History, Epidemiology and Control of Filariasis

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1 History of filariasis

1.1 Scientific discovery

Early scientific milestones in filariasis history abroad include the following.

1863: Demarquay in Paris found microfilariae in hydrocele liquid of a Cuban.

1866: Wucherer found microfilariae in chyluria.

1872: Lewis found microfilariae in blood.

1877: Bancroft found a female adult filarial worm in the ulcer of lymph node of the arm.

1877: Manson found microfilariae in the stomach of blood-sucked mosquito, which was practically the “birth” of medical entomology.

1879: Manson found microfilarial nocturnal periodicity.

1888: Sibthorpe found male adult worms.

Those in Japan include the following.

1876: Erwin Von Baelz detected microfilariae in blood (in Tokyo).

1896: Yushitaro Matsuura found a female adult worm in an inguinal lymph node (in Kumamoto).

1903: Shichiro Hida found a male filaria in the left seminal hydrocele.

1.2 Ancient filariasis

About 600 B.C., a singular symptom of bancroftian filariasis (elephantiasis arabum) was described by ancient Hindus and Persian doctors. However, there is an indication that lymphatic filariasis existed as early as 1500 B.C. The funeral temple of Queen Hatshepsut (1501-1480 B.C.) is located at the foot of a mountain that commands a fine view in Thebes (now Luxor city), Egypt. To the back (north) of the mountain is the Valley of the Kings where the tomb of Tutankhamen was found. Replicas of illustrations possibly depicting elephantiasis can be seen on the right side second layer limestone wall of the funeral temple along the middle terrace (Fig. 1a). The original reliefs have been exhibited at the Egyptian Museum in Cairo (Fig. 1b), with the following explanation: ‘Very fine painted limestone reliefs from Terrace of Queen Hatshepsut’s temple at EL-Deir Bahari which record a trading expedition to Punt, a locality near the sea and South of Egypt. The center block depicts the prince of Punt and his wife, the latter obviously suffering from elephantiasis (Fig. 1d), followed by bearers of merchandise. On the left is the princess’ ass, above which is inscribed “the ass which carries his wife” (Fig.1c).

In Japan, pictures of a female with elephantiasis-like lower extremities and a male with suspected hydrocele/elephantiasis of the scrotum, which date back to about A.D. 1100-1200, were found. One picture in the “Diseases Picture Scroll”, which is the property of Tokyo National Museum, depicts a female with possible elephantiasis of the legs (Fig. 2a,b,c,d). The pictures in the “Strange Diseases Picture Scroll”, which is the property of Kyoto National Museum, show leg elephantiasis and hydrocele/elephantiasis of the scrotum (Fig. 3a,b,c,d).

Concerning a big scrotum, the “Unofficial History of Kuma” describes an episode of a young soldier named Yo-hyo Kitazaki. During the war between the Satsuma (Kagoshima) and Sagara (Kumamoto) clans fought in 1555, Kitazaki showed his comrades a wrapped head of a Satsuma enemy, which indicated his war achievement. In fact, however, in the cloth wrapper was a hydrocele of human-head size cut off from a dead soldier. The story suggests that a huge hydrocele was not uncommon in Satsuma in those days. Hokusai Katsushika (1760-1849), a renowned Japanese artist, portrayed huge elephantiasis of the scrotum in paintings (Fig. 4).

2 Epidemiology and control of filariasis

2.1 Prevalence in Kagoshima prefecture

Between 1911 and 1961, a year before the government-sponsored National Filariasis Control Program was started, there were 176 published reports on filariasis. The reported endemicity in mainland Kagoshima and coastal islands is shown in Table 1a, b. The microfilaria positive rate among people living on coastal islands was 16.6% (4,337 positives out of 26,069 examined), and the rate was especially high in Amami Oshima Island at 19.6%. In mainland Kagoshima, the microfilaria positive rate was 11.3% (1,629 positives out
of 14,359 examined), revealing that filariasis was widely spread in Kagoshima prefecture.

2.2 Filariasis treatment with diethylcarbamazine

For filariasis treatment, antimonials or arsenicals had been used without satisfactory results. In 1947, Hewitt and his colleagues used one of the piperazine derivatives, 1-diethyl-carbamyl-4-methylpiperazine hydrochloride (Hetrazan), for the first time and reported that it showed remarkable effects in the treatment of *Litomosoides carinii* and *Diriglaria immitis*. Afterwards, Santiago-Stevenson et al. (1947), Hewitt et al. (1950), and others reported, one after another, the disappearance of microfilariae in blood by using the drug. In Japan, Suganuma (Department of Pharmacology, Tokyo University, 1950) synthesized 1-diethylcarbamyl-4-methyl-piperazine citrate (Supatonin). Notable anti-microfilarial effects of Supatonin were confirmed and reported by such famous researchers as Kitamura and Katamine (1951), Sasa and Hayashi (1951), and Hachiro Sato (1952).

The drug, Supatonin, came into our possession in 1950 for trial use, and was proven to exert remarkable effects in filariasis control programs.

Kiyohara district, Bonotsu, Kagoshima prefecture, was heavily affected with filariasis and there were many symptomatic cases. Different doses of diethylcarbamazine citrate (DEC) were tested in the district and anti-microfilarial effects were followed up for as long as 5 years (Fig. 5). The study revealed that DEC was most effective when adminis-
Fig.2 A millennium-old picture scroll depicting elephantiasis.
(a) Tokyo National Museum, (b) The "Diseases Picture Scroll" (left) and its wooden container (right). (c) & (d) A picture of a woman with elephantiasis on both legs.
Fig. 3 A millennium-old picture scroll ("Strange Diseases Picture Scroll") depicting elephantiasis and hydrocele. 
(a) Kyoto National Museum, (b) A lady with elephantiasis, (c) & (d) Hydrocele (or elephantiasis of the scrotum) cases.
tered at a total dose of 71 mg/kg of body weight (BW). As the efficacy persisted for 5 years, it was considered that the dose could affect not only microfilariae but also adult worms.

2.3 Basic issues considered in conducting filariasis surveys

In the early stage of filariasis studies when a large-scale treatment campaign was expected in the near future, it was necessary to answer several basic questions, such as i) suitable treatment scheme (optimal dose of DEC and treatment period), ii) occurrence of side reactions after treatment, iii) suitable time for blood sampling, iv) amount of blood to be used for microfilaria detection, v) capability of examiners to collect blood samples, and vi) how to secure people’s cooperation.

(1) Treatment scheme:

The same dose of 5 mg/kg BW was given in 3 differ-
ent treatment schedules, that is, 5 mg/kg daily for 10 days, once a week for 10 weeks, and once a month for 10 months. The study revealed that there was no difference among the 3 schedules (microfilaria reduction 74-80% at 1 year). Results of a 10-year follow-up study on the effect of 10 weekly treatments at 5 mg/kg, followed by another treatment at 6 mg/kg x 5 times 1 year after the weekly treatments, are shown in Fig. 6.

(2) Occurrence of side reactions after treatment:
A variety of side effects developed after DEC administration, especially in microfilaria positive persons (Table 2). The most problematic one was fever, which occurred in 25.9% of those treated. The fever appeared 1-3 days after the start of DEC administration in most cases, and became highest when microfilariae decreased rapidly in blood (Fig. 7). The fever lowered gradually even when the drug was taken continuously. It has been assumed that fever is the result of allergic or pyrogenic reaction caused by killed worms. In the case of Brugia malayi high fever is common, while in Wuchereria bancrofti it is around 37.0°C. People used to accept the explanation that they should continue

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### Table 1. Prevalence of filariasis in Kagoshima prefecture (1912-1961)

| Districts          | No. report | No. examined | No. positive | Positive rate (%) |
|--------------------|------------|--------------|--------------|-------------------|
| (a) Results of examinations in the islands of Kagoshima |            |              |              |                   |
| Amami-Oshima       | 58         | 15,206       | 2,976        | 19.6              |
| Mishima and Toshima| 13         | 2,304        | 369          | 16.0              |
| Tanegashima and Yakushima | 21       | 5,933        | 597          | 10.1              |
| Koshikijima        | 11         | 1,788        | 267          | 14.9              |
| Nagashima          | 9          | 838          | 128          | 15.3              |
| Total              | 112        | 26,069       | 4,337        | 16.6              |
| (b) Results of examinations in the mainland of Kagoshima |            |              |              |                   |
| South Satsuma      | 30         | 9,084        | 1,025        | 11.3              |
| Central            | 9          | 793          | 102          | 12.9              |
| Northern           | 15         | 2,504        | 293          | 11.7              |
| North Osumi        | 1          | 97           | 0            | 0.0               |
| South Osumi        | 12         | 1,881        | 209          | 11.1              |
| Total              | 67         | 14,359       | 1,629        | 11.3              |

Fig. 5 Change in microfilaria (Mf) counts after DEC treatment at different dosages (results of 5-year follow-up).
Pre-treatment counts are regarded as 100%.
taking DEC even when fever appeared, because the fever was a sign that the drug was killing parasites.

(3) Suitable time for blood sampling:

Nocturnally periodic \textit{W. bancrofti} was endemic in Japan. In order to decide the proper time for blood collection, 63 known microfilaria positives were examined at 18:00, 19:00, 20:00, 21:00, and 22:00 hours, and microfilaria rates and counts were compared (Table 3). At 21:00, the count was only about a half of that at 22:00. However microfilaria detection rate was 98.4% (100% at 22:00). It was concluded that sampling at 21:00 was acceptable as long as careful microscopical examination would be done. Another factor necessary to decide sampling time was the relationship with people. People were requested to gather at a public hall for blood collection, and expected to be examined as early as possible. Considering the fact that a usual sample collection needed 3 to 4 hours to complete, the start at 21:00 was considered reasonable.

| symptoms                  | Study site (No. examined) | A (81) | B (27) | C (21) | D (8) | E (44) | Total (181) | % |
|---------------------------|--------------------------|--------|--------|--------|-------|--------|-------------|---|
| fever                     |                          | 18     | 10     | 2      | 4     | 13     | 47          | 25.9 |
| shivering                 |                          | 8      | 8      | 2      | 0     | 10     | 28          | 15.5 |
| lymphnode swelling        |                          | 5      | 3      | 2      | 0     | 1      | 11          | 6.1  |
| scrotal swelling          |                          | 2      | 1      | 1      | 0     | 1      | 5           | 2.8  |
| malaise                   |                          | 27     | 14     | 9      | 7     | 25     | 82          | 45.3 |
| headache                  |                          | 22     | 15     | 4      | 7     | 20     | 68          | 37.6 |
| dizziness                 |                          | 9      | 4      | 1      | 2     | 2      | 18          | 9.9  |
| headache dull             |                          | 15     | 7      | 2      | 4     | 11     | 39          | 21.5 |
| nausea                    |                          | 7      | 2      | 3      | 1     | 4      | 17          | 9.4  |
| vomiting                  |                          | 2      | 1      | 1      | 0     | 0      | 4           | 2.2  |
| anorexia                  |                          | 11     | 4      | 3      | 2     | 11     | 31          | 17.1 |
| diarrhea                  |                          | 4      | 6      | 3      | 3     | 8      | 24          | 13.2 |
| gurgle                    |                          | 21     | 11     | 3      | 2     | 11     | 48          | 26.5 |
| abdominal pain            |                          | 10     | 2      | 1      | 0     | 7      | 20          | 11.0 |
| no reactions              |                          | 33     | 4      | 7      | 0     | 8      | 52          | 28.7 |

Table 2. Side effects caused by Supatonin
(4) Amount of blood to be used for microfilaria detection:

Different quantities of 10 µl (sample A), 20 µl (sample B), and 30 µl (sample C) were smeared on each slide glass to compare the efficiency of microfilaria detection (60 µl in total was collected from each person). With 76 microfilaria positive persons, the positive rates according to different blood quantity were 66/76 (86.8%) in (A), 72/76 (94.7%) in (B), 74/76 (97.4%) in (A+B, 30 µl of blood), 73/76 (96.1%) in (C), and 76/76 (100%) in (A+B+C, 60 µl of blood). The total number of microfilariae detected was 579, 982, 1561, 1277 and 2838, respectively, which are in the ratios of 1 : 1.7 : 2.7 : 2.2 : 4.9. Although collecting 60 µl of blood was ideal, it was decided to use 30 µl samples.

(5) Capability of examiners to collect blood samples:

After a few days of training, an examiner became efficient enough to process about 100 blood smears in 3 hours, from 21:00 to 24:00 hours.

(6) How to secure people’s cooperation:

It became apparent that the most important and effective strategy to control filariasis was to obtain the support of people. At the same time, it was understood, by a questionnaire-based survey, that people did not have sufficient knowledge on filariasis transmission and its control. The survey revealed that 87 (25.1%) of 346 people questioned gave the answer that filariasis was a hereditary disease. Only about a half (52.8%) of those questioned knew that filariasis was an infectious disease. As for the night blood survey, 72 people (20.8%) answered that the survey was conducted at night for the convenience for the people gathering, while 230 (66.4%) correctly related it to the nocturnal periodicity of microfilariae. Activities to enlighten people were then intensified both by academic institutions and administrative agencies. Circulars explaining the importance of mosquitoes as a vector, and the necessity of blood examinations and DEC treatment were distributed. In vil-

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**Table 3. Effects of time of blood collection on Mf detection rate and the number of Mf**

| Hours of blood collection | 18:00 | 19:00 | 20:00 | 21:00 | 22:00 |
|---------------------------|------|------|------|------|------|
| A  | No. Mf positives | 19 | 44 | 53 | 62 | 63 |
| B  | Mf positive rate 100 x (A/63) | 30.1% | 70.0% | 84.1% | 98.4% | 100.0% |
| C  | Total no. of Mf | 29 | 653 | 2437 | 3596 | 7410 |
| D  | Average no. of Mf (C/A) | 1.5 | 14.8 | 46 | 58 | 117.6 |

* 63 known Mf positives were examined.
lages, live microfilariae were demonstrated using a microscope.

In conclusion, the following policies were proposed for filariasis surveys: i) 30μl of blood is taken starting from 21:00 hours, ii) one examiner collects 100 blood samples per night, iii) DEC is given at 70 mg/kg BW in total, which can be administered continuously (daily) or intermittently (weekly or monthly), and iv) to secure people’s cooperation, publicity and education activities are essential. Thorough explanation is needed on side reactions, especially fever.

### 2.4 The National Filariasis Control Program

After the end of World War II, such leading researchers as Hachiro Sato (Kagoshima University), Daisuke Katamine (Nagasaki University) and Manabu Sasa (Tokyo University) clarified the situation of filariasis prevalence in Japan. The disease was spread widely, affecting many people. The researchers urged the government to establish a national project to control filariasis, and the National Filariasis Control Program was inaugurated in 1962. The program continued for 10 years until 1971.

The filariasis control measures included two components: anti-vector mosquito activities (residual spraying of DDT) and treatment of microfilaria carriers. However, it became apparent that the two components could not be performed together particularly in remote areas and islands. Accordingly, an emphasis was put on detecting microfilaria positives by night blood survey and treating them with DEC. The standard treatment recommended by the Ministry of Health was as follows. Using a 50 mg DEC tablet, adults are given 2 tablets/day for 3 consecutive days, 6 tablets/day for the next 3 days, followed by weekly dose of 6 tablets/day for 8 weeks. Thus 9 weeks were needed to complete the treatment. For younger people, reduced dosages were used

| Year | No. examined | No. Mf positive | Mf Positive rate (%) |
|------|--------------|-----------------|----------------------|
| 1962 | 135,557      | 8,968           | 6.6                  |
| 1963 | 167,604      | 6,597           | 3.9                  |
| 1964 | 99,864       | 4,498           | 4.5                  |
| 1965 | 81,503       | 2,918           | 3.6                  |
| 1966 | 61,969       | 1,958           | 3.2                  |
| 1967 | 68,446       | 1,186           | 1.7                  |
| 1968 | 61,116       | 755             | 1.2                  |
| 1969 | 66,102       | 345             | 0.5                  |
| 1970 | 18,118       | 134             | 0.7                  |
| 1971 | 11,645       | 91              | 0.8                  |
| Total| 771,924      | 27,450          | 3.6                  |

Table 4. Changes in microfilaria (Mf) positive rate in Kagoshima prefecture during the National Filariasis Control Program

![Fig.8 Skin test results according to age group. (a) Age groups under 40 years, (b) Age groups of 40 years or more](image)
but with the same time schedule, that is, for junior high
school students, 2 tablets/day in the first 3 days and 4 tab-
lets/day thereafter, and for elementary school and younger
children, 1 tablet/day first and then 3 tablets/day.

Nine local governments (Tokyo and 8 prefectures) partici-
pated in the National Filariasis Control Program for 10
years (1962-1971), during which time 2,039,728 people
examined and 27,450 (1.7%) microfilaria positives
were found. Particularly in Kagoshima prefecture, as many
as 27,450 (3.56%) positives were found among 771,924
people examined, and in Nagasaki prefecture, 6,214 (0.88%)
out of 709,300 were positive. The known microfilaria posi-
tive persons were treated with DEC with remarkable suc-
cess. Yearly changes in microfilaremia prevalence in
Kagoshima prefecture are shown in Table 4.

2.5 Follow-up studies by means of the nuclepore filtration
method and skin test

(1) A study in Kiyohara district, Bonotsu:
In this district, all 802 people examined in 1970 were
proven to be microfilaria negative as a result of past DEC
treatments. In 1979, a follow-up study was conducted by
means of 60μl blood smears using earlobe blood and 1 ml
nuclepore membrane filtration using venous blood. No mi-
crofilaria was detected by either method. Skin test using
FPT antigen (Tada, 1964), which was extracted from Dirofi-
laria immitis, was also employed to obtain information on
sensitization to filariae. Positive rates by skin test in differ-
ent age groups were 0% for 0-9 years, 5.3% for 10-19 years,
11.1% for 20-29 years, 35.3% for 30-39 years, 40.0% for
40-49 years, 42.6% for 50-59 years, 40.4% for 60-69 years,
54.8% for 70-79 years and 42.9% for 80 years and over.

The positive rates increased gradually by age and reached a
plateau after 40 years. A remarkable finding was that 56
children of age 0-9 years, who were born after treatments
had eliminated microfilaraemia were all negative (Fig. 8a,b).
The skin test results from various endemic and non-
endemic areas are compared in Fig. 9. Endemic areas show
very high positive rates already at age 10 years, while Bo-
notsu shows a similar pattern to Nishinoura a non-endemic
area, suggesting that the transmission of filariasis had been
interrupted.

(2) A study in Kuroshima island Yaeyama arehipelago, Oki-
 nave:
Kuroshima had a population of 570 in 1967, but this
decreased to 176 in 1980 for social and/or economic rea-
sons. The microfilaria rates in 1967 and 1968 were 13.2%
and 12.5%, respectively.
DEC treatment (6 tablets/day for 12 days) was given in
1968. The microfilaria rate by blood smear was 0.3% in
1976, which decreased to 0% in 1980. The nuclepore filtra-
tion method also detected no positive case in 1980.
The skin test results showed that the positive rate in the
age group of 0-9 years declined steadily from 55.3% in
1967 to 11.3% in 1973 and to 0% in 1980, while adults of
30 years and older maintained high positive rates of 65-70%.
These results suggested that children born after 1970 were
not sensitized by filarial antigen, or that there had been no
new infection over the previous 10years.

2.6 Change in prevalence of chyluria after treatment

Between 1961 and 1965, 32,397 out-patients visited
the 2nd Department of Internal Medicine, Kagoshima Uni-
versity Hospital, of whom 147 (0.45%) were chyluria cases.
In the period of 1975-1979, there were 25 (0.09%) chyluria

Fig. 9 Skin test results from various endemic and non-endemic areas.

| Area                        | Mf rate (%) |
|-----------------------------|-------------|
| Nagate (Nagasaki)           | 13.0        |
| Cheju (Korea)               | 20.9        |
| Kuroshima (Okinawa)         | 13.2        |
| Bonotsu (Oita)              | 13.2        |
| Nishinoura (Oita)           | 0.0         |

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cases out of 27,037 out-patients. At Kagoshima Prefectural Oshima Hospital in Amami Oshima Island, where filariasis was highly endemic, chyluria patients in the same periods decreased from 176 (0.86% of 20,514 outpatients) to 30 (0.13% of 22,951 outpatients), indicating that DEC treatments contributed to the reduction of chyluria (Table 5a,b).

It is interesting to note that at the same Oshima Hospital, the number of chyluria patients did not decrease between 1981 and 1990 (Kimura E. This issue: 58-59)

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