodia findings on 21 June. The somewhat delayed incubation of the Diapromin-treated case lies within the customary limits of incubation and is not to be considered as an effect of Diapromin.

Summary: The Diapromin tests performed by the author so far have not shown any efficacy of the substance.
War Dept. Combined Intelligence Objectives
Subcomm. Report #56

Undated