A Report on the Medicinal Treatment of Filariasis Bancrofti (1945)

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INTRODUCTION

Filariasis is the comprehensive name for a group of diseases which are connected with an infection by any of the nematodes of the superfamily Filarioidea. From this group, infections with the filaroids Onchocerca volvulus and Loa loa are usually segregated by the separate names of onchocerciasis and loiasis. Of the remaining forms of filariasis, "Bancroft's filariasis" (Filariasis Bancrofti) which represents an infection with Wuchereria bancrofti is of preeminent importance and it alone will be considered in the following report.

The morphology of W. bancrofti is well known and described in most text books of tropical medicine (93, 127). The adult worms live in the lymph system of the human host and after copulation and a period of maturation the so-called microfilariae are liberated by the female adult. The microfilariae are enveloped in a sheath, a structure which the adult worm does not possess. Eventually, microfilariae reach the peripheral blood where they may be ingested by a mosquito vector. It is in the mosquito that the microfilariae undergo a process of transformation until they reach its mouthpart in the form of infective larvae. The latter may now be transferred to another human host, where they develop into adult worms.

W. bancrofti exists in various parts of all continents, transmitted by a large number of potential mosquito vectors. The microfilariae, if present in the peripheral blood of an infected individual, usually appear at certain hours only and thereby show a definite nocturnal or diurnal periodicity. No such periodicity, however, can be observed in the Pacific Islands. The question is still under discussion, whether this non-periodic form really is identical with W. bancrofti or whether it represents a separate entity for which the name Wuchereria pacifica has been proposed by Manson-Bahr (86). The pathogenic properties and effectiveness of transmission of this form also have been pointed out as additional reasons for putting it into a category of its own (55). In the Samoan area, moreover, Aëdes scutellaris var. pseudo-scutellaris is the only transmitter of importance as was shown by Byrd et al. (23). In as much as filariasis has been encountered during the present war mainly in the Pacific theatre, experiences in that zone will be given particular emphasis.

There is little doubt today that infection with W. bancrofti in a large number of cases leads to symptoms of the disease filariasis. But the respective rôles of adult worms and microfilariae, of living and dead parasites, and of secondary infections are not equally clear, nor has the mechanism involved in the

production of the symptoms been fully elucidated. Besides, war-time experience has been mainly concerned with the early manifestations of the disease which in previous years had not received the same attention as had chronic and complicated cases. The resulting clinical and pathological problems have a decisive bearing on the treatment of filariasis. Whereas in most bacterial, protozoan and helminthic infections the object of the therapeutic attack is well defined, this is not quite the case in filariasis. No absolute consensus has yet been reached on the rôle of the various pathogenic factors and restorative reactions of the infected organism. The different conclusions drawn offer different therapeutic possibilities. Empirical results with various drugs, on the other hand, have been largely negative, so that the Subcommittee on Tropical Diseases of the National Research Council (94) in December 1943, acknowledged the "absence of an effective chemotherapeutic agent" for the treatment of filariasis. A survey of the literature shows that very different criteria of cure or improvement have been applied by the authors. Moreover, the chronic character of the disease which may lead to complications after many years makes an evaluation of the relatively short war-time experiences difficult.

The foregoing considerations have determined the scope and arrangement of the present report. The first part will discuss clinical, pathological and immunological aspects of the disease in as far as they have a direct bearing on a possible rational treatment. The second part will then add some data on a number of drugs which have been tried in the last 25 years. The report aims at general orientation and makes no claims to bibliographical or factual completeness.

I. PROBLEMS OF RATIONAL TREATMENT

A. Symptomatology and Diagnostic Tests

Symptomatology. Medieval Arabic authors described a condition which is now called elephantiasis (arabum). Although this condition can be caused by quite different factors, it is very likely that even among the medieval cases of elephantiasis, many were connected with filarial infections. But it was only in the second half of the 19th century that such a connection was established. Some investigators, among whom the names of Wucherer, Lewis and Patrick Manson deserve special mention, noticed the frequent occurrence of filarial parasites in elephantiasis, chyluria, lymph scrotum and other complaints (121). Thus the concept of "filariasis" as a disease caused by filariae but manifold in its symptoms originated. With increasing knowledge of the symptomatology there was also increasing need for classification, and two classificatory methods stand out at the present time. First, the main syndromes together with their subdivisions can be enumerated. This was done by Napier (91) in 1944 who distinguished 6 main categories: 1. Absence of signs and symptoms, 2. Lymphangitis and lymphadenitis, 3. Elephantiasis, 4. Lymph varix, 5. Chyle varix, 6. General symptoms. Second, the symptoms can be divided into inflammatory and obstructive. Thus O'Connor and Hulse (103) in 1935 used the following arrangement:

1. Inflammatory
   a. Lymphangitis
   b. Elephantoid fever
   c. Funiculitis, epididymitis
   d. Adenitis, acute and chronic
   e. Filarial fever
   f. Abscess
2. Obstructive
   a. Elephantiasis of limbs and appendages
   b. Hydrocele (chylocele, haemochylocele)
   c. Chyluria
   d. Fistula, varicose lymphatic glands, varicose lymphatics of skin

This type of classification, often used today (93), recommends itself by its convenience but implies a pathological theory in as far as it attributes such syndromes as elephantiasis, etc., to an obstructive process. On what grounds this theory, or even a direct causal relationship between filarial infection and the symptoms of filariasis, rests will be discussed in a subsequent section. At present, the question of the earliest clinical symptoms has to be considered, a question which has received much attention in recent years.

It has been known for a very long time that elephantiasis can be associated with frequent inflammatory attacks (121). Likewise, recurrent attacks of lymphangitis and lymphadenitis have been known as the outstanding symptoms in many cases of filarial infection of long standing. However, observations usually were related to native populations or Europeans of many years residence in endemic regions among whom the earliest manifestations were difficult to trace. Thus the opinion prevailed that one or more years had to pass before a filarial infection could become clinically manifest, and, up to the present war, experiences to the contrary did not impress themselves with sufficient force.

In 1911, Leber and Prowazek (80), reporting on their experiences in Samoa, wrote: "As evinces from all observations up to now, this filaria is first of all connected with the mumu fever (Mumufieber) which we ourselves acquired after eight weeks' stay in Samoa, Upolu and Savaii." (80). These authors described the mumu fever as an erysipeloid edema of the skin, particularly of arms and feet, causing a pronounced and disagreeable itching sensation, and accompanied by an irregular fever. They added that "microfilariae are usually absent." Later on, they said, complications might occur in the form of filarial abscesses, varicose swellings of the inguinal lymph glands, cord-like lymphangitis, lymph scrotum, etc. It is interesting to note that they considered lymphangitis a complication of, rather than identical with mumu. One year later, Bahr (9), in the account of his expedition to the Fiji Islands, noted the case of an American citizen who had shown lymphangitis after three months' residence in Fiji. Next in chronological order comes the case of O'Connor's assistant who was accidentally infected during O'Connor's work (100) in the Western Pacific in 1920-1921. The infection probably occurred on April 17, 1921, in the course of feeding experiments with Stegomyia pseudo-scutellaris in Samoa. On that date, mosquitoes with larval filariae were found feeding on the arm. Recent mosquito bites showed swellings which "varied in size from a shilling to half-a-crown, and consisted of a pale centre with hard, brawny red surroundings, fading into healthy tissue." The swellings lasted for 5 to 7 days and were accompanied by continuous irritation. They were said to differ markedly from the usual mild reaction following the bite of the same mosquito. Forty-three days later (May 30), the right epitrochlear gland was enlarged and slightly tender, and by July 7, the enlargement was much more marked. From September 20 to October 6, the patient suffered from a severe attack of lymphangitis in the right arm, he felt ill and had a temperature up to 100° F. Repeated attacks of lymphangitis occurred in October and January, and from January 16 to 22 the left epididymis was slightly

painful and swollen. "Microfilaria have not yet been found in the blood." (100). While these symptoms were developing, O'Connor saw several cases of lymphadenitis, with or without lymphangitis in persons who had resided only a few months in Samoa. Summarizing his impression he said: "I believe that lymphadenitis of the glands draining the area of infection is a very early and common symptom of filarial infection, and that it is often missed owing to the mildness of the symptoms accompanying the condition." With Buxton (22) in 1928 a level of generalization was reached which covers a good deal of present war experience. Defining mumu as "a Samoan word for acute lymphadenitis and lymphangitis," Buxton said that it might appear in Europeans "within a few months of arrival in Samoa." The same author remarked that the lymphangitis was centrifugal in contrast to the centripetal form of ordinary septic lymphangitis. He also drew attention to the epitrochlear gland, enlargement of which he considered an almost pathognomonic sign in the absence of syphilis. Furthermore, Buxton believed that the lymphadenitis preceded the lymphangitis.

This series of observations made in the Pacific in the prewar era may now be compared with some reports dealing with wartime conditions. There is widespread agreement that the onset of symptoms takes place "from within a few weeks (six to ten) to many months after arrival." (23). According to King (76), the early symptoms of filariasis consist in "characteristic lymphangitis of extremity or genitalia and the adenopathy particularly in the epitrochlear region." Flynn (54), while reaffirming the primary appearance of lymphadenitis, noticed only two cases of true lymphangitis among 125 cases admitted to a base hospital with the tentative diagnosis of filariasis. Glauser (56), on the other hand, covering 172 marines who had served in the Samoan Islands, stated that very few enlarged epitrochlear glands were palpated, the testes being the most frequently (53 percent) indicated location. Fogel and Huntington (55), who presented a detailed description of genital symptoms, considered swelling and edema of the spermatic cord the most characteristic finding. Englehorn and Wellman (49) found general complaints (anorexia, nausea, pains) the first, although undiagnosable, symptoms. From 10 to 14 days afterwards, the scrotal contents were affected (75 percent of their 127 soldier patients) and lymph vessels and nodes of the extremities were involved. In between such different views fall the data of other observers who have recently described the onset of symptoms, the relative frequency of the sites involved, and the time interval between exposure and the beginning of complaints (20, 23, 42, 71, 76, 127).

A few words have to be added about another type of symptoms. Thompstone (133) in 1899 described "peculiar fugitive swellings

about the size of half a goose egg, painless, though somewhat hot, both objectively and subjectively, not pitting on pressure, and usually disappearing in three days." Thompstone's description was based on white and native patients in Lower Nigeria, in whom his search for filariae or other parasites in the blood had remained fruitless. Bahr (9) in 1912 mentioned "fugitive swellings like Calabar swellings" in Fiji, but his description puts them very close to lymphangitis. A perusal of the later literature gives the impression that such fugitive swellings are not commonly considered as a well defined symptom but have been variously interpreted as lymphangitis, Calabar swellings, etc.

Altogether, the earliest symptoms of filariasis are manifold and variable, and the clinical diagnosis, particularly the differentiation from "pseudofilariasis," is very difficult at this stage (125). Yet, generally speaking, it can be said that attacks of lymphedema, lymphadenitis and lymphangitis, of one form or another, are at present considered among the early symptoms (several weeks or months after infection) of filariasis in the Pacific. The initial attacks usually cease spontaneously after a few days but tend to recur after shorter or longer intervals. The local symptoms are associated with varying degrees of general complaints such as rise of temperature ("filarial fever"), fatigue, etc., none of them being of a severe nature, but often complicated by psychic trauma, particularly fear of impotence or sterility (56). Whereas the complaints do not necessarily incapacitate the soldiers from duty, they are usually aggravated by exercise, rest offering the best chance for recovery (42, 55, 56).

Scrotal masses (55) and hydrocele (76) have also been observed, whereas such obstructive phenomena as chyluria, lymph varix and elephantiasis have so far not been recorded. Chyluria and lymph varix will, therefore, not be discussed in the present report. Yet there remains the important question as to the relationship of the inflammatory symptoms to elephantiasis. Lymphangitis and lymphadenitis form the most frequent clinical manifestation of filariasis in early as well as old cases with or without elephantiasis. In the chronic cases, the attacks of lymphangitis often cease without obvious reason, or become less frequent "and may recur only after long periods of years without any treatment." (57). From a merely symptomatological point of view it seems, therefore, that even if early inflammatory attacks cease spontaneously, their reappearance cannot be excluded with certainty before many years have passed. Likewise, the symptomatological evaluation of treatment of inflammatory attacks appears very difficult and the danger of the "post hoc ergo propter hoc" fallacy particularly great. There is no doubt that elephantiasis usually is of the "secondary"

type, i.e. "developing subsequent to several attacks of lymphangitis" (103) and the possible causal relationship will be discussed later. But there remains the possibility of "primary" elephantiasis "occurring without an attack of filarial lymphangitis or with the first attack of that condition." (103). The existence of such primary elephantiasis which has repeatedly been asserted (103, 111) would mean that the absence of early symptoms in cases of filarial infection were no absolute guarantee against the development of this complication.

In contrast to these possibilities it is all the more important to stress the benign features of the disease where the patient is removed to favorable surroundings and reinfection prevented in the early stage. The beneficial effect of a removal from endemic areas upon attacks of lymphangitis has long been recorded (9, 103). Recent authors are practially unanimous in their favorable prognosis of those cases among the armed services which are evacuated to the United States. Moreover, it has been pointed out, that elephantiasis even in native populations constantly exposed to infection is relatively limited (30). If justified, this optimistic belief will influence the choice of antifilarial drugs. For a disease that is self limited and benign does not require the use of such drastic remedies as would be allowed in a progressively crippling malady.

Diagnostic tests. The symptomatological point of view offers no certain criteria for the curative effect of antifilarial drugs. Of course, the finding of living adult worms in biopsy material is certain proof that the parasite has not yet been eliminated. For obvious reasons, however, the search for living worms does not recommend itself as a routine procedure, quite apart from the fact that the necessary excision of lymphducts or lymphatic tissues has met with strong objections from some sides (93). Besides, a negative result does not justify any conclusions as to the absence of adult parasites.*

Microfilariae are a much more accessible test object. The examination of the peripheral blood for microfilariae is a long established diagnostic method, particularly since microfilariae are often encountered when no clinical symptoms point to the disease. This has also been found among soldiers in the present war (137). Similarly, the disappearance or at least the decrease in the number of microfilariae has been widely used as a criterion for the effectiveness of antifilarial drugs. But the validity of this test is restricted by the mere fact that often microfilariae cannot be found although the disease manifests itself clinically. This may be the case in all stages of filariasis, but is especially true in the early period, and, therefore, of par-

*Similar considerations are valid with regard to the x-ray diagnosis of worms.

ticular importance for present war casualties. Investigations made long ago indicated that among native populations microfilariae were rarely observed in the low age groups, but became more frequently observed with advancing age. Reviewing the literature, Lane (78) in 1937, found 14 months to be the earliest age mentioned. There existed, therefore, strong evidence that a considerable length of time, possibly years, was required between the initial infection and the appearance of microfilariae in the circulation. Present war experience has not only confirmed this opinion but has also shown that, in the Pacific area at least, the appearance of early clinical symptoms is quite independent of the possible later appearance of freely circulating microfilariae. In the group of 46 cases investigated by Burhans et al. (20) "the time interval between possible exposure and the onset of symptoms varied from 3 months to 21 1/2 months" - but no microfilariae could be demonstrated. Similarly, among 268 American troops with filariasis diligent search at various times of the day led to the same negative result in the blood as well as tissues (48). Fogel and Huntington (55) emphasized that they could not find microfilariae in either blood or tissue fluid (from hydrocele) of American patients. Flynn (54) offered somewhat different data. Of a total of 125 cases diagnosed as filariasis, 8 (i.e. 6.4 percent) showed blood or lymph node aspiration material positive for microfilaria. In addition the following difference in the average time interval between arrival in Samoa and appearance of first complaints was observed by this author: "For the blood and aspiration material positive cases - 10.2 months, the shortest interval being 8 months and the longest being 14 months. . . . For the entire group - 7.6 months, the shortest interval being 1 month and the longest interval 15 months." It must, of course, not be forgotten that the frequency of positive microfilaria findings will also depend on the microscopic technique used (42), but even so the general rule seems to hold true that clinical symptoms of filariasis can be observed at a time when microfilariae do not yet appear in the tissues.

This result made it necessary to supplement the clinical and microscopic diagnosis by immunological tests, the importance of which has been stressed by Culbertson and coworkers (36). As early as 1930 a skin test for the diagnosis of filariasis was reported by Taliaferro and Hoffman who used an antigen from the dog filarid Dirofilaria immitis (32). With a technique recently described, Huntington (68) obtained 83 percent positive reactions in subjects manifesting early filariasis, but acknowledged that the test showed cross-activity with ascaris and was positive in pre- and subclinical filariasis. Huntington's technique was also used by Michael (88) who tested 307 patients known to suffer from filariasis, "268 or 87.3 percent showing

positive immediate and delayed reactions." Burhans (20) had 16 positive skin tests from a total of 46 patients, and King (76) recorded positive intradermal reactions in 90.8 percent of 164 patients. Bozicevich and Hutter (14) screened out false positive reactions in non-infected and allergic persons by using a 1:8000 dilution of an antigen from D. immitis. At the same time this dilution gave positive skin reactions in all of 25 persons suspected of harboring W. bancrofti. Whereas all the tests mentioned utilized antigens from D. immitis, Culbertson and coworkers (36) obtained an antigen from Litomosoides carinii, the filarial parasite of the cotton rat (Sigmodon hispidus). "Of 81 men tested after they had lived for about 1 year in an area where Wuchereria bancrofti was endemic, 66 (81.4 percent) gave immediate skin responses. Of 77 men of this group whose serums were tested for the precipitin antibody, 58 (75.3 percent) were positive. Of 77 men whose serums were tested for antibody by the complement-fixation test, 59 (76.6 percent) were positive." Positive complement-fixation tests have also been obtained with an antigen from Contortospiculum rheae from the South American ostrich (14, 32). Oliver-Gonzalez and Bercovitz (107) used dried pulverized microfilariae of W. bancrofti for the preparation of a test antigen. A preliminary report of these authors stated positive precipitin reactions in the serum from 2 of 26 patients "with circulating microfilariae but without clinical symptoms" and 3 of 14 patients "with clinical filariae but negative for parasites in the blood." Finally, Dammin and Weller (37) determined heterophile agglutinin and cold autohemagglutinin titers in 104 cases of filariasis. Thirteen percent had heterophile agglutinin titers above 1:32, while the search for cold autohemagglutinins was without any practical result. The authors did not feel justified in drawing any conclusions as to whether W. bancrofti contained a heterophile antigen that might produce significant antibody titers at some stage of the disease.

Intradermal and other immunological tests, it would be fair to say, have not yet reached the stage where they could unequivocally decide the diagnosis of filariasis. The conclusion seems justified that at present neither clinical nor laboratory criteria by themselves offer the possibility of ascertaining a definite cure. Therefore, the usefulness of antifilarial drugs has been largely appraised in the light of pathological theory. The alleged efficacy which such a drug is expected to possess rests on the picture of the disease process as a whole.

B. Pathology

Manson's theory. The pathological aspects of filariasis, so pertinent for a rational therapy of the disease, can best be de-

veloped by going back to Patrick Manson's hypothesis as presented at the beginning of the 20th century.

Manson (85) took it for granted that healthy microfilariae were harmless and that adult worms or ova, i.e. immature forms of microfilariae, caused the symptoms of the disease. One or many worms could plug some lymphatic vessel or could provoke inflammation and thickening of the wall of the vessel. In either case lymphatic circulation would be impeded and edema or varicosity of the lymphatic might ensue. But this explanation was insufficient for elephantiasis where Manson visualized a more complicated process. If an adult female filaria suffers an injury of some sort, it "miscarries" so to speak the ova before they have reached the microfilarial stage. These ova are carried in great number to a lymphatic gland where they act as an embolus and cause lymph stasis in the affected part. However, "lymph stasis alone does not produce elephantiasis, . . . lymphangitis from subsequent traumatism or other cause in the congested area" has to supervene. For the products of inflammation cannot be fully absorbed in the obstructed area, and the recurring attacks of lymphangitis lead to a progressive inflammatory hypertrophy and thus to elephantiasis.

In this way, Manson thought to account for a variety of facts. His hypothesis allowed him to establish a causal connection between elephantiasis and the repeated inflammatory attacks. Moreover, he knew that in many cases of elephantiasis microfilariae could not be found in the blood. Manson thought that they had disappeared either because of the death of the parent worm through injury or during an attack of lymphangitis, or because they could not pass the occluded gland. Since Manson it has often been assumed that the incidence of freely circulating microfilariae stood in reverse proportion to the degree of lymph stasis. As long as the lymphatics were patent, microfilariae could escape into the blood stream; after complete blockage this was no longer possible. Consequently, it has been claimed that a large microfilarial index represents a relatively slight case, whereas the absence of microfilariae indicates a more severe pathological lesion (22), and that in the early stages microfilariae would be much more frequently demonstrated in the peripheral blood than in the chronic and recurrent disease (25, 109).

Secondary infection. Although Manson (85) attributed the various symptoms of filariasis to the filarial infection itself, he still believed that, in addition, traumatism or some other cause was needed to provoke lymph stasis and lymphangitis. Here was an opportunity of challenging the sole etiological rôle of the filariae in the development of lymphangitis and elephantiasis. In the early years of the present century, considerable evidence was gathered to show that streptococci played an im-

portant part in a variety of filarial lesions. Attention began to shift from the filarial infection to secondary infections. The British Filariasis Commission (51) in its report of 1924 went so far as to say: "Infestation by Filaria bancrofti, per se, produces no symptoms; all the pathological manifestations associated with filariasis are due to secondary infection by pyogenic organisms." This opinion which was arrived at on the basis of observations in British Guiana was supplemented by some noteworthy experiences of Dubruel in Tahiti and surrounding islands (after Augustine) (5). Dubruel was able to obtain staphylococci in pure culture from blood sampled at the height of an attack of lymphangitis, but not in cases of elephantiasis when fever was absent. Likewise, streptococci were found more frequently in fluid withdrawn during attacks of lymphangitis than during the intervals. Experimental work by Drinker and associates (44, 45) tends to support these experiences. Blocking the lymphatics of a dog by repeated injections of a suspension of crystalline silica and a 2.5 percent solution of quinine hydrochloride, they obtained lymphedema and elephantiasis. When this condition is established, dogs "which are normally highly resistant to streptococcic infection become locally very susceptible to these organisms if they are injected into a part edematous from lymphatic obstruction." (45). Besides, such dogs experienced spontaneous attacks of lymphangitis during which a hemolytic streptococcus could be grown from the edema fluid; between attacks the organism could not be obtained.

Montestruc and Bertrand (89) claimed that lymphangitis needed the collaboration of two factors, one of which might be the filaria. Similarly, Chabeuf (24) thought that febrile attacks as observed among the natives of French Cameroons were paroxysms of pyogenic infections from which these natives were usually suffering. In one case he actually found a filaria but assumed that the latter really was the vector of the streptococci. Whereas to the minds of these French physicians, filariae play a more or less accidental rôle in the production of "tropical lymphangitis" (89) or "lymphatic filariasis," (24) Grace (61) tried to establish a closer relationship between filarial and streptococcal infection. He sketched a hypothesis according to which lymphangitis was produced by a combination of lymph stasis caused by the worms and subsequent infection by the beta hemolytic streptococcus. "Once infection has occurred, the tissues of the affected area become hypersensitive to the beta hemolytic streptococcus and its products, and attacks of lymphangitis may be occasioned by organismal or toxic stimuli of intensity too low to be appreciated by tissues previously uninvolved."

The emphais laid upon secondary infections in filariasis,

particularly lymphangitis, abscess, and the development of elephantiasis, did not remain unopposed (22, 101, 103, 111). But it was left to the present war experience in the Pacific area to impress the view that early lymphangitis is neither caused by nor conditioned upon the presence of streptococci. Dickson and associates (42), citing their studies on skin sensitivity to filarial extracts as additional evidence, urged a return to the orthodox opinion of the direct responsibility of W. bancrofti for the manifestations of filariasis. Huntington (68) in particular found that skin reactions to Dirofilaria immitis extract sometimes closely resembled "mumu." Michael (88) cultured 100 filariasis lesions, but noted bacterial complication in only one instance where contamination with Streptococcus albus had occurred from a superficial wound. King (76) stated that the lymphangitis of trunk or extremity did not conform with the clinical findings of bacterial infection. Zuckermann and Hibbard (142) discovered no histological evidence for bacterial infection as a cause of lymphangitis. Nevertheless, the discussion of the part played by bacterial infection is not yet closed (93). In the pathogenesis of elephantiasis this part has not been ruled out (123); and Augustine (5) referred to Grace, Dubruel and Drinker's work as challenging definite conclusions from "the negative findings recently reported for navy and marine personnel with a diagnosis of bancroftian filariasis."

The question as to bacterial infection in filariasis has an obvious bearing on the therapy of this disease. The report of the British Filariasis Commission (51) shows how the belief in such infection stimulated the use of vaccines, and how Rose in 1915 was led to prepare a stock polyvalent streptococcal vaccine by "isolating a number of strains of streptococci from a variety of filarial lesions." The commission itself, one of the most radical proponents of this belief, treated more than 80 cases with various staphylococcal and streptococcal vaccines. Although the treatment had no effect on the microfilariae, attacks of pyrexia, lymphangitis and lymphadenitis were greatly reduced, even complete disappearance being sometime recorded. Among the French workers who considered bacteria rather than filariae the main factor, Advier (3) instituted treatment with stock antistreptococcal vaccine (Institut Pasteur) in those cases in which recurrence of febrile attacks of lymphangitis could not be prevented otherwise. Paterson (110) too, although not insisting on a bacterial theory, claimed good clinical success in lymphadenitis, lymphangitis and myositis with repeated injections of T.A.B. vaccine. Bahr (9), however, who prepared a vaccine from Staphylococcus pyogenes aureus from a filarial abscess, and who was among the first to try this type of treatment, found injections of 100,000,000 cocci without effect on the microfilariae in 2 patients.

What has been said of vaccine treatment holds good to an even higher degree with respect to treatment with sulfonamide drugs. True, some investigators have recommended sulfonamides even in the absence of secondary streptococcal infection (127). But the majority of authors who have reported good results with these drugs in cases of "filarial" lymphangitis (3, 13, 24, 39, 46, 53, 89) or lymphadenitis (47) have attributed these results to the curative effect of the sulfonamides on bacterial invaders. Regarding symptoms in early filariasis, Neumann (97) has advanced the following opinion. The symptoms may be of the "allergic type" (diffuse edematous swelling with slight general symptoms as tissue reaction to dead filarial worm), in which case no treatment is required and the prognosis good. Second, they may belong to the "streptococcal superinfected type" (mumu, i.e. lymphadenitis and lymphangitis with pronounced general symptoms). Frequent repetitions of attacks of this type over a long time lead to elephantiasis, but the attacks respond to early sulfonamide treatment (about 3 grams daily for several days). Third, there is the "staphylococcal superinfected type" (fever, local pain, localized swelling and possible fluctuation) which is more frequent in natives than in white persons. Attacks of this type do not react to sulfonamide drugs but do not lead to elephantiasis either. On the other hand, the denial of any bacterial implication in early filariasis has been paralleled by the equally widespread denial of a marked influence of sulfonamide drugs upon filarial lymphangitis. Observers in the Pacific theatre of war have been practically unanimous in characterizing the effect of such drugs as indifferent (20, 42, 49, 55, 56, 76).

The rôle of microfilariae. Although some followers of the theory of bacterial involvement in filariasis went as far as to make the filarial infection a mere remote cause, the theory itself supplemented rather than denied Manson's original view. But the latter's assertion that the microfilariae did not cause pathological changes was contradicted by Lane (78) who placed microfilariae and the reticulo-endothelial system in the foreground. In Lane's view, it is the mobile cells of the reticulo-endothelial system which attack the helminths entering the tissues of the host animal. After the larvae have settled down in some part of the lymphatic system, they become adult and after some time - as yet unknown - mature and give birth to microfilariae. Such parturition is timed, i.e. takes place in definite intervals in all the worms in the host, and this explains the microfilarial periodicity so frequently observed outside the Pacific area. But a long "latent period" of months or even years elapses before any microfilariae reach the blood stream, for new reticulo-endothelial cells form around the adult worm as well as around microfilariae. When the latter appear in the

cortical sinuses of lymph nodes, the lymph becomes dammed due to the accumulation of the reticulo-endothelial cells and the microfilariae are destroyed; new lymph channels have to be formed which carry microfilariae to the next lymph node where the process repeats itself until the last node on the way to the blood stream is bypassed. Even after the "latent period," the reticulo-endothelial cells continue to destroy microfilariae "as long as lymph on its way to the blood takes others through active lymphoid tissue. It follows that the numbers of microfilariae counted in the blood are no measure of those which are being born, still less of the mother worms which bear them - another vexation for tidy minds, which treat the clinical medicine of helminthiasis as a branch of lower mathematics." (78). By accumulating around microfilariae and developing into fibroblasts, the reticulo-endothelial cells cause lymphatic obstruction and thereby create a medium eminently suited for the hemolytic streptococci and the development of lymphangitis. Streptococcal infection, in turn, further stimulates the growth of fibroblasts and this vicious circle favors the development of elephantiasis. Once microfilariae have begun to appear in the blood stream, their periodic disappearance can also be accounted for by the activity of the reticulo-endothelial cells. Under normal conditions, the cells of this system would soon be "blocked," but since the filarial infection leads to an increase of such cells, they are able to dispose of the microfilariae without evidence of protein shock.

Lane (78) reviewed various chemotherapeutic efforts in the light of his theory. Fuadin, he believed, did not kill circulating microfilariae, rather it damaged the ovaries of the adult female worms so that they were unable to form larvae. Aminoarsenophenol caused the microfilariae of W. bancrofti to disappear for a limited period of time, because the mother worms had been temporarily sterilized. À propos of a case of onchocerciasis which had been temporarily helped by a course of neostibosan (1), Lane (79) stated his belief that the microfilariae rather than the adult worms had been killed so that the latter could again resume their productivity. If, however, a drug were found that sterilized all female worms, such a drug would be of real benefit, even though it might not kill the adult parasites (78).*

**It is interesting to compare these views with more recent experimental results. In cotton rats infected with L. carinii, Culbertson and Rose (34, 35) found that neostam and neostibosan killed the adult worms, whereupon the microfilariae disappeared gradually. The same authors believe to have obtained similar reactions in man (see p. 29). But in dogs infected with D. immitis, where the circulating microfilariae had yielded to treatment with trivalent antimony compounds, live, though sterile female parasites were found up to 3 1/2 months after the last treatment. According to Ashburn et al. (143) who described*

Woodman and Bokhari (140) who concurred with Lane doubted whether any drug could be found which would destroy microfilariae while sparing the host, and expected more promising results from sterilization of female worms. In particular, they believed that any dyes (such as methylene blue) might "block" the reticulo-endothelial cells and hamper the defense mechanism. Regarding the alleged harmlessness of microfilariae, Dhayagude and Amin (40) were able to report multiple gross nodular lesions in the spleens of eleven patients. In every case these nodules contained microfilariae of W. bancrofti, while on the other hand none of these cases had a clinical history of filarial symptoms. Hartz (62) found epitheloid cell endo- and perilymphangitis in 5 out of 10 cases of filariasis with occasional analogous changes in the lymph nodes. "These processes," he wrote, "seem to be caused by the presence of living microfilaria, though they can still be present some time after the death of the worms." Van der Sar and Hartz (134) tried to establish a relationship between tropical eosinophilia and microfilaria. Their conclusions were based on a number of cases described in the literature and others observed by themselves. In addition to the well known clinical picture of tropical eosinophilia, the authors drew attention to the enlarged lymph-glands which showed eosinophilic abscesses and, in a few cases, microfilariae. A cure with mafarside immediately stopped the bronchial phenomena, increased weight and changed the blood picture. Observations of filariasis in the garden lizard of India (Calotes versicolor) led Menon and coworkers (87) to ascribe a significant part in the production of lesions to microfilariae.

Lane's postulate of a "latent period" during which microfilariae - even if born - would not appear in the blood stream is suggestive in view of the recent reports from the Pacific where adult female worms have been found with morphologically mature microfilariae in the uterus, but none in the blood or tissues (48, 137).

Whereas Lane assumed that lymph nodes formed a barrier to microfilariae, Drinker and associates (5, 43) from observations with the microfilariae of D. immitis and Loa loa inferred that microfilariae of W. bancrofti would not be impeded by lymph nodes on their way to the blood stream. Utilizing this suggestion, Khalil Bey (73, 74) elaborated a view according to which thermotropism was the basis of the clinical and pathological manifestations of filariasis (74). Cold and moderately warm weather forced the worms to the deeper lymphatics, warm weather made them travel to the lymphatics of the sper-

the characteristic changes in the ovary and uterine contents of these worms (see p. 26) absence of microfilariae over a similar period in man would not necessarily prove the death of the adult parasites.

matic cord. In most cases, such migrations took place without any disease manifestations. If, however, a considerable number of worms produce some obstruction "the lymphatic dilates; a lymph cyst may be formed and later it leaks or ruptures into the surrounding tissues and an attack of filarial lymphangitis ensues. The fluid enveloping the embryos escaping from the genital organs of the female worms is irritant and toxic. It forms the basis of the allergic filarial skin reactions. The worms are also more active in laying embryos at a higher temperature." Afterwards the hole in the lymphatic closes "and the cycle is repeated again at practically equal intervals." (74). Thermotropism, in Khalil Bey's opinion explains the favorable influence of a sojourn in colder climates upon recurrent filarial lymphangitis. From this he draws the therapeutic conclusion that cold applications are of great value. "These either chase the worms away if the lumen of the lymphatic permits and then they disperse in the pelvic and abdominal lymphatics or it depresses their fecundity." (74). Cold applications (ice) as well as their opposites (heat and diathermy) have been used with varying effect in the Pacific (49, 56). Removal to the United States, on the other hand, has been of definite benefit (71) although this may be due to the prevention of reinfection (88) and other circumstantial factors rather than to the thermotropism of the filarial worms.

The rôle of the adult worm. At the present time, most authors consider neither secondary infection nor microfilariae as essential in the pathogenesis of filariasis. Attention centers around the adult parasites and the body reaction to filarial infection itself. Since Manson's time many steps have been made in this direction, but it is O'Connor's work (101, 103) which deserves special attention as a basis for discussion of more recent pathological investigations.

As a result of their work in Puerto Rico, O'Connor and Hulse (103) gave the following account of the histological changes taking place around the filarial worm. While living worms might lead to dilatation of the lymphatic vessel in which they were situated, hypertrophy of the vessel marked by thickening of the intima which formed protruding polypi was only present if there existed some obstruction centrally from the living worm. A different picture was revealed when the worm was about to die. Fibrin appeared on the endothelium of the vessel, foreign body giant cells and possibly eosinophile cells followed, and the granulomatous mass became organized into fibrous tissue steadily growing in size. After the death of the worm, the latter either calcified or was embedded in a caseating focus gradually to disintegrate and to be absorbed. But whatever the process might be, it resulted in an obliteration of the lymphatic vessel by fibrosis or the disorganization of the lymph gland.

O'Connor (101) tried to connect these pathological findings with the following theory of the genesis of symptoms: Neither bacteria nor the living worms per se cause the manifestations of filariasis. But when adult worms die and are in process of disintegration, toxic substances are liberated or produced, leading to sensitization of the human host. When this process is repeated, and toxic substances liberated again, an allergic acute reaction is the result. As long as small amounts of protein are freed, the reaction may be subclinical and manifested by localized urticaria, transient rises of temperature, local pain without signs of inflammation, etc. However, when the amounts of protein are large they will give rise to the typical inflammatory manifestation. Since time is required for the sufficient accumulation of toxin, the filarial attacks will occur periodically. On the other hand, living or degenerating worms near a lymphatic gland, fibrosis following calcification of worms or resulting from the degeneration of microfilariae, and destruction of chains of lymphatic glands by the degeneration of worms may cause varying degrees of mechanical obstruction which will account for elephantiasis and other obstructive symptoms. According to O'Connor's theory then, the acute inflammatory attacks represent an allergic or anaphylactic reaction, whereas elephantiasis is due to mechanical obstruction caused directly or indirectly by the worms or their embryos. The theory, particularly the explanation of the acute filarial attacks, "presupposes, of course, the existence of hyperfilariation and the death and disintegration of large numbers of parasites at different times." For this presupposition O'Connor tried to adduce satisfactory evidence (101, 102).

O'Connor also drew therapeutic inferences from his theory. He recognized a number of palliative measures as valuable for the treatment of acute lymphangitis: magnesium or sodium sulphate taken at the very onset of the attack, bed-rest, aspirin, ice bag or cooling lotions applied to the affected limb that should be raised, ethylchloride spray once a day on the area of intense inflammation and bandaging of the limb from below upward in order to reestablish the lymph supply and prevent permanent swelling. This latter method has also been recommended by Knott (77). But O'Connor was very pessimistic as far as any drug therapy for the prevention of the recurrence of lymphangitis was concerned. "Tartar emetic and various arsenical compounds have been administered intravenously without success. That these drugs should be ineffective when administered in this way is not surprising, since the parasites are not in the blood stream, and if degenerating are largely cut off from nutrition." (103). Clearkin (29) likewise assumed a pessimistic attitude. He argued that in case the allergic hypothesis were correct, the killing of large numbers of worms

might lead to a serious anaphylactic shock. Following this line of thought he tried to desensitize the organism with extracts of Dirofilaria immitis. O'Connor himself was more hopeful of local injections or roentgen irradiation. Assuming that symptoms of lymphangitis might be due to a toxic reaction from an adult worm situated in a localized spot, he injected sulfarsphenamine into the focus (99). Poynton (113) also believed that injection of drugs into enlarged inguinal glands and neighboring thigh muscles reduced or stopped attacks of fever and slowed or arrested elephantiasis. On the other hand, O'Connor together with Golden (57) administered local roentgen irradiation over the involved extremity in 15 cases of filarial lymphangitis some with, others without elephantiasis, but all of many years standing. Although the results were not decisive enough to permit an appraisal, the authors nevertheless deemed it advisable to continue the roentgen treatment of lymphangitis. Encouraging results with copper filtered radiation were obtained by Burhans et al. (20) in patients who had had recurrences of lymphangitis or a residual adenopathy. Fogel and Huntington (55), on the other hand, who applied x-ray to the inguinal region in a few cases of genital manifestations of the disease did not observe any definite benefit and Glauser's (56) experiences with infra-red rays were likewise not promising. In this connection it is worth noting that as far back as 1909 Sir Havelock Charles advised radium treatment of lymphatic obstruction in a patient suffering from "Filaria nocturna." The swollen glands yielded to the treatment and, moreover, the fever too disappeared (136).

Recent observations. It is but fair to say that, apart from the therapeutic consequences, O'Connor's pathological observations and theories have remained basic and have in many points been confirmed by recent investigations of early filarial symptoms (88, 139). Michael (88) distinguished two different kinds of reactions, one in the "foci" where parasites were present, the others in parts distant from a focus. The latter reactions were allergic in character and manifested themselves in "fugitive swellings" on the skin or analogous changes in deeper structures, where they appeared as funiculitis, scrotal enlargement, etc. In the foci, the reaction was not merely allergic. "When a living worm is present in the lymphatic channels, fibrin becomes deposited upon the endothelial surface, the wall of the lymphatic vessel becomes edematous and markedly thickened and there is a heavy cellular infiltration of eosinophilic cells. As degeneration ensues, the tissue reaction becomes more specific in appearance. . . . The vessel becomes thickened by proliferation of the filarial granulation tissue which is almost pathognomonic of this disease." The lesion, surrounded by granulation tissue, is avascular throughout. The histo-

pathological picture strongly suggests "that the lymphangitis is due not only to a specific allergic reaction in response to the worm or microfilariae, but to partial obstruction of the lymphatics as well." If a focus is in a lymph node, conditions are somewhat different. As long as the worm is alive, enlargement of the node is caused by the presence of the parasite, edema and generalized hyperplasia of the node. But when the worm is dead and in process of degeneration, the reticulo-endothelial system responds by endothelial hyperplasia, and the cellular granulation tissue is replaced by proliferative granulation tissue.

Among the factors which decided the prognosis of the patients, Michael mentioned the degree of parasitism on a quantitative basis. In the patients under his observation the degree of parasitism did not appear to be very high. This might favorably influence the outcome, particularly if reinfection was prevented by removal from endemic areas. Wartman (137) too noticed but few adult worms in 24 specimens (20 lymph nodes and 4 cord-like structures) removed from 17 soldiers, and emphasized the contrast to O'Connor and Hulse's findings. Wartman summarized his histological findings as follows: "The tissue reactions in the nodes consisted of granulomatous inflammation with marked hyperplasia of the macrophage (reticulo-endothelial) system and tissue eosinophilia. The lymphatic vessels showed reticulo-endothelial hyperplasia, lymph thrombi, and varying degrees of inflammation with or without thrombosis." Where the lesion in the lymphatic vessel had resulted in a dense cord-like structure, the basis existed for the development of lymph blockage and elephantiasis. In one particular point Wartman differed from both Michael and O'Connor: he was unable to observe any essential difference between the tissue reactions of lymph nodes with living worms and those where the worms were dead, "and no evidence was obtained to indicate that, as is often stated, only degenerating or dead worms cause reaction in the tissues." (137). Besides, lymph nodes which did not harbor any worms at all, often showed similar changes.

From a somewhat different point of view, Zuckerman and Hibbard (142) arrived at conclusions which might be made to harmonize with those of Wartman. In the opinion of these authors, infection with W. bancrofti "is accompanied by a generalized disturbance of the reticulo-endothelial system which manifests itself as a hyperplasia of these specialized cells. The endothelium of the lymph channels is similarly affected and the end-result is an obliterative endolymphangitis." Retrograde lymphangitis is due to the backing up of toxic products by worms which plug the lymphatic vessel. But where lymph nodes enlarge without evidence of a lymphangitis, "the entire process should be considered as based on a generalized reaction

to the toxic or metabolic products of the worm itself, not to its disintegration products."

From the therapeutic point of view, all these observations suggest the following interpretation. The symptoms of early filariasis are partly allergic and partly due to inflammatory reactions caused by the adult worm. It is not yet possible to tell accurately whether dead or living worms are preponderantly responsible for the pathological changes. But the rôle of the living adult parasite can hardly be excluded (139). Any drug that would kill the worms would, therefore, carry promise of at least shortening the course of the disease. Incidentally, it would also lead to elimination of the microfilariae as a possible contributory morbid factor. However, it is not certain that a drug that will kill the filariae will also cure the disease, since the process of eliminating the dead parasites may in itself be responsible for some manifestations of filariasis (93). What danger sudden death of many worms and the concurrent release of toxic material may involve is at present a moot question, offering little more than a basis for speculative arguments pro and con. However, the following point may be worth considering. Clinical observation so far indicates that filarial infection has a relatively good prognosis if reinfection is prevented and the patient put under favorable climatic, physical and psychological conditions (144). Hence any future antifilarial drug must fulfil the postulate of being practically harmless to the human host, lest the danger of the treatment surpass the danger of the disease.

II. EXPERIENCES IN THE CHEMOTHERAPY OF FILARIASIS

The great majority of investigators working on the chemotherapy of filariasis, have aimed at the destruction of the living adult worm. But they have been confronted with the difficulty of gauging the therapeutic effect of the drugs tested. Various methods have been used which can be arranged under the following headings.

A. Action of drugs on parasites in vitro
B. Effects of drugs on related filarial infections in animals
C. Effect of drugs on clinical symptoms or on microfilariae in the blood of man.

A. Experiments in Vitro

Brunwin (19) in 1909 was one of the early authors to test the antifilarial action of drugs by bringing microfilariae and diluted drug together on a slide and observing the effect under the mi-

croscope. In the course of his investigations in the Fiji Islands in 1910, Bahr (9) took occasion to ascertain the survival time of microfilariae (W. bancrofti) in different sera and solutions. Blood from an infected person was citrated, centrifuged, and the microfilariae "placed in definite quantities of different solutions and sera in sterilized welled slides." In suitable sera, the microfilariae survived several days. With "antimony tartrate" 1/2000 or quinine bihydrochloride 1/2000 or weaker solutions of "antimony tartrate," quinine bihydrochloride or atoxyl they lived from several hours to several days.

In 1921, MacCallum (83) reported on the effects of some drugs on the larvae of Dirofilaria immitis in the blood of dogs by tests in vitro under the microscope. Quinine in dilutions of 1:5000 was lethal to the microfilariae but, if injected intravenously, it killed the dogs. Emetin in dilutions of 1:7000 was microfilaricidal as well as tolerated. Strong (128) tested the toxic action of plasmochin, quinine, neosalvarsan, mercurochrome, tartar emetic, sodium antimony thioglycollate, antimosan and fuadin upon the microfilariae obtained from onchocercal nodules in the skin. Plasmochin in dilutions of 1:10,000 destroyed the microfilariae in vitro effectively, and in dilutions of 1:100,000 killed part of them and slowed the movements of others. The effect of tartar emetic 1:100,000 was similar to that of plasmochin in the same solution. All the other drugs mentioned, including fuadin, were inferior in their microfilaricidal action. Strong's results are interesting in so far as the efficacy of plasmochin observed by him was also noticed by Chopra and Rao (27) in tests on microfilariae of W. bancrofti (and malayi) in vitro. Among other authors who used in vitro experiments with a limited number of drugs, Phelbs and coworkers (111) have to be mentioned. They prepared a watery extract of oil of chenopodium 1:1000, one drop of which if mixed with one drop of fresh blood killed microfilariae in 5-15 minutes. However, this action did not take place regularly, even if oil of chenopodium was added directly to the blood on the slide.

The action of a large number of drugs on microfilariae was investigated by Chopra and Rao (27) in 1939 and by Hawking (66) in 1940. These two studies differ in the material used, the technique applied and the results obtained.

Chopra and Sundar Rao (27) aspirated hydrocele fluid harboring microfilariae (bancrofti or malayi) and found that the microfilariae were fairly evenly distributed and lived for 48 hours at room temperature in this fluid. During this period, the activity of the embryos was not decreased. Equal volumes of the aspirated fluid and of the diluted drug were mixed in the circular depression of a glass slide which was covered with a cover glass, and sealed with vaseline. The action of the drug was determined by observing the movements of the microfilariae

every few minutes.

TABLE 1 [from Chopra and Rao (27)]

SHOWING THE EFFECT OF THE DRUG IN DIFFERENT DILUTIONS ON MICROFILIARIA IN VITRO

A = active; S = sluggish; D = slow death; K = killed immediately

Drug	Dilution				Remarks
	1/10,000	1/5,000	1/1,000	1/100	
Fouadin	A	A	A	A	Sluggish movement after 1 hour
693 (Neostibosan)	A	A	A	A	
Sdt. 561 (Bayer)	A	A	A	A	
Tristibine (Meurice)	D	D	D	K	5 to 15 minutes
Stibilase (Meurice)	D	D	D	K	" "
'A 534' (P.D. & Co.)	A	A	A	A	
Anthiomaline (M. & B.)	A	A	A	A	
Soamin	A	A	A	A	1 hour.
N. A. B.	A	A	A	A	"
Sulfarsenol	A	A	A	A	"
Arsiminol	A	A	A	S	"
Arsylene 'Roche'	A	A	A	A	"
Carbarsone (Lilly)	A	A	A	A	
Stovarsol (M. & B.)	A	A	A	A	
Cuprochin (Meurice)	A	A	S	K	20 minutes.
Cuprion (Bayer)	A	A	A	A	
Atebrin	D	D	K	K	10 "
Plasmochin	D	D	K	K	" "
Cilional	A	S	D	D	½ hour.
Prontosil (Bayer)	A	A	A	A	
Soluseptasene (M. & B.)	A	A	A	A	
Rivanol	A	A	S	D	
Trypaflavine	A	A	S	D	
Cobra venom	A	A	S	D	15 minutes = S, ½ hour = D
Russell's viper venom	A	A	A	A	

Hawking's (66) experiments were carried on on Mf. bancrofti exclusively. They were obtained by centrifuging citrated human blood (with the addition of a small amount of heparin) and "suspended in a medium of three parts of hydrocele fluid and one part Locke solution, containing 0.4 percent gulcose." Hawking stated that in this way, the larvae could be kept alive for 5 or 6 days at 37° C. Microfilariae were exposed to suitable solutions of drugs for about 19 hours, after which time the "minimum filaricidal concentration" of the drug was noted. For practical reasons Hawking gave the minimum concentrations "required to kill Microfilariae bancrofti in vitro at 37° C. after 20 hours exposure."

Chopra and Rao (27) believed that in vitro studies generally did not indicate the usefulness of a drug in vivo. Of the compounds effective in vitro some could not be employed in similarly high concentrations in man, whereas others were definitely ineffective in vivo. On the other hand, some drugs which had proved active in man, had not exhibited microfilaricidal prop-

TABLE 2 [from Hawking (66)]

SHOWING THE MINIMUM CONCENTRATION OF VARIOUS COMPOUNDS REQUIRED TO KILL MICROFILARIAE BANCROFTI IN VITRO AT 37° AFTER 20 HOURS EXPOSURE

Compound	Minimum filaricidal concentration mg. per ml.
Reduced tryparsamide thioglycollate	0.0125
Phenyl arsenoxide	0.00025
Neoarsphenamine	0.0125
Arsenious oxide	0.025
Halarsol	0.00625
Arsant	0.0125
Espurdal	0.00625
Tartar emetic	0.0125
Fouadin	0.1
Mercuric chloride	0.05
Acriflavine	0.1
Atebrin musonate	0.025
Plasmoquin chlorhydrate	0.05
Quinine bisulphate	0.1
Trypan blue	0.4
Iodo-acetic acid	0.025
Emetine	0.1
Yatren	0.1
Parafuchsin	0.025
Sulphanilamide	0.4
Sulphanyl-sulphanilic acid	0.4
4 : 4 diamino-diphenyl-sulphone glucoside	0.1
Undecane diamidine	0.2
Diamidino-stilbene	0.1
Phenyl guanidine nitrate	0.4
Octamethylene-diguanidine-dihydrochloride	0.4
Do-decane-diamidine dihydrochloride	0.1
Decamethylene di-isothio-urea	0.1
Trimethyl octadecyl ammonium idodide	0.4
Bayer T. 222 (Beludon)	0.1
Bayer Me 798	0.4
Bayer Me 827 A	0.4
Acaprin	0.4
Surfen	0.4
Surfen C	0.1

erties in vitro. In comparing his own results with those of Chopra and Rao, Hawking pointed to some differences, particularly in the case of acriflavine, atebrin, and plasmochin. He agreed, however, that the substances which he had found active, i.e. arsenicals and tartar emetic, required concentrations not to be obtained in vivo. Nevertheless, he thought that the in vitro method might yield a clue if an animal "carrying a filar-

ial infestation suitable for laboratory experiment" could be found.

Such an animal seems to exist in the Florida cotton rat infected with Litomosoides carinii. Rose and coworkers (118) worked out a method by which adult filariae as well as microfilariae of this parasite could be kept viable for not less than one week at 37° C., and would live from one to three weeks at room temperature. Adult worms were removed from the thoracic cavity, and microfilariae washed out from the pleural space with sterile physiological saline. The adult parasites and larvae were then kept in 10 milliliters of solution prepared as follows (118):

Solution A	Gm. per liter
Na Cl	160.0
K Cl	4.0
$Ca Cl_2 - 2 H_2O$	0.88
$Mg Cl_2 - 6 H_2O$	4.06
Solution B	
$Na H_2 PO_4 - H_2O$	2.2
Na_2HPO_4	18.4
$Na H CO_3$	1.3
Dextrose	20.0
Phenol red	0.2

Dilute one volume of Solution A with 18 volumes of distilled water and autoclave. Sterilize Solution B by filtration through a sintered glass filter. For the final solution (pH 7.4) add one volume of B to 19 volumes of diluted A, plus sufficient normal horse serum to make a concentration of 10 per cent.

As Rose et al. point out, this is the first method that allows the testing of drugs in vitro against adult filariae and microfilariae. In concentrations of from 1-5 mg. percent or more, neostam and neostibosan killed adult L. carinii after about 4 days in vitro at 37° C. (35), an effect which is closely paralleled in the living infected rat (34, 35, 118).

B. Experiments in Animals

In the search for chemotherapeutic agents active against human filariasis, naturally occurring infections of dogs with Dirofilaria immitis and of Florida cotton rats with Litomosoides carinii have been utilized.

Various substances have been used in treating infected dogs (16, 72, 122, 138). Intravenous injections of atoxyl and formalin, as tried by Zibordi, did not reduce the number of microfilariae. Itagaki and Makino injected sodium antimony tartrate intravenously. The microfilariae disappeared, but living worms were found post mortem; besides, the drug had caused toxic reactions. Wada used neostibnal in 7 dogs: the microfilariae disappeared in all of them and a dead adult worm was found in one animal. Philip in 1931 apparently was the first to use fuadin in infections with D. immitis successfully. He was followed by Wright and Underwood and Popescu. In order to obtain good results it seemed essential to push the dosage to the limit of tolerance. Wright and Underwood (138) defined the counterindications for the use of the drug, pointed out its cumulative action, and warned of any attempts at killing a large number of adult worms at the same time since this might lead to embolic pneumonia or acute toxemia. Cheu and Khaw who used "concentrated fouadin" in daily intramuscular injections claimed that this preparation was 4-5 times as potent as fuadin.

While fuadin was in the state of trial, Hayes developed and employed filsol, described as a double salt of antimony. In 1939, Brown and Austin (16) introduced stibsol (antimonial-3-cathechol-thiosalicylic-acid-sodium) which "has proved effective in removing microfilariae from the blood stream and sterilizing or killing the adult female worms in the heart." (16). The drug was observed to lead to a characteristic peak in the microfilaria count after two or three injections and again immediately before the disappearance of microfilariae from the blood stream. "It was concluded that the antimony concentration in the tissues or blood stream must rise to a certain level before the destruction of the microfilariae is effected." (16).

The therapeutic trials described so far had been made with the aim of curing the heart worm disease of dogs. Few investigators (51) had used infected dogs preliminary to the trial of the drug in man. Johnstone (72) in 1936 analyzed the literature on the chemotherapy of D. immitis and performed some experiments with the expectation of finding a drug that would be effective in human filariasis. In 4 dogs that were given fuadin in toxic doses over a short period, the microfilariae disappeared but no effect on the adult worms was observed. Hexylresorcinol, sodium iodo antimonite, carbarsone (4-carbamino-phenylarsonic acid) and trypan blue, each tried separately, gave negative results. In 1943, Brown and coworkers announced their findings with anthiomaline in the treatment of dogs, and since the drug seemed effective they considered it worth while to try it in human infections (17).

Another experimental animal has been discovered in the Florida cotton rat (Sigmodon hispidus) which is subject to in-

fection with the filarial worm Litomosoides carinii (34). Whereas the adult parasite lives in the pleural space, the microfilariae appear in the peripheral blood without regular periodicity (12) yet subject to daily and even hourly variations (18, 12). Since infected animals are readily available it is possible to study the action of drugs on the microfilariae - a rapid method for counting was described by Brown and Williams (18) - and then observe the effect on the adult worms at autopsy (18). In testing a number of drugs, Culbertson and Rose (34, 35) obtained remarkable results with neostam and neostibosan. It appeared that the adult worms were more susceptible to the action of these drugs than were the microfilariae. The latter disappeared gradually in the course of the treatment, but the adult worms were usually dead two weeks from the beginning of the treatment. In some animals the parasite was eliminated by a single dose, 40 mg., of neostam. Neostibosan has now been administered by Culbertson et al. to human patients with results which will be discussed in the following section (146, 147).

Infected dogs as well as cotton rats have been made test objects by a group of workers (15, 143, 145, 148, 149) from the National Institute of Health who, moreover, in cooperation with the Carnegie Institution of Washington, have utilized new methods of tracing radioactive arsenic and antimony in the tissues.

Lawton et al. (148) tried mercury cyanide, mercury oxycyanide and mercury succinimide in a total of 4 dogs. Although the animals showed evidence of mercury poisoning, no effect on adult D. immitis or the microfilariae was observed. Positive results, however, were obtained by the same investigators with a large number of antimony compounds in infected dogs and cotton rats which were observed for 2-6 months after treatment (microfilariae counts being made weekly) and then sacrificed. Apart from antimony oxide, the antimony compounds were derivatives of phenols, alpha hydroxy acids, or polyhydric alcohols. Twenty-five trivalent antimony compounds were used in treating 50 dogs. The intravenous administration of 6 doses weekly, each dose containing 0.8 mgm. of antimony per kg. of body weight, appeared as the most favorable schedule upon preliminary investigations. With this dosage regime, 16 different compounds led to the elimination of microfilariae from the peripheral circulation of 28 of 29 infected dogs. No recurrence was observed for 2 to 6 months following the treatment. Autopsy revealed changes in the uterine contents of living worms* while

**Ashburn et al. (143) found striking changes in the ovary and uterine contents of live adult female D. immitis from dogs treated with therapeutically active trivalent antimony compounds. Early degeneration or necrosis of ova characterized these changes. Microfilariae were absent in most worms. In some worms the uteri were entirely empty while areas of necrosis were evident in the ovaries.*

some adults had been killed by the treatment. In cotton rats, the results were somewhat different. The animals infected with Litomosoides carinii were treated with 9 antimonyl compounds. Five of these compounds (dose rate of 3.3 mgm. of antimony per kg. of body weight), well tolerated, led to the death of the adult worms. Four other compounds (dose rate of 0.8 mgm. of antimony per kg. of body weight), which had been effective in eliminating D. immitis in dogs, had no effect at all on L. carinii.

The acute toxicity of antimonyl compounds determined by the L D_{50} dose in albino mice did not show a definite correlation with the number of injections required to eliminate the microfilariae from dogs. An index for the selection of the more promising compounds was obtained by dividing the number of necessary treatments by a figure denoting the acute toxicity (148).

Valuable as these experiments were in suggesting the use of new compounds they did not indicate the possibilities of therapeutic agents in human infections with W. bancrofti or Onchocerca volvulus where the adult parasites are situated in the lymphoid or dermal tissues. Answers to such questions needed exact determination of the distribution of antimony in the tissues, and it was with this view in mind that compounds synthesized with radioactive antimony were used (15). Whereas the general pharmacological results of this work will be discussed in a later section (see p. 32) some of the points which have a direct bearing on the fate of D. immitis and L. carinii have to be mentioned here.

Brady et al. (15) gave a single injection of tartar emetic prepared from radioactive antimony and containing 0.8 mgm. of antimony per kg. of body weight to each of 4 naturally infected dogs. The animals were sacrificed 36 hours after the injection. One male parasite found in one of the dogs contained 0.6 microgram of antimony per gram; the male and female parasites recovered from the other three dogs had an average of 1.8 micrograms of antimony per gram. Cowie and coworkers (145) administered multiple injections of sodium antimonyl xylitol (prepared from radioactive antimony) to one naturally infected dog. The animal received one intravenous injection containing 0.8 mgm. of antimony per kg. of body weight "daily, except Sunday, for two weeks or a total of 12 injections." The dog was sacrificed 36 hours after the last injection. The microfilariae disappeared after 9 injections, but at autopsy 6 live adult male D. immitis were recovered in the right ventricle. No living female worms were found "but numerous fragments of recently dead and degenerated worms were removed from the pulmonary arterial tree." The filarids contained 3.28 micrograms of antimony per gram. An interesting relationship existed between the blood level of antimony and the therapeutic effect. The element accumulated in the blood so that the clearance rate was

exceeded. "During the 24 hours preceding the elimination of circulating microfilariae, the highest recorded blood concentration was 0.218 microgram and the lowest was 0.096 microgram per gram of blood." (145). The authors assumed "that a certain threshold of antimony must be reached before beneficial therapeutic results can be obtained."

These studies by Brady, Cowie and their coworkers (15, 145) had proved a specific uptake of antimony by the adult D. immitis, and similar results were obtained with trivalent arsenic (149). The question now arose whether the relatively high concentrations of these elements in the adult filarids of dogs were connected with the location of the worms in this particular host. To answer this question, Lawton et al. (149) administered radioactive arsenic to 6 cotton rats naturally infected with Litomosoides carinii. The radioactive element was converted to sodium arsenite and each animal received 1.6 mgm. of arsenic per kg. of body weight intraperitoneally. The animals were killed 24 hours afterwards and the arsenic content determined in 12 tissues. The authors gave the following conclusions of their investigation: "Adult Litomosoides carinii of five of six infected cotton rats showed a specific affinity for arsenic after the injection of sodium arsenite. Lack of uptake in the sixth rat is attributed to the presence of a fibrous pleurisy. A specific localization of arsenic was shown in kidney cortex, liver, epidermis, spleen and lung of cotton rats." (149). Moreover, these results suggested that the effect of trivalent antimony and arsenic was independent from the localization of adult parasites.

C. Drugs Tested in Human Filariasis

In some respects the attempts at finding an effective chemotherapeutic agent against filariasis in man echo the history of modern chemotherapy. In the first decade of the present century, quinine, methylene blue, thymol and atoxyl stood in the foreground, i.e. drugs which at that time were known for their anti-parasitic and anthelminitc action (9, 132). In 1910, antimony preparations were used, "émetique d'aniline" by Thiroux (132) and "antimony tartrate" by Bahr (9). Since that time a large number of substances have been tried with varying success and, above all, with varied criteria of success. More systematic comparative tests were made in 1922 by the British Guiana Filariasis Commission (51) with the result that preparations of antimony were considered more promising than others although far from satisfactory. Chopra and Rao in 1929 (28) investigated the microfilaricidal action of the following preparations: bisnene (urea compound of para-amino-phenyl bismic acid), antimosan, stibosan, neo-stibosan, stiburea, novostiburea, antimony sulphur compound, mercurochrome, plasmochin, em-

etine and tryparsamide. Of the last named the authors said that, apart from making chyluria disappear, it "decreases the frequency of attacks of lymphangitis." In 1939 the same authors (27) tested 74 different substances including some sulfonamide compounds, and, in addition, induced human as well as monkey malaria on filarial patients. Soamin (an arsenic compound) did not diminish the number of microfilariae, but had a "very satisfactory" clinical effect, some patients remaining free from fever and inflammatory attacks for several years. Fuadin, believed to sterilize the parasites temporarily came next. Oil of chenopodium [used by Phelbs et al. (111)] was said to reduce the microfilariae count as well as the recurring attacks of lymphangitis - although the injections were painful. All the remaining preparations were without effect, sulfonamide drugs being useful in secondary infections. Hawking (66) in 1940 summarized his experiences as follows: "The following substances were administered to patients with filariae (W. bancrofti): Fouadin, anthiomaline, tartar emetic, neoarsphenamine, acetylarsan, espundal, arsant, emetine, sulphanilamide, 4:4 - diaminodiphenyl-sulphone, glucoside. No filaricidal action could be demonstrated, judging by the persistence of microfilariae in the blood stream." Hawking thought it conceivable but unlikely that a drug might kill the adult worms without at the same time damaging the microfilariae. In the light of Culbertson and Rose's experiences with the action of neostam and neostibosan in Florida cotton rats this possibility deserves greater attention.

More concrete data are available for anthiomaline and neostibosan. After some trials in vitro as well as in vivo by previous investigators (95), Brown and coworkers used anthiomaline in the treatment of dogs, and in 1944 Brown (17) reported on his results in 12 patients from St. Croix, Virgin Islands. The majority of the patients showed microfilariae in the blood and slight general glandular enlargement with a history of recurrent lymphangitis. They were given totals of 15 cc - 76 cc of the 6 percent solution of the drug intramuscularly. The result of the treatment was based on microfilaria counts which in 10 patients was reduced 85 to 100 percent 4-7 months after the treatment, meaning "presumably that a corresponding number of the adult worms were killed." (17).

Culbertson and associates (146, 147) administered neostibosan intravenously to 30 native Puerto Ricans infected with W. bancrofti. With the exception of one patient suffering from periodic chyluria, all were free of symptoms of filariasis. During the first week 3 injections were given on alternate days, containing usually 50 mgm., 100 or 150 mgm. and 300 mgm. of the drug respectively. Afterwards injections of 300 mgm. each were given daily or on alternate days until treatment ended in

33 to 48 days. Of the 30 patients treated, 13 apparently had lost all microfilariae 12 months after the end of the treatment, and 5 had lost between 87 and 99 percent of the microfilariae (147). In the remaining 12 patients the microfilariae had declined from 4 to 74 percent after 9 months of observations. This latter group was retreated more intensively, apparently with good results. In a control group of 15 patients, 3 showed increases from 3 to 1200 percent during 14 months of observation. The side effects of the drug were relatively slight with occasional nausea or vomiting (especially in the first 7-10 days of treatment) exhibited by about 15 patients. Later in the course of treatment, 4 patients showed low-grade fever. After the end of the treatment no symptoms occurred that could be attributed to the drug.

Apart from the final therapeutic effect, the tardiness of its development was a most remarkable feature. When the actual course of treatment had ended, the microfilaria levels of the patients showed little or no change. A small but decided decrease was observed in about 75 percent of the patients two and one-half months later. From then on, the microfilaria levels were maintained or continued to decline until the above mentioned results were recorded 12 months after the end of the treatment. The authors suggest that this slow action may be attributable to a direct action of neostibosan on the adult parasites rather than on the microfilariae. The adult worms are killed, whereupon the number of microfilariae gradually declines because of loss of replacement. If this hypothesis (which is supported by the findings in cotton rats) is correct, then the absence of any symptoms of early elephantiasis in these patients in whom adult worms had been killed would make it possible to evaluate adequately the essential danger of the chemotherapy of filariasis (147).

This brief survey indicates that of all the drugs tried, antimony compounds still hold the highest promise. For this reason they deserve a more detailed discussion. As for the other remedies it may suffice to summarize them in tables at the end of this report together with such references to the literature as may be helpful in finding further information.

1. Antimony Compounds

a. General remarks on pharmacology and toxicity

The literature on the pharmacology of antimony compounds was reviewed by Oelkers in 1937 (104) and shortly afterwards in the English edition of Schmidt and Peter's work (122). Goodwin and Page (60), using a rapid polarographic method of analysis, in 1943 studied the excretion of organic antimonials the

toxicity of which was examined by Goodwin (58) in 1944. These publications supplemented above all by recent work from the National Institute of Health and the Carnegie Institution of Washington (15, 143, 145, 149) and by some articles of a more limited scope have been used for general information on such antimonials mainly as have been tried in human filariasis.

Accumulation and excretion. If administered orally, the bulk of the antimony is not absorbed and leaves the body with the faeces (122). If administered parenterally, antimony, after one injection, disappears rapidly from the blood, is distributed more or less equally over the body organs and is later on found principally in the liver and the kidneys through which it is excreted (60, 104, 122). In the blood, concentration of the metal in the plasma prevails by far over that in the corpuscles (60).

After a series of injections, the liver is the main place of storage. Dogs and monkeys who had received 9 injections of fuadin in doses of 0.1 cc per kg. of body weight were killed 72 hours after the last injection. In the liver, 0.009 to 0.039 mg. Sb per gram of tissue were found; whereas the accumulation in other organs was much smaller (64).

In mice, Goodwin and Page (60) found that 30-40 percent of the antimony of a single injection of fuadin or of a quinquevalent compound were excreted during the first 1 or 2 hours, the excretion rate slowing down afterwards. Tartar emetic and anthiomaline, on the other hand, did not show the high initial outflow. These authors also observed that small doses of fuadin or quinquevalent compounds were excreted more slowly than large ones. This observation agrees with Weese's experiences in dogs where excretion following therapeutic doses of fuadin was slightly higher on the first day than on the two following days, whereas with large doses, 25-50 percent of the total antimony was excreted on the first day (122). In man too, excretion rates depend on the compound used. The injection of 0.05 gm. of tartar emetic (18.7 mg. of Sb^{III}) showed a slow excretion from the beginning, whereas 0.3 gm. of p-aminophenylstibinate of diethylamine (123 mg. of Sb^{V}) administered intravenously showed a urinary excretion of 41 percent of antimony during the first 24 fours, 6 percent during the second and 1 percent during the third 24 hours interval. In patients with normal kidney function, 8.5-10.8 percent of antimony were recovered during 24 hours after a single injection of fuadin, and 11.3-13.8 percent after an injection of tartar emetic (122). If fuadin (Sb^{III}) and sodium-antimony^{V} gluconate containing equal amounts of antimony were administered, excretion in the case of the quinquevalent compound was more rapid than with the trivalent one (60). With repeated doses of antimonial drugs as usually given in the course of treatment, a gradual accumulation of antimony in the body seems to take place. In a number

of cases of bilharziasis treated with antimosan or fuadin, the urine was analyzed daily, in one case up to 54 days after the beginning of the treatment. About 50 percent of antimony was recovered in the urine, and 2.3-4.6 in the faeces (122).

The valency of various compounds appears unchanged in the urine excreted during 24 hours after injection (60). There are, however, indications that the quinquevalent metal stored in the liver is reduced to the trivalent state, a reduction which is also shown by living tissues in vitro (60).

The data given so far concerning accumulation and excretion of antimony have quite recently been supplemented by investigations of the distribution of radioactive antimony and arsenic in the tissues of dogs infected with D. immitis and cotton rats infected with L. carinii. This sensitive method (15, 143, 145, 149) which has already been referred to in a former section (see p. 27) has shed new light on the pharmacology of antimony and corrected some of the earlier concepts.

Brady et al. (15) treated infected dogs with single intravenous injections of tartar emetic, sodium antimonyl xylitol, and an aqueous suspension of antimony trioxide. Each of the compounds was prepared from radioactive antimony. Following the injection of tartar emetic and sodium antimonyl xylitol, the blood showed a rapid initial decrease of antimony during the first hour followed by a slow removal for the next 4 to 16 hours. In some cases, a slight secondary rise in the blood level was observed at 24 or 36 hours. In the 4 dogs that had received tartar emetic at an antimony dose of 0.8 mgm. per kg. of body weight, 9.9, 21.2, 4.0 and 21.2 percent, respectively, of the total injected, was excreted in the urine in 36 hours. In one dog injected with sodium antimony xylitol the urinary excretion of antimony was 13.7 percent in 36 hours. The dogs were sacrificed 36 hours after the injection. Examination of the dry tissues of the 4 dogs which had received tartar emetic proved that the largest amount of antimony was contained in the liver (average of 10.7 micrograms per gm.). Surprisingly enough, the combined thyroid and parathyroid tissues came next (average of 3.8 micrograms per gm.) and the adult D. immitis, third (average of 1.48 micrograms per gm.). Concentration in the kidney cortex was only one tenth as compared with the liver and was of very low degree in dermal and lymphatic tissues. In two dogs injected with 0.8 mgm. of antimony per kg. of body weight in the form of sodium antimonyl xylitol, the blood level and liver content were approximately the same as those found in the dogs after injection of tartar emetic.

A significant extension of these results was obtained by Cowie et al. (145) who gave 12 injections, each containing 0.8 mgm. of antimony (radioactive) per kg. of body weight, in the form of sodium antimonyl xylitol over a period of 2 weeks, to

one infected dog. Blood samples were drawn before as well as 15 minutes after each injection, and 36 hours after the last injection when the dog was sacrificed. Each injection caused "the 15 minute postinjection level to exceed the previous 15 minute level, and the residual antimony in the blood at the end of each 24 hour period after injection remained above the previous residual. . . . With the cessation of treatment the antimony rapidly left the blood stream." (145). Thirty-five tissues examined for their antimony content showed the greatest concentration in the thyroid gland; the liver came next, to be followed by the parathyroid, the filarids, the spleen and other tissues in ever decreasing order. Although all of the tissues showed some accumulation of antimony, the reversal of the order between thyroid and liver as compared with single injections was the most remarkable phenomenon. As a possible explanation, the authors (145) suggest "that the thyroid may continue its specific uptake of antimony whereas the liver may reach a point of equilibrium more quickly and the uptake and discharge of the antimony from the hepatic tissue may become equalized." (145). The specific activity of the thyroid gland in the metabolism of antimony seems further confirmed by the experiments of Lawton et al. (149) who administered radioactive arsenic to infected cotton rats. The thyroid of these animals showed no specific uptake of arsenic. The tissues ranking highest were kidney, liver and adult filarids, the latter holding about the same place as in treatment with antimony.

Pharmacological action and toxicity. For purposes of orientation it seems advisable to give here a short outline of the effects of antimony compounds upon tissues and organs as well as some comparative data of their toxic action in animals. Clinical observations made in man will then be discussed briefly under the heading of those drugs that have been used in filariasis.

In many respects, antimony has properties analogous to those of arsenic. Its effect on enzyme actions, according to the studies of Oelkers and his coworkers (104) is similar to, although weaker than, that of arsenic. Thus, e.g., tartar emetic, fuadin and stibenyl inhibited the action of lipase on tributryn to a much smaller degree than did potassium arsenite and atoxyl (104). The effect of antimony on leucocytes is not quite clear, authors differing in their assertions (104, 122). In healthy hamsters (Cricetus frumentarius) Ermen (50) observed leucocytosis (after transient decrease) with neostibosan, but leucopenia with fuadin. Both drugs led to the appearance of histiocytes in the peripheral blood.

Tartar emetic is highly irritative, presumably because it rapidly frees antimony, which is more strongly bound in the trivalent or quinquevalent preparations. Some insight into the

chemical fate of fuadin in the human body has lately been obtained by Goodwin and Page (59) through measuring the rates of urinary excretion of the Sb and catechol fractions. The latter was execreted in approximately 6 hours, the Sb, however, much more slowly. Hence the authors conclude: "The function of the catechol appears to be to keep the circulating Sb in solution in a non-toxic form while it is being absorbed by the liver or excreted by the kidney. Meanwhile, excretion of the catechol takes place independently of that of the Sb and . . . at the same rate as that of an equivalent dose of Na catechol disulphonate." (59). In solustibosan, the high degree of tolerability seems dependent on the quick excretion of the Sb, which appears in about 80 percent in the urine during the first 24 hours, as compared with approximately 50 percent in the case of neostibosan (122).

Antimony exerts its main toxic effects upon the circulatory system, the liver and the kidney. The musculature of the heart is weakened, the heart itself becomes dilated and the blood pressure falls. At the same time, the blood vessels of the liver, spleen and intestine widen. On the other hand, it is possible that bradycardia and transient fall of blood pressure in course of tartar emetic and antimosan treatment are due to an influence of the potassium upon the central nervous system (104, 122). If rabbits were given tartar emetic intravenously in doses of 15-20 mg. per kg. body weight, marked hyperemia and cloudy swelling were observed in the kidney. If, however, the dose was 11 mg. per kg. body weight, the animals surviving 48 hours or more, necrotic changes as well as fatty degeneration in the liver predominated (104, 122). Whereas by-effects on liver and kidney have been provoked with toxic doses, therapeutic doses of antimony compounds usually do not lead to noticeable damage of the liver or kidney. Even bilharzia patients with diseased livers did not show any deterioration upon treatment with tartar emetic or fuadin (122). The initial 4 hour excretion of Sb, on the other hand, is relatively slow in patients with diseased kidneys (65). It has been suggested that patients with multiple sclerosis are prone to severe accidents when treated with antimony. Also, Chinese kala-azar patients showed greater toxic reactions than did Indian patients if treated with the same compounds (122).

It may, therefore, be said that the toxicity of antimony depends 1) on the compounds used, quinquevalent ones as a rule being less toxic than trivalent ones; 2) on variations and idiosyncrasies of the patients, due either to their pathological condition or to possible geographic and racial factors as well as personal idiosyncrasies. A comparative survey of the relative toxicity of a number of antimony compounds as studied in mice may be obtained from a table simplified after Goodwin (58)

(see table 3) and a survey of clinical side-effects from a table adapted after Struthers et al. (129) (see table 4). The last named authors treated 700 patients suffering from kala-azar, 303 of whom showed toxic reactions of some kind during treatment. The drugs not used in human filariasis have been omitted from this tabulation. Further experimental as well as clinical data will be given in the following discussion of individual drugs.

TABLE 3* [simplified after Goodwin (58)]

THE TOXICITY OF SOME ORGANIC ANTIMONY COMPOUNDS INJECTED INTRAVENOUSLY INTO MICE

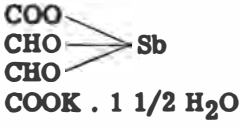
Substance	Total No. of mice used	L.D. 50 mg./20 gm.
1. Tartar emetic (a) Stock crystalline sample	120	1.53
(b) Methyl alcohol precipital sample	80	0.93
2. Sodium antimony^{III} tartrate (a)	60	1.14
(b)	100	1.15
3. Anthiomaline	90	3.62
4. Stibophen (Fuadin)	80	31.2
5. Stibsol	80	1.11
6. Sodium antimony^{III} gluconate	70	3.44
7. (a) Solustibosan	46	32.5
(b) Sodium antimony^{V} gluconate	80	33.0
8. Sodium mannitol antimoniate	70	102.2
9. Tartar emetic (Sb^{V})	60	5.14
10. Stibophen (Sb^{V})	70	66.6
11. Neostam	70	29.5
12. Neostibosan	90	9.44
13. Ureastibamine	120	4.26
14. Stibacetin	65	5.65

All mice weighed 20-25 gm. except those for substances 4, 10, 11 and 12; these weighed 13-19 gm.

*The figures in this table should be compared with the data recently obtained by Lawton et al. (148) in white mice.

b. Tartar emetic

Tartar emetic (Tartarus stibiatus, Tartarus emeticus) is Antimony tartrate of potassium. Its formula is



Tartar emetic is one of the oldest antimony compounds and also the first to find a place in modern antimony chemotherapy, when its trypanocidal action was demonstrated by Plimmer and Thomson in 1907 (122). Whereas often used formerly as an emetic, this action of the drug is now considered an undesirable

TABLE 4 [adapted after Struthers et al. (129)]

Number of cases	45	187	10	2	3	39	4	1	10	56	93	228
Drug	Pot. ant. tartrate	Sod. ant. tartrate	Amon. ant. tartrate	Aniline ant. tartrate	Sod. ant. thioglycollate	Antimosan	Urea stibamine	Stiburea	Novostiburea	Stibosan	Neostam	Neostibosan
Reactions												
Fever	14	50	1		1	11	3	1	1	11	33	21
Cough	8	18			3	2			2	4	11	16
Vomiting		13	1		1	4			2	4	26	13
Nausea		15				2			3		28	14
Headache	5	6				1	2	1	1		9	3
Lymphadenitis	2	7			2	1			1	2	5	7
Diarrhoea	1	11	2			1				2	2	2
Pain in abdomen		6				1					5	2
Pain in legs	2	14									3	
Pneumonia	4	9										1
Urticaria		1				1				1	1	1
Gangrene of gums											1	1
Other uncommon reactions	14	46	4	0	0	3	0	0	0	7	18	13

side effect, repeated vomiting necessitating its discontinuance. In order to avoid the pain and local irritation following subcutaneous or intramuscular injections, tartar emetic is chiefly administered intravenously (104). However, severe and often prolonged coughing fits may follow upon injection. This phenomeon has been attributed to precipitation of Sb_2O_3 in the capillaries of the lungs, an explanation rejected by Oelkers who found antimony tartrate of potassium as well as of sodium relatively durable in neutral and slightly alkaline reactions (106).

One of the most frequent toxic manifestations in course of treatment with tartar emetic is the appearance of articular and muscular pain. Other toxic symptoms which have been attributed to this drug include nausea, dizziness, fever, diarrhoea, icterus, conjunctivitis, dermatitis, bronchopneumonia as well as injury to the heart, liver and kidneys (104). Among filariasis patients, Bär (8) had one case of poisoning, marked by sore mouth and acute nephritis, after a total dose of 0.755 gm. of tartar emetic had been injected (highest single dose 0.10 mg.).

A number of fatalities have been reported with tartar emetic, among them sudden death several hours after injection. It was the relatively high toxicity of tartar emetic which stimulated the search for other antimony compounds less toxic but of equal

TABLE 5

TARTAR EMETIC IN HUMAN FILARIASIS

Author	No. of patients	Total dosage in gm.	Remarks
Bahr (9)	3	0.065	No effect on microfilariae
Macfie (84)	1	0.39	" " " " "
Low and Gregg (81)	1	1.14	" " " " "
Low and O'Driscoll (82)	2	1.2 and 2.02	" " " " "
Diamantis (41)	1	0.83	Chyluria, urine still clear 10 months afterwards
Mühlens (90)			No results
Fil. Comm. 1921 (51)	1	0.11	No result
Bär (8)		single dose not exceeding 0.10	Acute attacks of lymphangitis stopped or diminished in frequency
Paterson (110)	not certain	not certain	In 1 case of lymphadenitis no relapse 12 months since treatment (total dos. 0.2 gm.)
Hawking (66)	10	0.6-2.3	No effect on microfilariae

if not more effective therapeutic action. For the same reason, tartar emetic has often been used as a measure of comparison for other antimonials.

c. Analogues to tartar emetic

A series of preparations in which the potassium of tartar emetic was replaced by other metals or complexes has been tried in human filariasis. These preparations and their toxicity relative to tartar emetic as expressed in minimal lethal doses (intravenous injection) for mice are given in the following table (table 6) adapted from Oelkers (104) (after Fargher and Gray).

TABLE 6 [adapted from Oelkers (104)]

Drug	Formula	Sb%	Minimal lethal dose mg/kg	Content of Sb in mg.
Tartar emetic	$C_4H_4O_7SbK.1/2\ H_2O$	36.17	16	5.7
Sodium antimony tartrate	$C_4H_4O_7SbNa.1/2\ H_2O$	38.01	25	9.5
Ammonium antimony tartrate	$C_4H_4O_7NSb.1\ 1/2\ H_2O$	36.51	20	7.4
Aniline antimony tartrate	$C_{10}H_{12}O_7NSb.H_2O$	30.33	20	6
Quinine antimony tartrate	$C_{24}H_{29}O_9N_2Sb.H_2O$	19.13	150	31.0

Sodium antimony tartrate has been used chiefly by Indian investigators from 1919 on when Rogers (116) noticed a diminution of microfilariae in the blood after having injected total doses of 0.41-0.92 gm. to 8 patients. Rogers (115) reaffirmed this result in 1920 with total doses extended to 0.79-1.99 gm.

In the same year Das (38), reporting on another series of 8 cases found disappearance or diminution of microfilariae after total doses of 1.60-2.94 gm. of sodium antimony tartrate and Roy and Bose (119) had similar results in their patients. Rao (114) too, in general terms spoke of good symptomatological results from biweekly injections of 0.065-0.10 gm. of sodium antimony tartrate, although pains in the joints were markedly present. He cured one case of hydrocele after tapping and injecting 0.2 gm. of sodium antimony tartrate in 10 cc. of water into the sac. Noc (98) who did not belong to the group of Indian investigators gave a total dose of 6 mg. of the same preparation to a patient suffering from schistosomiasis in addition to filariasis, but obtained a transient effect only on the microfilariae. The British Filariasis Commission (51) tried the drug in 2 cases without positive result, recording "sickness and vomiting" in one case. It will thus be noticed that the favorable results with sodium antimony tartrate of the Indian investigators stand in contrast to the largely negative findings with tartar emetic, particularly as emphasized by Low and coworkers (81, 82). This discrepancy is not without interest in view of the fact that these two drugs have not always been distinguished in the literature (122).

Of the other preparations in this series only few trials seem to have been made. Antimony ammonium tartrate was included by O'Connor (100) among the drugs which had no effect whatsoever on circulating microfilariae. Aniline antimony tartrate was given by Thiroux (132) to 2 patients in the total amount of 0.01 gm., and although the microfilariae in the blood were diminished in number, they were not all destroyed. It was given to two patients in total doses of 0.3 gm. and 1.0 gm. respectively by the British Filariasis Commission (51) with negative result. This Commission (51) also employed quinine antimony tartrate, first without effect in a filariated dog, then in one patient (total dose 0.15 gm.) where a drop in the number of microfilariae was noted.

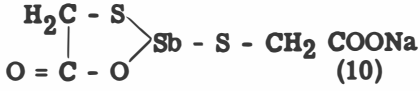
d. Trivalent antimony compounds of other aliphatic hydroxy- and mercapto-acids (anthiomaline and sodium antimony thioglycollate)

In this series, tartaric acid is replaced by other aliphatic hydroxy- and mercapto-acids. As far as employment in human filariasis is concerned, the two preparations belonging to this series are anthiomaline and sodium antimony thioglycollate.

Anthiomaline (95) is the lithium salt of stibiothiomalic acid and has the formula

$$\left[\begin{array}{l} \mathrm{Li\,O\,.\,CO\,.\,CH - S} \\ \mathrm{Li\,O\,.\,CO\,.\,CH_2} \end{array}\right]^{3} \mathrm{Sb\,.\,9\,H_2O}$$

The pharmacological properties of anthiomaline and its value in the treatment of various diseases were reviewed on the basis of current literature in a report prepared by the Office of Medical Information of the National Research Council (95). This report included observations of Poynton (113), Chopra and Rao (27) and Hawking (66). The former mentioned "a few cases" which received injections of anthiomaline into the enlarged glands and thigh muscles, injections which were less painful than similar local injections with fuadin and did not cause giddiness and vomiting. "The attacks of fever were reported reduced in number and intensity." Chopra and Rao (27) treated 7 patients with intramuscular injections of anthiomaline in doses from 180 mg. to 300 mg. twice weekly up to a total dosage of 1.8 gm. The patients reacted with pain at the site of the injection and the result of the treatment was a slight transient reduction in microfilariae. Clinically, fuadin was superior to anthiomaline. Hawking (66) used anthiomaline in 10 patients to the total dose of 0.42-1.50 gm. No marked filaricidal action was noted. Not included in the report of the National Research Council were the studies of Brown (17) who gave totals of 0.3-4.59 gm. of anthiomaline to 12 patients, in 10 of whom the microfilaria count was reduced 85-100 percent 4-7 months after the treatment (see above p. 29). Among the toxic reactions, Brown recorded vomiting accompanied by epigastric pain in 40 percent of the patients, whereas arthritic pain was experienced by one patient only, beginning after 1.71 gm. of the drug had been given. Rises in temperature and transient rashes were also met with, but none of the toxic symptoms were considered severe enough to stop further trials of this drug in filariasis.

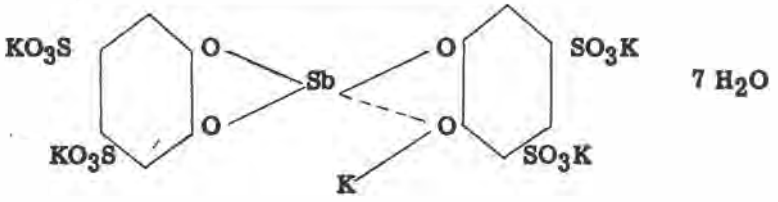
Sodium antimony thioglycollate.  (10)

According to Roy and Bose (119) it has proved "very efficacious in extirpating microfilariae." The toxicity of the drug has been studied in detail by Pak and Read (108) who found it more stable and, by comparison of the lethal dose (L D_{50}) less toxic than tartar emetic; also it was much less depressant on the circulation than tartar emetic and its chronic toxic effects in repeated injections were less pronounced.

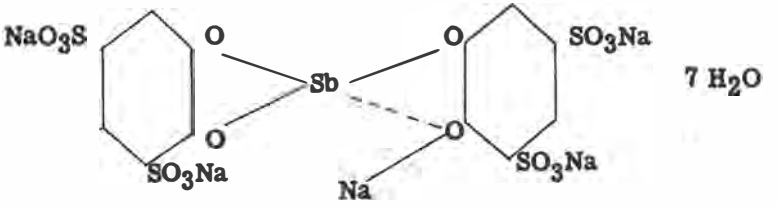
e. Antimosan and fuadin (neo-antimosan)

On the assumption that the toxic reactions of tartar emetic were due to a weak complex combination of the trivalent antimony, Uhlenhuth, Kuhn and Schmidt in 1924 attained a stronger complex formation in the potassium-antimony^{III}-bis-pyrocat-

echindisulphonate of potassium (antimosan, potassium antimosan) with the formula (122):



In experiments on mice, rabbits and dogs, antimosan proved considerably less toxic than tartar emetic, but it was not free from serious side effects, particularly on the heart and circulation. Intramuscular injection was painful, nausea and vomiting were frequent incidents, whereas coughing spells were absent (104). Since many of these untoward effects were attributed to the potassium, the latter was replaced by sodium. The new product (neo-antimosan, sodium antimosan) received the name of fuadin and has the formula (122):



Toxicity tests made with fuadin (antimosan vet.) in mice, rats and guinea pigs gave the following comparative figures. (See table 7.) In rabbits, the minimum lethal dose upon intravenous injection was 7 mg. (=2.7 mg. Sb) per kg. for tartar emetic and 80 mg. (=10.8 mg. Sb) per kg. for fuadin. In chronic poisoning the liver was the damaged organ, whereas fuadin did not exert any appreciable toxic effect upon the kidneys of these animals (122).

Khalil and Betache (75) who treated 1474 cases of bilharziasis with fuadin and 311 with tartar emetic, found the following incidence of complications after injection. (See table 8.)

Another symptom which occurs upon prolonged medication with fuadin is rheumatic pain but this too is less frequent and milder than with tartar emetic. Even over-dosage up to 0.897 cc. per kg. body weight in human individuals only led to transient weakness in 2 cases and, in addition, nausea and vomiting in one case (122). However, these data are contradicted in some cases of filariasis. The experience with the treatment of heart

TABLE 7 [adapted from Schmidt and Peter (122)]

	Dose of fuadin in cc. (6.3% solution)	Containing Sb in mg.	Mortality %
Mice	5	42.5	22
	10	85.0	55
	15	127.5	60
	25	212.5	100
	50	425.0	100
Rats	2	17.0	0
	3	25.5	0
	5	42.5	60
	10	85.0	60
Guinea pigs	1	8.5	0
	2	17.0	0
	3	25.5	0
	5	42.5	40
	10	85.0	40
	20	170.0	60

TABLE 8 [from Khalil and Betache (75)]

Symptoms	Tartar emetic	Fouadin
Nausea	1.6 per cent.	0.0 per cent.
Vomiting	3.8 " "	0.36 " "
Dizziness	0.64 " "	0.018 " "
Cough	9.64 " "	0.0 " "
Abscess	5.3 " "	0.13 " "
Local induration	2.4 " "	0.0 " "

worm in dogs had shown that fuadin, in order to be effective, had to be administered in high doses. The dogs seemed to tolerate such treatment if no disease of the liver and kidney were present. But Hawking (66) who, in 7 cases of human filariasis, pressed the course up to a total dosage of 8.5-59.5 cc. observed vomiting, diarrhoea, fever, nausea, papular rash, stomach pain and articular pains. In two of his patients vomiting was so severe that the administration of fuadin had to be stopped. Besides, the occurrence of sudden death (in schistosomiasis and multiple sclerosis) suggests that cumulative action or a predisposing factor may make the drug dangerous.

The therapeutic action of both antimosan and fuadin in human filariasis is indicated by the summary presented in the following table. (See table 9.)

f. Trivalent antimony complex salts of oxyquinolinesulphonic acid (stibilase and trystibine)

This series comprises stibilase and trystibine, both of which

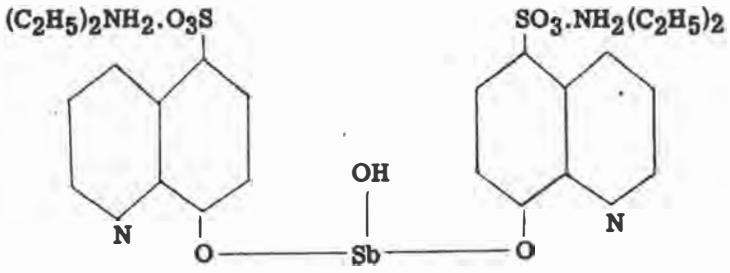
TABLE 9

ANTIMOSAN AND FUADIN IN HUMAN FILARIASIS

Author	No. of patients treated	Total dosage	Remarks
Antimosan			
Peter (122)	25	not stated	Temporary disappearance of Mf. from blood.
Chopra and Rao (28)	3	60 cc.	Severe toxic reaction; no effect on Mf.
Fuadin			
Paterson (110)			No clinical improvement
Brug and de Rook (122)			Diminution of Mf.
Haran y Talice (122)	1		Chyluria disappeared
Chopra and Rao (27)	14	80 cc.(i.v.)	Gastritis, enteritis; temporary reduction of Mf.
Poynton (113)	160	not stated	Injection into inguinal glands (very painful) or surrounding muscles
Hawking (66)	7	8.5-59.5 cc. (i.m.)	Severe toxic reactions; diminution of Mf.

have been tried by Chopra and Rao (27) in human filariasis.

Stibilase (Dn 7) is the diethylamine salt of antimony oxyquinoline sulphonate (122) to which the following formula (10) has been assigned:



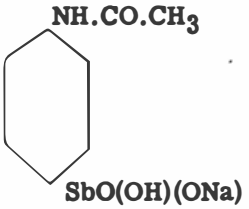
It was given (27) intravenously to 6 patients in a total dosage of 1 gm. and effected a temporary reduction of microfilariae. It proved highly toxic causing fever and articular pains, and the individual dose could not be tolerated at an amount higher than 0.10 gm. The same experiences as to dosage, toxicity and therapeutic effect were obtained in 6 patients treated with trystibine (27).

Trystibine (Dn 18) is antimony amino-methylenebisulphite oxyquinoline sulphonate of sodium. Its formula apparently has not been ascertained.

g. Quinquevalent antimony compounds and solustibosan

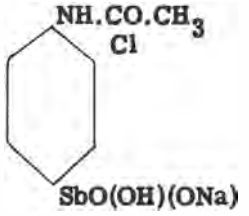
With the exception of solustibosan, the quinquevalent antimony compounds to be discussed here are derivatives of 4-aminobenzenestibonic acid. Solustibosan, according to Schmidt and Peter (122) is a quinquevalent antimony compound of hexonic acid. With the exception of neostibosan, they have been used relatively little in the treatment of human filariasis, and neostam is only being included because of the good results Culbertson and Rose obtained with this drug in the cotton rat (cf. above p. 26). For this reason it seems appropriate first to comment on their toxic action and then give their therapeutic effect in human filariasis in tabulated form.

Stibenyl (stibacetin) is the p-acetylaminophenylstibinate of sodium (38.5 % Sb) and its formula (104) is:



Administered perorally to dogs of 5 kg. body weight it caused vomiting from about 2.5 gm. on. In man 2 gm. distributed over 8 days could be tolerated relatively well (104, 122) but vomiting, rise of temperature, disturbances of the circulation and even death have been reported too (104). The isomere of stibenyl, m-acetylaminophenylstibinate of sodium is supposed to be chemically more stable, but therapeutically less effective. Its minimum lethal dose in mice is 0.2 gm. per kg. (51).

Stibosan (471) is the m-chlor-p-acetylaminophenylstibinate of sodium (30 % Sb) and its formula (104) is:



In rabbits the toxic dose upon intravenous injection is about 0.12 gm. per kg. body weight; and in man vomiting and jaundice have been noted with this drug which is assumed to be more toxic than stibenyl (104).

Neostibosan (693 B). The unsatisfactory side effects of the

above drugs (104) led to the preparation of compound 693, the para-aminophenylstibinate of diethylamine with the formula (10):

"The defects of the preparation (toxicity and insufficient stability) were removed by modifications of the complex chemical and colloidal chemical structure; the result of this chemical modification was the preparation 693 B" (122) i.e. neostibosan (42% Sb) (122). Neostibosan, injected into a rabbit's ear subcutaneously did not provoke tissue reactions. In the dog (5.78 kg.), only very high doses (total of 2.78 gm.) caused damage to the liver (104). The relatively low toxicity of neostibosan is shown by comparison with some other antimony compounds. Thus the tolerated dose per 20 gm. mouse was (subcutaneous injections) (104):

Tartar emetic	(36.6 % Sb)	0.4 mg. = 0.15 mg.	Sb^{III}
Antimosan	(12.5 % Sb)	6.0 mg. = 0 75 mg.	Sb^{III}
Stibosan	(30.0 % Sb)	15.0 mg. = 4.65 mg.	Sb^{V}
Neostibosan	(42.0 % Sb)	40.0 mg. =16.8 mg.	Sb^{V}

Basu (11) studied the action of neostibosan and ureastibamine on the heart of frogs by a perfusion method. Neostibosan was non toxic in concentrations of 4.5 mg. percent, 7 mg. percent, 9 mg. percent and 13 mg. percent, i.e. far beyond usual human doses. Ureastibamine, with a concentration of 0.5 mg. percent caused slight augmentation of the heart beat; with 1.0 mg. percent the augmentation was more pronounced while the frequency was slowed. With 3.8 mg. percent temporary augmentation was followed by depression and 4.5 mg. percent produced marked toxic symptoms.

The observations of Struthers et al. (129) are interesting as regards the relative toxicity of neostam and neostibosan in human adults (59 patients and 135 respectively). They tabulated their findings as follows:

TABLE 10 [from Struthers et al. (129)]

	Fever	Nausea	Vomiting	Cough	Lymph-adenitis	Headache
Neostam	39 per cent	27 per cent	24 per cent	15 per cent	5 per cent	15 per cent
Neostibosan	10 per cent	6 per cent	5 per cent	8 per cent	3 per cent	0 per cent

Neostam (stibamine glucoside) is the nitrogen glucoside of p-aminophenylstibinate of sodium (about 30 % Sb) (122). Napier (92) in 1929 remarked on the "particularly low" relative toxicity of this compound and stated that a dose of 10 gm. had never killed more than half the mice to which it was administered. Yet the above quoted data of Struthers et al. (129) (see table 10) seem to indicate that in view of toxicity, neostibosan is superior to neostam.

Urea-stibamine, Stiburea, Novostiburea. The product obtained by the action of urea upon p-aminophenylstibinic acid became known as urea-stibamine. Its composition is not certain (it may even be a mixture of different compounds) (122) and its antimony content varies. In guinea pigs, the lethal dose with intramuscular injection is given as 0.7 gm. per kg. and the tolerated dose as 0.35 gm. per kg. (104). In man, intravenous injection of up to 0.4 gm. is supposed to be well tolerated, whereas nausea and vomiting were observed regularly with 0.5 gm. Besides vomiting, diarrhoea and even collapse are among the toxic reactions of this drug (104). Stiburea and novostiburea (sodium salt) are preparations the composition of which is believed to be similar to that of urea-stibamine (104, 122).

Solustibosan (Sdt. 561), an antimony hexonate, has been in use since 1937. One cc. of the solution contains 20 mg. Sb.(122). In rabbits, intracutaneous, intramuscular and intravenous injections were tolerated without local irritation. The minimal lethal dose in mice was 28.5 cc. (= 570 mg. Sb) per kg. upon intravenous injection, and in rabbits it was 20 cc. (= 400 mg. Sb) per kg. (122). In patients suffering from multiple sclerosis, chronic epidemic encephalitis, or tabes, total doses up to 480 cc. (= 9.60 gm.) showed no by-effects, although in some cases 10 cc. of the drug were injected daily towards the end of the treatment. Neither albumen nor increase in urobilinogen was observed in the urine, nor were any rheumatic pains present (122).

h. Miscellaneous antimony compounds

The following represents a short résumé of some other antimonials used in the treatment of human filariasis.

Colloidal antimony. Roy and Bose (119) injected colloidal antimony intravenously to a total amount of about 97 cc. in 4 cases. No effect was obtained in 3 patients, whereas in the fourth the microfilariae disappeared for an unknown length of time since the case could not be followed up. The British Filariasis Commission (51) administered "oscol" stibium (strength of metal 1 in 2000) intramuscularly to 8 patients in total doses of 4 cc.-21 cc. Except in one case, the microfilariae were not markedly affected. But the clinical condition was improved in several cases, while in one case treatment had to be discontinued

TABLE 11

QUINQUEVALENT ANTIMONY COMPOUNDS IN HUMAN FILARIASIS

Drug and Authors	Total no. of patients	Total dosage	Remarks
Stibenyl			
O'Connor (100)	not stated	not stated	No effect upon microfilariae
Brit. Fil. Comm. (51)			
p.-stibacetin	1	3.51 gm. i.v.	Sickness and vomiting. Drop in Mf.
m.-stibacetin	2	0.59 and 0.88 gm. i.v.	No effect on Mf.
Stibosan			
Chopra and Rao (28)	5	3 gm. i.v.	Severe reaction. No effect on Mf.
Neostibosan			
Chopra and Rao (28)	2	2.1 gm. i.v.	Fever. No effect on Mf.
Sherwani (124)	1	2.94 gm. i.v.	Chyluria; urine cleared completely.
Chopra and Rao (27)	10	3 gm. i.v.	Temporary reduction of Mf.
Culbertson et al. (146,147)	30		13 patients cured. Slight side effects.
Urea-stibamine			
Rao (114)	not stated	not stated	Less toxic than sodium antimony tartrate.
Stiburea			
Chopra and Rao (28)	6	3 gm. i.v.	Slight reaction. No effect on Mf.
Novostiburea			
Chopra and Rao (28)	6	3 gm. i.v.	" " "
Solustibosan			
Chopra and Rao (27)	4	87 cc. i.m.	Temporary reduction of Mf.

because of the discomfort of the injections (local pain and swelling).

Colloid antimony sulphide. Rogers (116) treated two patients with "1 in 500 colloid antimony sulphide" in total doses of 22 cc. and 22.5 cc. without effect upon the microfilariae.

Antimony sulphur compound. A soluble compound "containing antimony and sulphur in organic combination" was given by Chopra and Rao (28) to 2 patients intravenously in total amounts of 1.7 gm. and 3 gm. without effect upon the microfilariae.

"A 534" is stated to contain antimony in quinquevalent form, the solution containing 26 percent Sb and being without toxic reaction upon intramuscular injection. Chopra and Rao (27) gave it to 4 patients in total dosage of 87 cc. and obtained a temporary reduction of microfilariae.

Arsant according to Hawking (66) is "a compound of the salvarsan type, in which one of the arsenic molecules is replaced by antimony." This author administered the drug intravenously to 2 patients in total dosages of 2.4 gm. and 3.0 gm. The treatment resulted in a slight reduction of microfilariae.

After this relatively detailed discussion of antimonials, a summary of several groups of other drugs used in human filariasis follows in tabulated form. These tables which indicate the variety of drugs tried are merely to be considered as an appendix. In most cases the names used by the authors have been given without any attempt at identification of the compound.

2. ARSENICALS (TABLE 12)

Drugs and Authors	Total no. of patients	Total dose	Remarks
"Oscol" arsenium (colloidal preparation of 1:2000)			
Brit. Fil. Comm. (51)	3		No effect.
Arsaminol (Jap. arsphenamine)			
Ikegami (70)	1	0.6 gm.	Chyluria cleared.
Arsiminol (=Arsaminol?)			
Chopra and Rao (27)	2	12 cc. i.m.	Fever, pain in the loins; no effect on Mf.
Salvarsan			
Noc (98)			No results.
Eparseno ("amino-arséno-phénol")			
Noc (98)	3	1.2-18 mg.	Transient effect on Mf.
Kharsivan (substitute for arsphenamine hydrochloride)			
O'Connor (100)			No results.
Neoarsphenamine (neosalvarsan, novarsenobillon)			
Mühlens (90)			Occasional good effects believed due to chance.
O'Connor (100)			No results
Paterson (110)			No results
Chopra and Rao (27)	9	2 gm. i.v.	No effect on Mf., but clinically beneficial in attacks of fever and inflammation.
Hawking (66)	1	3.15 gm.	No marked influence on Mf.
Sulfarsphenamine			
Chopra and Rao (27)	4	1.4 gm. i.v.	Fever; no effect on Mf. but improvement of attacks of fever and inflammation.
O'Connor (99)	20	up to 0.8 gm. locally	Injections of 0.2 gm. in 2 cc. of 1% novocaine were made into focal spot 1-4 times. 18 patients had no recurrence of lymphangitis about half a year after treatment. But similar results with subcutaneous injections of serums!
Sulfarsenol (brand of sulfarsphenamine)			
Chopra and Rao (27)	12	2 gm. i.v.	No effect on Mf., but good clinical effect on attacks of fever and inflammation.

ARSENICALS (CONTINUED)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Hectine (=sodium benzosulfoparaminophenylarsenate)			
Tanon and Giraud (131)	3	0.1 gm. (?) subcutaneously	Cure (blood normal, fever and other symptoms disappear).
Galyl (= tetraoxydiphosphaminodiarsenobenzene)			
O'Connor (100)	?	?	No result.
Atoxyl			
Bahr (9)	2	0.13 gm.	No effect on Mf.
Soamin (= sodium paraaminophenylarsonate)			
Brit. Fil. Comm. (51)	3	(1.07-2.21 gm.) i.m.	No effect on Mf.
Chopra and Rao (27)	28	1.3 gm. subcutaneously	No effect on Mf., but good clinical effect on attacks of fever and inflammation.
Arsylene 'Roche' (= equivalent to soamin?)			
Chopra and Rao (27)	15	24 cc. i.m.	No effect on Mf.
Acetylarsan (= diethylamine-3-acetylamino-4-hydroxyphenylarsonate)			
Hawking (66)	1	9 cc.	Slight diminution of Mf.
Stovarsol (brand of acetarsone = acetylamino-hydroxy-phenylarsonic acid)			
Chopra and Rao (27)	5	5.2 gm. orally	No effect.
Carbarsone (= para-carbamino-phenyl-arsonic acid)			
Chopra and Rao (27)	20	5.0 gm. orally	No effect on Mf. or clinically.
Tryparsamide (= sodium salt of normal phenylglycinamide-para-arsonic acid)			
Chopra and Rao (28)	12	12 gm. i.v.	No effect on Mf; but cleared urine in chyluria, checked attacks of lymphangitis for 1 year and more.
Espundal			
Hawking (66)	1	2 gm. i.v.	Slight diminution of Mf.

ARSENICALS (CONTINUED)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Mapharsen King (76)	38	0.16 gm.	In 3 cases lymphangitis after injection; exacerbation of epididymitis 24 hours after injection.
Van der Sar and Hartz (134)	1		Tropical eosinophilia; striking clinical improvement.

3. MERCURY COMPOUNDS (TABLE 13)

Drugs and Authors	Total no. of patients	Total dose	Remarks
"Oscol" hydrargyrum (colloidal preparation, 1:2000) Brit. Fil. Comm. (51)	5		No effect.
Mercurochrome Chopra and Rao (28)	3		No effect on Mf.
Mercury succinimide Brit. Fil. Comm. (51)	2	0.14 and 0.30 gm. i.v.	Abdominal pain and slight diarrhoea in one case; Mf. disappeared in one case. One dog of 6 kg. died 90 hours after 0.065 gm. i.v.; autopsy showed extensive necrosis of liver, hyperemia of lungs, liver, kidney (also destruction of tubular epithelium) and stomach.
Liquor Hydrarg. perchloride (solution 1 in 1000) Brit. Fil. Comm. (51)	1	10 cc.i.v.	Case of general septicaemia; gradual improvement, Mf. disappeared.
Mercury cyanide Poynton (113)	3	4 cc.-8 cc.	Injection into enlarged glands resulted in marked improvement regarding frequency of febrile attacks. - Intravenous injection less effective.
Salyrgan Chopra and Rao (27)	5	20 cc. i.m.	No effect on Mf.
Novasurol Chopra and Rao (27)	4	20 cc. i.m.	No effect on Mf.

4. COPPER COMPOUNDS (TABLE 14)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Collosol of copper O'Connor (100)			No effect.
"Oscol" cuprum (colloidal preparation 1:2000) Brit. Fil. Comm. (51)	2		No effect.
Copper Glycine Brit. Fil. Comm. (51)	1	0.20 gm. i.v.	Headaches; no effect on Mf.
Cuprochin Chopra and Rao (27)	6	6.5 gm. i.v.	No effect on Mf.
Cuprion Chopra and Rao (27)	10	0.15 gm. i.m.	Pain at site of injection; no effect on Mf.
Sdt. '242' Copper in oil Chopra and Rao (27)	3	10 cc. i.m.	Pain at site of injection; no effect on Mf.

5. ZINC COMPOUNDS (TABLE 15)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Sdt. '409' Chopra and Rao (27)	2	0.13 gm. i.m.	Pain at site of injection; no effect on Mf.
Sdt. '322' Chopra and Rao (27)	2	0.13 gm. i.m.	Pain at site of injection; no effect on Mf.

6. TIN COMPOUNDS (TABLE 16)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Sodium stannitartrate Brit. Fil. Comm. (51)	1	1.27 gm. i.v.	No results.
Tin complex salt Chopra and Rao (27)	2	0.13 gm. i.m.	Pain at site of injection; no effect on Mf.
Stannoxyl (protochloride of tin in glycerine) Brit. Fil. Comm. (51)	1		Used externally on ulceration. Ulcer healed; Mf. not affected.

7. BISMUTH COMPOUNDS (TABLE 17)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Bisnene (urea compound of p.-amino-phenyl bismic acid) Chopra and Rao (28)	7	2.7 gm. i.v.	Slight reaction; no effect on Mf.
Bivatol Chopra and Rao (27)	3	10 cc. i.m.	Pain at site of injection; no effect on Mf.
Bismostab Chopra and Rao (27)	5	10 cc. i.m.	Pain at site of injection; no effect on Mf.
Troken Amp. Chopra and Rao (27)	2	0.13 gm. i.m.	Pain at site of injection; no erfect on Mf.
S.W. 277 Chopra and Rao (27)	2	0.13 gm. i.m.	Pain at site of injection; no effect on Mf.

8. LEAD AND SILVER COMPOUNDS (TABLE 18)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Sdt. '302' Chopra and Rao (27)	2	0.13 gm. i.m.	Pain at site of injection; no effect on Mf.
"Oscol" argentum (strength of metal 1:2000) Brit. Fil. Comm. (51)	3		No results

9. GOLD COMPOUNDS (TABLE 19)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Solganal B Neuber (96)	2		Good effect on local symptoms and attacks of fever. One case cured in combination with malaria therapy.
Chopra and Rao (27)	12	3-6 gm. i.m.	No effect on Mf.
Crisalbine Chopra and Rao (27)	2	1.5 gm. i.v.	Fever; no effect on Mf.

10. MANGANESE COMPOUNDS (TABLE 20)

Drugs and Authors	Total no. of patients	Total dose	Remarks
"Oscol" magnesium (strength of metal 1:2000) Brit. Fil. Comm. (51)	4		No effect.
Manganese collosal O'Connor (100)			No effect.

11 CHROMIUM, MOLYBDENUM, THORIUM, VANADIUM COMPOUNDS (TABLE 21)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Sodium chromate Brit. Fil. Comm. (51)	1	0.20 gm. i.v.	Vomiting, nausea; lymphangitis during treatment; no effect on Mf.
Sodium molybdate Brit. Fil. Comm. (51)	1	1.61 gm. i.v.	No effect. "Singing in the ears."
Thorium sulphonate Brit. Fil. Comm. (51)	1	3 mg. i.v.	No effect on Mf.
Sodium Vanadate Brit. Fil. Comm. (51)	1	0.26 gm. i.v.	Vomiting, diarrhoea; no therapeutic effect.

12. SULFONAMIDE COMPOUNDS AND SULFONES (TABLE 22)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Rubiazol			
Floch (53)	8	40 tablets	Clinical cure of recurrent lymphangitis.
Montestruc et Bertrand (89)	1		Attacks of lymphangitis improved by rubiazol and septazine.
Proseptasine (and septazine)			
Berny et Gippet (13)	12	up to 68 tablets	Attacks of lymphangitis improved, stopped or prevented.
Advier (3)		6 gm.	Improvement of febrile attacks, but no prevention of recurrence.
Chopra and Rao (27)	12	15 gm.	No effect on Mf.
Donovan (39)	1	8 tablets	Lymphopathy disappeared.
Soluseptasine			
Chabeuf (24)	6	5-20 cc. i. v. plus 1-11 gm. of septazine orally	Attacks of lymphangitis stopped.
Chopra and Rao (27)	5	100 cc. i.m.	No effect on Mf.
Prontosil			
Chopra and Rao (27)	18	15 gm.orally	No effect on Mf.
Prontosil soluble and Prontosil album			
Hawking (66)	1	70 cc. i.m. 21 gm.orally	No effect on Mf.
Sulfanilamide			
Hawking (66)	7	18-90 gm.	No effect on Mf.
Sulfapyridine			
Earle (46,47)			Good effect on secondary infections; no diminution of Mf.
Sulfathiazole			
Glauser (56)	56		No result.
King (76)	3		No apparent effect in severe cases with fever.
King (76)	4		Developed acute lymphangitis while receiving sulfathiazole or sulfadiazine for treatment of gonorrhea.
Sulfadiazine			
Englehorn and Wellman (49)			No appreciable benefit in lymphangitis.
4:4' - diamino-diphenyl-sulfone glucoside			
Hawking (66)	1	81 gm.orally	Slight diminution of Mf.

13. IODINE COMPOUNDS (TABLE 23)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Iodine (solution in Pot. iodide and water, 0.08 gm. iodine per minim of solution) Roy and Bose (119)	2	1 gm. i.v.	No effect on Mf.
Pot. iodide Chopra and Rao (27)	10	19.5 gm.	No effect on Mf.
Yatren Chopra and Rao (27)	6	32.5 gm. orally	No effect on Mf.
Abrodil Chopra and Rao (27)	5	10 cc. i.v.	No effect on Mf.
Per-abrodil Chopra and Rao (27)	4	10 cc. i.v.	No effect on Mf.
Uroselectan B. Chopra and Rao (27)	6	20 cc. i.v.	No effect on Mf.
Entero-vioform Chopra and Rao (27)	6	0.75 gm. orally	No effect on Mf.

14. ANTHELMINTICS (TABLE 24)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Thymol			
Roy and Bose (119)			Coughing and fever after injections. Slight reduction of Mf. in one case after total of 3.5 gm.
Chopra and Rao (27)	5	2.73 gm. orally	No effect on Mf.
Carbon tetrachloride			
Adler (2)	4	2.5 cc.-5.6 cc. i.v.,i.m.	Coughing and sleepiness on i.v. injection. No effect on Mf.
Chopra and Rao (27)	10	1 cc. orally	No effect on Mf.
Tetrachlore ethylene			
Chopra and Rao (27)	9	1 cc. orally	No effect on Mf.
Santonin			
Chopra and Rao (27)	2	0.39 gm. orally	No effect on Mf.
Sodium santoninate ($2NaC_{15}H_{19}O_4$, $7\ H_2O$)			
Brit. Fil. Comm. (51)	1	1.17 gm. i.v.	No effect.
Oil of chenopodium			
Phelps et al. (111)	338	up to 15.30 cc. and more i.m.	Severe pain and swelling at site of injections; general reactions similar to filarial fever; general improvement of patients and reduction of attacks of lymphangitis.
Chopra and Rao (27)	12	10-15 cc. i.m.	Pain at site of injection; slight reduction of Mf.

15. EMETINE AND OTHER VEGETABLE AND ANIMAL DRUGS (TABLE 25)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Emetine			
Mühlens (90)			Good result in one case; no effect in others.
Chopra and Rao (28)	8	0.39 gm. i. v. and hypo.	No effect on Mf.
Hawking (66)	1	0.78 gm. i.m.	No effect on Mf.
O'Connor (100)			No effect.
Emetine hydrochloride			
Brit. Fil. Comm. (51)	3	0.52-0.78 gm. hypo.	Nausea; slight collapse in 1 case; no effect on Mf., but improvement in 2 cases of chyluria.
Low and O'Driscoll (82)	1	0.78 gm.	No effect on Mf.
Chopra and Rao (27)	6	0.39-0.78 gm. i.m.	Pain at site of injection; no effect on Mf.
Simaruba			
Mühlens (90)			Good effect believed due to chance.
O'Connor (100)			No effect.
Sodium margosate			
Roy and Bose (119)	1	0.36 gm. i.m.	Fever and vomiting after each injection; no therapeutic effect.
Kurchi Extract Liquid			
Chopra and Rao (27)	6	248.82 gm. orally	No effect on Mf.
Caesalpina bonducella			
Chopra and Rao (27)	4	4 nuts orally	No effect on Mf.
Extract Lodh Liquid			
Chopra and Rao (27)	5	373.24 gm. orally	No effect on Mf.
Berberine sulphate			
Chopra and Rao (27)	6	1 gm. i.m.	Pain at side of injection; no effect on Mf.
Oil Hydnocarpus			
Chopra and Rao (27)	6	100 cc. i.m.	No effect on Mf.
Cobra venom			
Chopra and Rao (27)	6	500 mouse units hypo.	No effect on Mf.
Viper venom			
Chopra and Rao (27)	6	200 mouse units hypo.	No effect on Mf.

16. ANTIMALARIAL DRUGS (TABLE 26)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Quinine hydrochloride			
Bahr (9)	1	0.325 gm.i.v.	No effect on Mf.
O'Connor (100)			No effect.
Chopra and Rao (27)	6	4.55 gm. i.m.	No effect on Mf.
Quinine and acid salicylic			
Chopra and Rao (27)	2	3.25 gm. i.m.	No effect on Mf.
Cinchona febrifuge			
Chopra and Rao (27)	10	9.75 gm. oral.	No effect on Mf.
Plasmochin			
Chopra and Rao (28)	6	0.38 gm. oral.	No effect on Mf.
Chopra and Rao (27)	4	0.25 gm. oral.	No effect on Mf.
Plasmochin Simplex			
Chopra and Rao (27)	4		No effect on Mf.
Atebrin			
Chopra and Rao (27)	6	1.5 gm. oral.	No effect on Mf.
Atebrin Musonate			
Chopra and Rao (27)	5	1 gm. i.m.	No effect on Mf.
Tebetrin			
Chopra and Rao (27)	4	1 gm. oral.	No effect on Mf.
Malarcan			
Chopra and Rao (27)	5	1 gm. oral.	No effect on Mf.
Gametoxan			
Chopra and Rao (27)	6	1 gm. oral.	No effect on Mf.
Cilional			
Chopra and Rao (27)	6	1.10 gm. oral.	No effect on Mf.

17. PICRIC ACID AND GENTIAN VIOLET (TABLE 27)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Picric nitrate of potash			
Scheube (121)	1		Hemato-chyluria cleared; number of Mf. decreased.
Picric acid preparation			
Sugáruma (130)			Effective in chyluria; number of Mf. decreased.
Gentian violet			
Ashford and Snyder (4)	13	4.10-9.55 gm. orally	Decrease in Mf. count.
Chopra and Rao (27)	2	20 cc. (2%) i.m.	Pain at site of injection; no effect on Mf.

18. MISCELLANEOUS DRUGS (TABLE 28)

Drugs and Authors	Total no. of patients	Total dose	Remarks
Sodium phenylselenonate Brit. Fil. Comm. (51)	1	0.59 gm. i.v.	No effect on Mf.
Hexamine (combined with acid sod. phosphate) Brit. Fil. Comm. (51)	2		Cleared chyluria; no effect on Mf.
Congo-red Chopra and Rao (27)	2	35 cc. (1%) i.v.	No effect on Mf.
Paludex Chopra and Rao (27)	6	4.88 gm. oral.	No effect on Mf.
Quino-paludex Chopra and Rao (28)	6	4.88 gm. oral.	No effect on Mf.
Bayer 205 Chopra and Rao (28)	2	2.75 gm. i.v.	Slight reaction; no effect on Mf.
Rivanol Chopra and Rao (27)	2	20 cc. (5%) i.m.	Pain at site of injection; no effect on Mf.
Trypaflavine Chopra and Rao (27)	4	35 cc. (3%) i.v.	No effect on Mf.
Surfen Chopra and Rao (27)	6	10 cc. (1%) i.m.	Pain at site of injection; no effect on Mf.
Atophan Chopra and Rao (27)	2	5.85 gm. oral.	No effect on Mf.
Caprokol Chopra and Rao (27)	5	3.75 gm. oral.	No effect on Mf.
Sodium mandelate Chopra and Rao (27)	4	4 days' course oral.	No effect on Mf.
'A 539' Chopra and Rao (27)	10	1 gm. i.v.	No effect on Mf.

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