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## THE CONTROL OF FILARIASIS WITH HETRAZAN

### A FIELD TRIAL IN A RURAL VILLAGE (KENEBA) IN THE GAMBIA

BY

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During the last three years the interrelationships and relative importance of parasitization and nutritional deficiency as factors in the causation of ill-health and low capacity for performance among Gambian villagers have been investigated by members of the M.R.C. Human Nutrition Research Unit, in collaboration with the Gambia Government Medical Department. This investigation has involved, among other things, the making of detailed surveys in the village of Keneba, in the West Kiang District of the Gambia Protectorate. The general plan of this work, and the results of the base-line survey, have already been reported (McGregor and Smith, 1952). In Keneba, after the initial surveys, measures were instituted to control or eliminate the major parasitic diseases prevalent in the area. As part of this work, an attempt was made to control filariasis on a village scale by the use of hetrazan (diethyl-carbamazine). The present paper is concerned only with the results of the hetrazan trial. The general effect of control measures on health and performance of the population will be reported later. The treatment was directed primarily against microfilariae of *Wuchereria bancrofti*, but, as some of the people with this infection also carried microfilariae of *Acanthocheilonema perstans*, some information was gained concerning the effect of the drug on the latter parasite also.

#### Methods

Blood for enumeration of microfilariae was taken by finger-prick between the hours of 9 p.m. and midnight. It was spread thickly over a measured area of slide marked by grease pencil. The amount of blood required to cover

the marked area had previously been found by measurement to be approximately 20 c.mm. It is to this volume of approximately 20 c.mm. that all microfilaria counts are referred in this paper. The thick films were dehaemoglobinized, fixed in methyl alcohol, and stained with haemalum.

The dosage of hetrazan chosen was 25 mg. base per kg. of body weight given in five equal daily doses—that is, 5 mg. per kg. daily for five days. This dosage was based on results reported by the East African Filariasis Research Unit (1950), and seemed to be the smallest dosage likely to remove most of the microfilariae permanently. Tablets of hetrazan citrate were used, each tablet containing 250 mg. of the salt, equivalent to 125 mg. of the base. One of us invariably saw that the prescribed dose was actually swallowed. The occurrence of unpleasant effects attributed to the drug was recorded and investigated, but no attempt was made to question individuals who did not themselves complain.

#### Incidence of Filariasis

The total population of Keneba is 710. In February, 1951, the night blood of the 603 persons present at that time in the village was examined. It was found that 118 were infected with *W. bancrofti* alone, 101 were infected with *A. perstans* alone, and 102 carried microfilariae of both parasites; thus, in all, there were 220 cases of *W. bancrofti* infection and 203 of *A. perstans*. The age and sex distribution of these infections is summarized in Table I, and has

TABLE I.—Age and Sex Incidence of Filariasis in Keneba Villagers Before Treatment (February, 1951)

| Age Group (Years) | Male         |                          |                         | Female       |                          |                         |
|-------------------|--------------|--------------------------|-------------------------|--------------|--------------------------|-------------------------|
|                   | No. Examined | No. having Mf. bancrofti | No. having Mf. perstans | No. Examined | No. having Mf. bancrofti | No. having Mf. perstans |
| 0-10              | 93           | 10 (11%)                 | 7 (8%)                  | 83           | 13 (16%)                 | 5 (6%)                  |
| 11-20             | 83           | 33 (40%)                 | 39 (47%)                | 69           | 23 (33%)                 | 14 (20%)                |
| 21-30             | 35           | 19 (54%)                 | 19 (54%)                | 63           | 28 (44%)                 | 21 (33%)                |
| 31-40             | 35           | 19 (54%)                 | 25 (71%)                | 55           | 33 (60%)                 | 23 (42%)                |
| 41-50             | 18           | 9 (50%)                  | 10 (56%)                | 29           | 12 (41%)                 | 17 (59%)                |
| Over 50           | 19           | 9 (47%)                  | 11 (58%)                | 21           | 12 (57%)                 | 12 (57%)                |
| Total             | 283          | 99 (35%)                 | 111 (39%)               | 320          | 121 (38%)                | 92 (29%)                |

been discussed in the communication already quoted (McGregor and Smith, 1952). In the course of repeated clinical examinations during the previous year, three individuals were found suffering from elephantiasis and three had hydroceles. This gives a total incidence of such filarial sequelae of less than 1%.

It was our original intention to treat all the 220 persons found to be carrying microfilariae of *W. bancrofti*. In effect, 22 individuals were treated with another drug and 17 were not available in the village at the time the treatment was started; thus 181 persons began the course and 171 completed it. Of these, 164 were present in the village at the time of re-examination in December, 1951, 10 months after treatment, when, in all, 569 people were examined.

#### Results

(a) *W. bancrofti*.—Of the 154 infected persons who completed the prescribed course of treatment, 99 (64%) had blood free of microfilariae 10 months later (Table II). In the remaining 55 patients infection was still present, but the parasitaemia was substantially reduced; before treatment the sum of the microfilaria counts in the films of these 55 patients was 2,859, whereas 10 months later it was 305, a reduction of 89%. The overall reduction of microfilariae in the 154 infected and treated persons was 94% (5,131 in February; 305 in December). In the group of 10 cases in which treatment was incomplete and in which dosage varied from 5 to 15 mg. per kg., total elimination of microfilariae was achieved in two cases only; the remaining eight subjects showed a considerable reduction (80%)

TABLE II.—Incidence and Density of *Microfilariae* in the Blood of Persons Treated with Hetrazan, Before and Ten Months After Treatment, and of Persons Untreated

|  |                                  | Examina-<br>tion of<br>February,<br>1951 | Examina-<br>tion of<br>December,<br>1951 | Percentage<br>Change |
|--|----------------------------------|--|--|----------------------|
| <i>W. bancrofti</i> . Persons present on both occasions who: |                                  |  |  |                      |
| Originally positive  | (a) received 25 mg. per kg.      |  |  |                      |
|  | No. positive ..                  | 154                                      | 154                                      |                      |
|  | No. positive ..                  | 154                                      | 55                                       | 64.3% cleared        |
|  | Sum of mf. in all positive films | 5,131                                    | 305                                      | 94.0% reduction      |
|  | (b) received 5-15 mg. per kg.    |  |  |                      |
|  | No. positive ..                  | 10                                       | 10                                       |                      |
| No. positive ..  | 10                               | 8  | 20% cleared                              |                      |
| Sum of mf. in all positive films                             | 691                              | 141                                      | 79.6 reduction                           |                      |
| Originally negative  | (c) received no treatment        |  |  |                      |
|  | No. positive ..                  | 299                                      | 299                                      |                      |
|  | No. positive ..                  | 0  | 26                                       | 8.7% new infections  |
| <i>A. perstans</i> . Persons present on both occasions who:  |                                  |  |  |                      |
| Originally positive  | (a) received 25 mg. per kg.      |  |  |                      |
|  | No. positive ..                  | 69                                       | 69                                       |                      |
|  | No. positive ..                  | 69                                       | 19                                       | 72.5% cleared        |
|  | Sum of mf. in all positive films | 614                                      | 51                                       | 91.7% reduction      |
|  | (b) received no treatment        |  |  |                      |
|  | No. positive ..                  | 71                                       | 71                                       |                      |
| No. positive ..  | 71                               | 48                                       | 32.4% cleared                            |                      |
| Sum of mf. in all positive films                             | 402                              | 598                                      | 48.7% increase                           |                      |
| Originally negative  | (c) received 25 mg. per kg.      |  |  |                      |
|  | No. positive ..                  | 85                                       | 85                                       |                      |
|  | No. positive ..                  | 0  | 11                                       | 13% new infections   |
|  | Sum of mf. in all positive films | —  | 19                                       | —                    |
|  | (d) received no treatment        |  |  |                      |
|  | No. positive ..                  | 247                                      | 247                                      |                      |
| No. positive ..  | 0                                | 43                                       | 17.4% new infections                     |                      |
| Sum of mf. in all positive films                             | —                                | 145                                      | —  |                      |

in the sum of microfilariae present. Among the 299 persons found uninfected in February and untreated there were, in December, 26 new infections—8.7%.

(b) *A. perstans*.—One hundred and forty people carrying microfilariae of *A. perstans* in February were again examined in December. Of these, 69 had received treatment for their associated *W. bancrofti* infection; the remaining 71 had been untreated. In the treated group, 50 were found clear of microfilariae 10 months after treatment, a reduction in incidence of 72.5%. Of the 71 untreated cases 48 remained infected. In the 19 treated patients remaining infected the level of microfilarial infection was reduced from a total of 225 in February to 51 in December, a fall of 78%, whereas in the 48 untreated subjects who remained infected the sum of microfilariae rose from 318 to 598, an 89% increase. The difference between the treated and untreated groups is highly significant ( $\chi^2=22.5$ ,  $P<0.001$ ). New infections with microfilariae of *A. perstans*, apparent for the first time in December, were found in 11 (13%) of 85 people previously negative and treated with hetrazan, and in 43 (17.4%) of the 247 untreated persons.

#### Toxicity of Hetrazan

The first doses of hetrazan were accepted eagerly by the villagers, but the incidence of disagreeable side-effects was so high that their enthusiasm rapidly diminished and it became increasingly difficult to persuade the subjects to complete the course. Many who had originally presented themselves for treatment had literally to be sought out in their dwellings, and were induced to take their later doses only after lengthy debate. In spite of all efforts, eight people refused to complete the course and received one

to three doses only; in two other cases treatment was discontinued because of persistent vomiting. Of the 181 persons treated, 45 (25%) complained spontaneously of unpleasant effects which were attributed to the drug, and many who did not actually complain looked unwell and miserable.

The following ill-effects were attributed to hetrazan (the figures in parentheses indicate the number of subjects affected and the percentage of the total number treated).

**Headache** (30=17%).—This appeared to be of general distribution. It persisted one to two days in most cases, but in eight patients it persisted throughout treatment. In most instances the heavy, stupid appearance of the sufferer suggested that the pain was of considerable severity.

**Anorexia** (18=10%).—This persisted throughout treatment in most cases.

**Nausea** (15=8%).—The duration varied from one to five days.

**Vomiting** (8=4.4%).—Onset variable, occurring after the first dose in some cases and in others only after the fourth or fifth dose. In three cases vomiting occurred within three minutes of the tablets being swallowed; presumably this was psychological in origin. In two instances, referred to above, the severity and persistence of vomiting were thought to justify termination of treatment.

**Abdominal Pain** (7=4%).—Stated by all sufferers to be severe and colicky in nature. Observation suggested that it was severe in some cases. Pain did not usually recur after subsequent doses.

**Diarrhoea** (4=2%).—This was mild and transient. Two of the patients reported passing ascarides.

**Dizziness** (3=1.7%).

**Cough, Pain in Chest, and Pyrexia** (5=2.8%).—In each case this syndrome appeared after the initial dose of hetrazan and was characterized by severe prostration, headache, cough, temperature rising to 103° F. (39.4° C.), and retrosternal pain, sometimes aggravated by deep breathing. Clinically the condition resembled the sudden onset of acute influenza bronchitis. After 24 hours' rest in bed and postponement of further treatment for one day, all cases recovered completely and were able to resume their course of treatment without subsequent ill-effects. Four of the five patients had fairly heavy microfilarial infections before treatment, the actual counts being 416, 80, 75, 50, and 9 microfilariae per 20 c.mm. (approximately).

**Cutaneous Eruption** (1=0.6%).—One patient developed a papular rash, widely distributed over the limbs and trunk, on the fifth day of treatment. It disappeared in two days.

**Localized Swellings** (6=3%).—Since localized painful swellings occurring during the course of treatment may represent a change in tissue reaction at the site of an adult worm, these cases will be briefly described individually:

**Case 1.**—Woman aged about 26; original microfilaria count, 24. Developed painful swelling of lymph nodes of left groin after third dose of hetrazan. This was rapidly followed by considerable oedema of left leg. The patient reported that a similar swelling of the same leg had occurred seven months previously after the birth of her first child. When re-examined nine months later, the lymph nodes were enlarged but painless, and the limb was still oedematous.

**Case 2.**—Man aged about 65; original microfilaria count, 25. Reported painful enlargement of lymph nodes of right groin, with noticeable oedema of right foot on fifth day of treatment. Nine months later the lymph nodes were still enlarged, but were painless; the oedema was still present.

**Case 3.**—Man aged about 60; original microfilaria count, 9. He reported the development of a tender, painful swelling in the left groin on the third day of treatment. This swelling enlarged, softened, pointed, and five days later burst, discharging a thin purulent fluid. Twenty days after treatment the wound had healed completely.

*Case 4.*—Woman aged about 45; original microfilaria count, 75. She developed the syndrome of cough, chest pain, and pyrexia after the first dose of hetrazan. Next day she complained of pain in the right arm. A tender elongated mass, 5 cm. long, was palpable, lying along the medial border of the biceps muscle. The axillary lymph nodes were not enlarged or tender. This mass slowly resolved, and in three weeks had disappeared.

*Case 5.*—Woman aged about 35; original microfilaria count, 168. Complained of pain and swelling of left arm on fourth day of treatment. Examination revealed a tender mass, about 2 cm. in diameter, in the body of the left biceps. The axillary glands were enlarged and tender. The mass resolved completely in 14 days.

*Case 6.*—Woman aged about 40; lactating; original microfilaria count, 6. Developed a painful tender swelling 2½ cm. in diameter in right breast on fourth day of treatment. The mass resolved slowly and disappeared three weeks after treatment.

### Discussion

Descriptions of the use of hetrazan for the treatment of hospital patients have been given by many workers and reviewed by Hawking (1950). An attempt at mass treatment of filariasis comparable to the present work was carried out by Hewitt and his collaborators (1950) in the West Indian island of St. Croix, which has a population of 12,000 to 14,000. After preliminary studies a dose of 100 mg. hetrazan citrate (that is, 50 mg. base), thrice daily for seven days, was adopted, and 10,300 "treatment units" of this amount were distributed to the population, who took it without supervision. Blood films taken from sample groups a year later indicated that the microfilaria rate had fallen by 60% from 16.6% to 6.8%, and the average microfilaria count in those remaining infected had fallen from 40 to 60 c.mm. to 4.5—that is, by 89%—the total reduction of microfilariae being 95%. A few minor toxic effects—fever, headache, and nausea—were reported, but apparently they did not cause the treatment to be unacceptable (although the amount of defaulting is unknown). Other reports on the effect of hetrazan for the long-term control of filariasis have been given by Maldonado *et al.* (1950) and Hewitt, Kennèy, Chan, and Mohamed (1950).

In the present trial hetrazan (5 mg. base per kg. daily for five days) appears to have given satisfactory therapeutic results against microfilariae of *W. bancrofti*, since complete elimination was achieved in 64% of the cases, while the reservoir of microfilariae available to infect mosquitoes was reduced by 94%. These results are similar to those reported by previous workers. Although it is not known what level of microfilariaemia is needed to allow transmission to take place in the field, most of the persons still harbouring microfilariae of *W. bancrofti* 10 months after treatment contained such small numbers in the blood that it was probably difficult for mosquitoes to become infected from them. Moreover, for further propagation of the parasites to continue in a new patient it is necessary that male and female worms should meet and fertilize; unless the number of worms in the host is considerable the chances against this happening must be great. Therefore the permanent reduction of microfilariaemia to a low level, as occurred in Keneba, might well be sufficient to prevent further spread of the infection; and its final dying out might result without the achievement of complete chemotherapeutic sterilization—an end-point which requires much higher dosage of hetrazan and more prolonged treatment. Since the effects of hetrazan on the microfilaria count persist for more than 10 months it is probable that hetrazan produces a permanent effect (death or sterilization) upon the adult worms of *W. bancrofti*, although it is difficult to demonstrate such an effect in experimental *Litomosoides* infection in cotton-rats. In a few patients there were signs suggesting a cellular reaction around a dying worm—

namely, localized swellings in the groin and limbs—but in most cases the death (or sterilization) of the adult worm must happen without outward manifestation.

*A. perstans* has usually been regarded as insensitive to hetrazan, since it is difficult to show a significant diminution of numbers of microfilariae in individual patients because of the wide fluctuations in density which occur spontaneously. In our series, however, complete elimination of microfilariae was effected in 72% of the 69 patients treated, and the sum of the microfilariae was reduced by 92%. This result suggests strongly that hetrazan exerts a considerable effect in infection by *A. perstans*, although, as the worm is not known to be pathogenic, the effect may not be of much practical importance. Since microfilariae of *A. perstans* appeared in the blood of 13% of treated subjects not previously showing infection, it is probable that the drug has no significant action upon immature developing worms.

Unfortunately, although therapeutically effective, the treatment was accompanied by unpleasant side-effects, which were more prominent and severe than those reported by other workers, with the exception of Wilson (1950) and Galliard and Mille (1949). These untoward effects may have been more disturbing because our subjects were quite unconscious of their infection and generally felt well before treatment, whereas most previous work has been done on hospital patients, who are generally not surprised at minor discomfort during their treatment. The effects may have been due to direct action of the drug (for example, nausea), to allergic reactions (fever and malaise), or to cellular reaction round a dying worm (swelling in the groin). The syndrome of cough, pain in the chest, and fever which occurred in five patients (2.8%) may have been related to the concentration of microfilariae in the lungs which occurs in the daytime as part of the microfilarial cycle (Hawking and Thurston, 1951).

This high incidence of ill-effects seriously jeopardized the success of the trial, although it was begun in most favourable circumstances. The people administering the drug were well known to the villagers, having lived and worked in the village for a year beforehand. Treatment of other diseases, such as yaws and trypanosomiasis, had established much confidence in Western medicine. Spraying of the village with BHC had enormously reduced the insect population and earned the delighted gratitude of the villagers, who altogether were in a highly receptive frame of mind. The surveys and treatment were so timed as not to interfere with agricultural activity. In spite of these exceptional initial advantages, however, it was only with the utmost difficulty that the trial was completed in face of the unpopularity of the drug occasioned by these toxic reactions. In this area the visible effects of filariasis are uncommon (less than 1%), and there is no fear of them. Consequently there is little inducement to complete a course of treatment whose ill-effects appear worse than those of the disease.

Another obstacle to mass treatment by hetrazan is the cost of the drug; this is considerable even for such a small population as that of Keneba. Unless these obstacles (unpopularity due to toxic effects, and expense) can be overcome, we are of the opinion that, at present, attempts to use hetrazan for mass treatment in areas where the people are not conscious of ill-effects from filariasis run a substantial risk of rather costly failure. On the other hand, the drug is so effective in diminishing the reservoir of microfilariae available for transmission that vigorous efforts should be made to overcome these disadvantages by diminution or different distribution of the dose or by any other possible means.

### Summary

As part of an investigation into the relative importance and interrelationships of parasitization and nutrition as factors in the production of ill-health and poor performance in Gambian villagers, steps were taken to control or eradicate the major parasitic diseases,

including filariasis, in Keneba, a village of 710 population in the West Kiang District of the Gambia Protectorate.

A preliminary survey showed that of 603 persons present 220 carried microfilariae of *W. bancrofti* and 203 carried microfilariae of *A. perstans*. Treatment was directed primarily against *W. bancrofti*.

Hetrazan, in five daily doses of 5 mg. base per kg. of body weight, was administered to 181 villagers in February, 1951. Of these, 69 had microfilariae of *A. perstans* as well as of *W. bancrofti*.

Re-examination ten months after treatment showed that 64% of those treated were free of microfilariae of *W. bancrofti*, and that the total microfilariae in all those originally found infected had been reduced by 94%.

Microfilariae of *A. perstans* had been eliminated from the blood of 72% of those treated, with a 92% reduction of total load; in untreated persons the microfilariae of *A. perstans* had disappeared spontaneously in 32%, but the total microfilaria count had increased by 49%.

Unpleasant side-effects attributed to hetrazan were spontaneously reported by one-quarter of those treated. These disorders were common and severe enough to make the drug very unpopular, and it was only with great difficulty that the trial was completed, in spite of the exceptionally favourable circumstances in which it had been started.

The conclusion was reached that, in spite of the very high therapeutic efficacy of hetrazan, its common toxic effects and high cost are disadvantages which seriously prejudice the chances of its successful use for mass treatment in areas, such as this, where filarial sequelae are rare and the people have no consciousness or fear of the disease.

We gratefully acknowledge our indebtedness to Mr. D. P. Gamble, socio-anthropologist to the Gambia Government, for his invaluable co-operation; to Mr. K. Broomfield for help in examination of the blood films; to Dr. E. J. Bury, Director of Medical Services, Gambia; and to Professor B. S. Platt, Director of the M.R.C. Field Research Station, for his help and encouragement and for making the investigation possible.

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A short account of the French Prosthetic Service for the nation's war disabled is given by Lieutenant-Colonel C. Abadie, medical director of the service, in the October issue of the *Rehabilitation Bulletin* of the World Veterans Federation. Appliances are supplied at State expense so long as the patient requires them. He is free to choose his appliance among the recognized types that suit his disability. The State also pays for repairs, which are mainly carried out at workshops in the service, and for replacements when required. Amputees are entitled to two appliances, identical or dissimilar in type, for each limb amputated. In addition to appliances, severely disabled war victims may receive a hand-propelled wheel-chair of one kind or another, and the State is responsible for the upkeep and repair. A pensioner with a head wound that has led to permanent baldness has a right to a wig, which can be replaced every three years.

## THE SKIN MANIFESTATIONS OF MALIGNANT DISEASE

### WITH SPECIAL REFERENCE TO VASCULAR CHANGES AND DERMATOMYOSITIS\*

BY

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Deposits of carcinoma in the skin usually occur late in the course of the disease. They are often few in number, and the diagnosis is established by excision and section. Of more interest to the dermatologist are the non-specific skin manifestations which can be related to the presence of a carcinoma.

When a visceral carcinoma is well advanced the skin may be pale, inelastic, and yellow in tint, without jaundice. These changes may be due to lack of appetite, diminished food intake, and difficulty in assimilation. Thus a carcinoma of the stomach or intestinal tract may interfere with iron and vitamin absorption. It is not unusual to see an atrophic dermatitis of the exposed areas of the face and arms comparable to the changes of pellagra, no doubt due to deficient intake or utilization of vitamin-B<sub>2</sub> complex.

Cochrane and Alexander (1951) described the case of a woman with an advanced carcinoma of the lower end of the oesophagus, who was found to have a generalized thickening and dryness of the skin, tongue, and mouth, besides numerous warts and pigmentation. With vitamin-A therapy, 700,000 units a day by mouth, "there was subjective improvement in the itching, and the skin felt much less coarse and more pliable."

As well as the nutritional deficiencies, the skin may be affected by toxic substances derived from the tumour, with degeneration of the connective tissue comparable to senile elastosis. When the liver is infiltrated the raised blood cholesterol will also contribute to the yellow colour.

#### Itching

The demands of rapidly growing malignant tumours on amino-acids and essential substances—for example, folic acid—may contribute to the deficiencies shown by the skin. Irritation or pruritus is the most common cutaneous symptom of malignancy, and is usually generalized. A rarity is the localized itching of the nostrils with some tumours of the brain. Itching occurs with carcinoma of the abdominal organs and of the thorax, and with Hodgkin's disease and the leukaemias. Pruritus may follow the x-ray treatment of an abdominal carcinoma or of a tumour elsewhere. This would suggest that a reaction comparable to a sensitization reaction occurs to protein substances released by degenerating cells. One may recall the pruritus and urticaria which have been observed following haematomata due to injury.

With the complaint of itching, inspection may reveal small, irritable, skin-coloured papules which usually disappear after the tops of the papules have been excoriated. Occasionally, however, these papules have been noted to persist, to enlarge, to ulcerate, and to display a neoplastic histology. This clinical observation has led to the suggestion that the transitory papules are an expression of a vital reaction on the part of the skin to single cells of the tumour. It is difficult not to concede that tumour cells must invade the circulation and may fail to establish themselves in the

\*Lecture given at the Institute of Dermatology, St. John's Hospital for Diseases of the Skin, on January 15, 1952.