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EFFECT OF REPEATED TREATMENTS WITH IVERMECTIN ON THE INCIDENCE OF ONCHOCERCIASIS IN NORTHERN CAMEROON

M. BOUSSINESQ, J. P. CHIPPAUX, J. C. ERNOULD, D. QUILLEVERE, AND J. PROD'HON

Antenne ORSTOM Aupres du Centre Pasteur du Cameroun, Yaounde, Cameroon; World Health Organization Onchocerciasis Control Programme in West Africa, Ouagadougou, Burkina Faso

Abstract. Mass treatments with ivermectin have been undertaken each year since 1987 in an area hyperendemic for onchocerciasis in northern Cameroon. The impact of these successive treatments on the incidence of infection in humans was evaluated by comparing the prevalence of skin microfilariae (PMF) and the mean microfilarial skin densities (MFD) observed in 1987 and 1992 in 5–7-year-old children who had never taken the drug but who were members of the treated communities. In 1992, the PMF and the MFD in children in this age group who never received ivermectin were reduced by 55% and 77%, respectively, in comparison with the values observed in 1987, before the first treatment round. These results reflect a pronounced reduction in the intensity of the transmission of *Onchocerca volvulus* in the treatment zone. The influence of the ivermectin treatment coverage in the human population, as well as the vectorial capacity and the dispersal of the vector blackflies, on the transmission of onchocerciasis is discussed.

Mass ivermectin treatment of populations infected with onchocerciasis brings about a reduction in the transmission of the parasite. This effect has been demonstrated in the course of various studies by comparing before and after treatment the infection rates in vector blackflies.[1–4] This impact on transmission was also demonstrated in an indirect manner in Liberia, where two successive treatments of a population with ivermectin brought about a decrease in the incidence of infection in untreated children.[5]

In Cameroon, community-wide ivermectin treatments have been carried out since 1987 in the North Vina Valley, a savanna area endemic for onchocerciasis.[2] By the end of 1992, more than 30,000 patients had received at least one ivermectin treatment. The purpose of the present study, conducted in the villages treated since 1987, was to evaluate the impact of five successive mass ivermectin treatments of a population on the prevalence and the intensity of the infection in untreated children belonging to the same community.

PATIENTS AND METHODS

Study area. The North Vina Valley lies in the Sudan-savanna zone of northern Cameroon between 13°30′ and 15°35′E and 7°20′ and 8°N. A map of the area has been presented in a previous paper.[2] The valley covers an area of 13,100 km². There are two distinct seasons with the rains lasting from May to October. The North Vina River rises at an elevation of 1,435 meters on the Adamawa Plateau, about 25 km northwest of the town of Ngaoundere. It flows in an easterly direction and after a course of some 314 km joins the Mbere River at the boundary between Cameroon and Chad to form the West Logone River. The North Vina River and the Mbere River are perennial, whereas their tributaries flow only during the rainy season. The valley is limited on the north and on the south by two ranges of mountains rising up to 1,920 meters. In the middle and eastern parts of the valley, the villages lay almost exclusively on a road that runs on the left bank of the North Vina River. The human population is sparsely distributed (density less than four persons/km²). The people belong mainly to the Mboum ethnic group. The major occupations are subsistence agricultural farming and cultivation of cotton.

The North Vina Valley is an area endemic for onchocerciasis that is part of the vast Vina-Pende-Logone focus, which extends across Cameroon, the Central African Republic, and Chad. Ophthalmologic studies conducted in this area before ivermectin distribution reported high prevalences of severe onchocercal eye lesions.[2,6] In the North Vina Valley *Onchocerca volvulus* is transmitted almost exclusively by *Simulium damnosum* s.s. and *S. sirbanum*.[7] Longitudinal entomologic studies have shown that transmission of onchocerciasis in the study area occurs principally during the rainy season.[8]

Study population: description, examination, and treatment schedules. The study was conducted in five contiguous communities situated several kilometers west of the town of Touboro, in the eastern part of the valley, on a road that runs parallel to the course followed by the river. The villages were Bonandika, Man Rigara, Voye, Mbailara, and Ngoumi. They were selected because of background information giving evidence of high endemicity levels. A total of 3,028 people were recorded in these villages during the nationwide census of 1987 (Table 1), a number close to the one recorded two years before by the cotton development project. No extra, specific census was conducted during the study. Pretreatment parasitologic examinations of subjects five years of age and older, and the first administration of ivermectin, were carried out in November 1987 in the five villages using the methods described below. The team stayed several days in each village to collect the most exhaustive data possible and to achieve an optimal treatment coverage. The other communities of the valley were not treated in 1987. The five villages treated in 1987, identified below as the initial treatment area, were treated again in 1988, six months after the first treatment round. The subsequent treatments in these communities were given at yearly intervals until 1992. In 1992, a parasitologic examination of all people was carried out just prior to the dosing. A particular effort was made to raise to a maximum the participation of children who never received ivermectin previously. We report in the present paper the parasitologic results obtained in 1987 and 1992 in children 5–7 years of age who lived in the original treatment area and who never took ivermectin.

In 1988, an initial ivermectin distribution was undertaken

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TABLE 1

Population recorded during the nationwide census of 1987, and pretreatment prevalence of skin microfilariae (PMF), and geometric mean microfilarial density (MFD) in the initial treatment area

Age (years)	Sex	Population census	Number examined	PMF (%)	MFD (mf/ss)*
0–4	M	397	0	–	–
	F	381	0	–	–
	Total	778	0	–	–
5–9	M	309	103	61.2	4.9
	F	297	129	55.8	2.8
	Total	606	232	58.2	3.6
10–14	M	110	101	88.1	29.6
	F	98	76	76.3	9.4
	Total	208	177	83.1	18.4
15–29	M	315	290	97.9	111.7
	F	485	314	93.9	41.4
	Total	800	604	95.9	67.0
30–49	M	216	180	97.2	113.3
	F	231	149	96.0	82.7
	Total	447	329	96.7	98.2
≥50	M	119	60	98.3	159.8
	F	70	41	95.1	175.7
	Total	189	101	97.0	165.9
≥5	M	1,069	734	91.3	28.5
	F	1,181	709	85.6	63.9
	Total	2,250	1,443	88.5	43.1

* mf/ss = microfilariae per skin snip.

in 29 additional villages situated west of the original treatment area. This first extension zone extended up to the village of Vongna, located approximately at the middle point of the valley. In 1989, the treatment area was extended again and ivermectin was distributed to a total of 73 communities, including the town of Touboro. During this treatment round, the villages located in the western (and upper) part of the valley and the area situated east of the original treatment zone (up to the boundary between Cameroon and Chad) were treated for the first time. In 1990 and 1991, ivermectin distribution was restricted to the most severely affected villages, and the treatment area extended from the boundary between Cameroon and Chad to the village of Lagoye, located about 35 km from the western limit of the original treatment area.

Drug administration. A meeting between the representatives of the communities and the distribution team was organized three or four days before drug administration to mobilize the population. In the smaller villages, ivermectin was given in the village chief's home, located at a central place in the village. In the larger communities, i.e., with a population of more than 1,000 inhabitants, the distribution was carried out in several sites corresponding to the village chief's and quarter chief's house and occasionally in a school. In the initial treatment area, Ngoumi was the only village with such a large population. In all villages, the most remote residents lived within 1 km of a dosing point, and the first treatment was given by a team of one or two physicians, two nurses, and two secretaries. During the distributions carried out in 1987 and 1992 in the initial treatment area, the dosing team stayed for three consecutive days between 8:00 AM and 6:00 PM at each treatment and examination site. The drug was administered at a dose of 150 μg/kg of body weight, taking into account the usual exclusion criteria: children less than five years of age, a weight less than 15 kg, pregnancy, first month of lactation, jaundice, central nervous system disease, and severe clinical illness. The full name, sex, age, and weight of every treated person was registered every year and the data concerning the children less than 10 years of age were gathered in a file. Thus, it was possible to know if a child received a treatment during the previous years. The tablets were swallowed by the subjects in front of the drug dispenser so that the drug could not be taken away and given to people ineligible for treatment.

Parasitologic examination. Before the first treatment round in 1987, a parasitologic examination was carried out in the original treatment area in 1,443 subjects five years of age and older who came to the ivermectin distribution point and agreed to be examined (Table 1). These individuals correspond to 64.1% of the population five years of age and older recorded during the nationwide census of 1987. Among the 1,443 subjects examined, 151 were five-, six, and seven-year-old children. This sample corresponds to 36.4% of the children of this age recorded in 1987. Two skin snips were taken with a 2-mm Holth corneoscleral punch (Storz Instrument GmbH, Heidelberg, Germany) from the two iliac crests of each patient. Each biopsy specimen was immediately placed in the well of a microtitration plate containing 300 μl of saline. The plate was then covered with Parafilm® (American Can Company, Greenwich, CT) to reduce evaporation. After incubation for 24 hr, the emerged microfilariae were counted under a low-power microscope. For each subject, we calculated the individual microfilarial load, defined as the arithmetic mean of the microfilarial counts from the two skin snips.

A parasitologic examination using the same method was carried out in 1992 in the same area before the sixth ivermectin treatment round among all five-, six-, and seven-year-old children who had never received the drug and who came to the dosing point for their first treatment. Seventy-three children were examined, corresponding to approximately 15% of the children of this age who lived in the initial treatment area in 1992. Examinations were not performed in older children because most of them had received at least one dose of ivermectin previously.

Data analysis. The pretreatment level of endemicity in the original treatment area was evaluated by means of two parasitologic indices used in the Onchocerciasis Control Progamme (OCP) in West Africa, i.e., the age- and sex-standardized prevalence of skin microfilariae, and the community microfilarial load (CMFL). The standardized prevalence of skin microfilariae was calculated using the age and sex distribution in the OCP area.[9] The CMFL is the geometric mean number of microfilariae per skin snip among adults 20 years of age and older in the community, including those with negative counts. This mean was calculated using the log (x + 1) transformation.[10] Two indicators have been used to describe the level of infection by age and sex: the prevalence of skin microfilariae (PMF) and the geometric mean microfilarial density per skin snip (MFD). The MFD were calculated using the log(x + 1) transformation, where x is the individual microfilarial load. This transformation was done to take into account negative microfilarial counts.[11]

Treatment coverages during the successive treatment rounds were calculated using the data of the nationwide census of 1987.

The effect of the community-wide ivermectin treatments on the transmission of onchocerciasis was evaluated by comparing parasitologic indices calculated, on the one hand, in children 5–7 years old before the first treatment round (in 1987) and, on the other hand, in children belonging to the same age group in 1992 and who had not received any prior ivermectin treatment. The PMF and the MFD were calculated in the 5–7-year-old children and separately in the five-, six-, and seven-year-old children. The Pearson's chi-square test was used to compare the PMF between 1987 and 1992. For the MFD, comparisons were carried out using the Student's *t*-test. In both tests, the differences were considered significant when $P < 0.05$.

RESULTS

Pretreatment endemicity levels in the original treatment area. The age- and sex-standardized prevalence of skin microfilariae in the overall population five years old and older was 87.6% prior to the first treatment round. The studied community was therefore hyperendemic for onchocerciasis. The initial CMFL was 85.5 microfilariae per skin snip (mf/ss). In males, the skin microfilarial densities showed a rapid increase with age during the first 15 years, and then leveled off (Table 1). In females, the microfilarial densities increased more gradually with age and reached a maximum in those more than 50 years of age. In the 5–9-, 10–14-, and 15–29-year-old age groups, the mean microfilarial densities were about twice as high in males as in females. In older age groups, the densities were similar in both sexes.

Drug coverage. In the original treatment area, a total of 2,244 and 2,024 persons received ivermectin during the first and second treatment rounds, respectively, (Table 2). The number of people treated in the younger age groups was higher than the number recorded during the nationwide census. Two explanations may be given for this result. It may be due to the fact that a proportion of young people living in the initial treatment area have not been recorded in the villages during the census (some of them are schoolchildren in the nearby town of Touboro). Alternatively, some children who have been treated in the villages might have come from Touboro, where they actually lived. The number of people treated decreased during the three subsequent treatment rounds: 1,794, 1,448, and 1,774 persons were treated in 1989, 1990, and 1991, respectively. Assuming that about 25% of the total population cannot receive ivermectin because they fall under the exclusion criteria, we can estimate that more than 80% of the eligible population in the initial treatment area were treated during the first and second treatment rounds. No significant migration occurred in the initial treatment area during the period of the study. Assuming that the annual rate of increase of the population in the study area corresponded to the one observed in similar regions in northern Cameroon (approximately 2.5%), we can estimate that the drug coverage obtained between 1989 and 1991 ranged from 60% to 80%.

A detailed analysis of the sex and age structure of the population treated during the successive rounds showed that the reduction in treatment coverage observed since 1989 concerned principally females 15–29 years of age. In 1987 and 1988, 392 and 356 subjects of this group, respectively, received ivermectin, whereas less than 200 women (average number 160) were treated during the following three rounds. In contrast, participation decreased only slightly in men 15–29 years of age. Between 1989 and 1991, an average number of 315 patients belonging to this group was treated every year, compared with 365 and 358 in 1987 and 1988, respectively. In children 5–9 years old, adolescents 10–14 years old, and people 50 years old and older, the decrease of participation during the three last treatment rounds was similar (about 25%) when compared with the number of subjects treated in 1987. The most regular attendance during the successive treatments was observed in the 30–49-year-old age group. The average participation of these individuals during the 1989-1991 distributions was reduced by only 10% in comparison with the number treated in 1987.

TABLE 2

Number of patients treated, according to sex and age, in the initial treatment area between 1987 and 1991

Age (years)	Sex	Number of patients treated				
		1987	1988	1989	1990	1991
5–9	M	305	278	228	204	271
	F	318	255	203	234	292
	Total	623	533	431	438	563
10–14	M	166	154	169	109	124
	F	127	109	117	52	96
	Total	293	263	286	161	220
15–29	M	365	358	366	267	313
	F	392	356	185	145	153
	Total	757	714	551	412	466
30–49	M	213	202	245	197	260
	F	186	170	142	114	146
	Total	399	372	387	311	406
≥50	M	82	74	78	70	53
	F	90	68	61	56	66
	Total	172	142	139	126	119
≥5	M	1,131	1,066	1,086	847	1,021
	F	1,113	958	708	601	753
	Total	2,244	2,024	1,794	1,448	1,774

Evolution of parasitologic indices in untreated children between 1987 and 1992. A total of 151 children 5–7 years of age was examined before the first treatment round and 73 children of the same age group were examined after the community had received five successive treatments (Table 3).

When one considers the total number of children examined and treated, the PMF decreased from 52.3% in 1987 to 23.3% in 1992 (reduction of 55.4%). This decrease is significant ($P < 0.0001$). When evaluated by age, the decrease in the PMF is significant for the five-year-old ($P < 0.01$) and the seven-year-old children ($P < 0.01$), but not for six-year-old children ($P > 0.10$).

Between 1987 and 1992, the MFD in the total number of children examined and treated decreased from 3.1 to 0.7 mf/ss (reduction of 77.4%). This decrease is significant ($P < 10^{-9}$). As with the PMF, the MFD decreased significantly in the five-year-old ($P < 0.05$) and the seven-year-old children

TABLE 3

Prevalence of skin microfilariae (PMF) and geometric mean microfilarial density (MFD) in untreated children before (1987) and after the community received five treatments (1992) with ivermectin*

Age (years)	1987			1992			Comparison of 1987 with 1992	
	No. snipped	PMF (%)	MFD (mf/ss)	No. snipped	PMF (%)	MFD (mf/ss)	PMF (%)†	MFD (mf/ss)†
5	47	48.9	1.7	22	13.6	0.3	<0.01	<0.05
6	54	44.4	2.6	38	28.9	1.2	NS	NS
7	50	64.0	4.7	13	23.1	0.2	<0.01	<0.01
Total	151	52.3	3.1	73	23.3	0.7	<0.0001	$<10^{-9}$

* mf/ss = microfilariae per skin snip; NS = not significant.
† *P* values.

($P < 0.01$), but no significant change in the MFD was observed in six-year-old children ($P > 0.10$).

DISCUSSION

In the North Vina Valley, repeated treatments with ivermectin brought about a significant decrease in the overall level of onchocerciasis infection in untreated children. When evaluated by age, this decrease was significant for the 5–7-year-old children, but not for the six-year-old ones. This is due to the fact that the only three children with high microfilarial loads in 1992 (defined as more than 50 mf/ss) were clustered in the six-year-old age group.

A study comparable with the one carried out in northern Cameroon was conducted in Liberia in an area endemic for onchocerciasis where the vector is *S. yahense*.[5] Two treatments with ivermectin were administered to the residents of a rubber plantation with a one-year interval. Before the first treatment, the prevalence of skin microfilariae in five-year-old children was 23.9%. One year after the second distribution of ivermectin, the prevalence was 19.0% (reduction of 21%) in children of the same age and who had not received any treatment. This decrease was significant.

In northern Cameroon, the decrease in the prevalence of infection in children between the ages of five and seven years is much greater than that observed in Liberia. This difference is probably linked to the number of doses administered. In Liberia, the parasitologic examinations of untreated children were conducted after two treatment rounds, while in Cameroon we evaluated the effect of five successive treatments. Previous studies have shown that an initial treatment with ivermectin brings about a dramatic decrease in skin microfilarial densities, whereas subsequent doses are followed by more gradual reductions.[12–15] The effect of ivermectin on the prevalence of skin microfilariae was also documented, and the figures show a progressive reduction in this indice after successive doses.[12–15] From these observations, we may assume that the reservoir of skin microfilariae available to the blackflies has continued to be reduced after the third treatment round in the Vina Valley, and that this progressive decrease led to an additional reduction in the transmission of onchocerciasis between 1989 and 1992.

The lower impact of ivermectin treatments on transmission in Liberia may also be linked to differences in the biology of the vectors: it is possible that in Liberia the blackflies coming from zones close to the treatment area may have maintained a pronounced transmission of onchocerciasis.[4] In northern Cameroon, this phenomenon of reinvasion is limited, on the one hand, by the presence of a range of mountains that geographically isolates the Vina Valley, and, on the other hand, by the fact that the vegetation is not favorable to wide dispersal of the blackflies. Moreover, the treatment area in the Vina Valley was extended widely after 1987. It is likely that these extensions led to an additional reduction in the infection rates of blackflies in the original area after the second treatment round.

Several factors make the results from northern Cameroon remarkable. First, in the Vina Valley, the coverage of the population that was achieved during the second and the subsequent treatment rounds was clearly less than that obtained in Liberia, where 97% of the eligible population was treated. Despite this, an important reduction in the transmission of the parasite has been achieved. This is probably due to the fact that in the Vina Valley, the treatment coverage during the first treatment round was high (more than 90% of the eligible population) and therefore this initial dose brought about a great reduction in the transmission of onchocerciasis infection in the original treated area. Thereafter, the microfilarial densities in the subjects who missed subsequent rounds increased to a higher level than in those who were treated, but previous studies have shown that this increase is very slow.[16, 17] In the original treatment area in the Vina Valley, the reduction of the microfilarial load was not significantly different (between 93 and 97% from the initial value) in people who received three, four, or five doses in a period of five years.[15] These observations could explain why a treatment coverage of the order of 60–70% is sufficient to produce a marked reduction of the transmission of onchocerciasis. Moreover, the reduction in treatment coverage observed since 1989 concerned principally the females 15–29 years of age. The pretreatment mean microfilarial densities in this population subgroup were not very high in comparison with the densities observed in males and in older females (Table 1). We may, therefore, assume that in the Vina Valley, the females 15–29 years of age contributed relatively little to the transmission of onchocerciasis and that the decrease in coverage in this group since 1989 had only a slight influence on the impact of the successive treatment rounds on transmission. The fact that treatment coverage decreased mainly for the 15–29-year-old females may be due to two factors. First, the clinical symptoms of onchocerciasis, which are related to the microfilarial load, are relatively low in this subgroup. Second, although we tried to avoid this phenomenon by staying in each village for a long time, the 15–29-year-old females were very busy with housekeeping activities, and therefore less disposed to come to the distribution

points. These factors may explain that this subgroup did not come for treatment as assiduously as the other people after the first two treatment rounds.

Second, the vectors of onchocerciasis in northern Cameroon belong to *S. damnosum* s.s. and *S. sirbanum* species. Among these species exists a phenomenon that limits the passage of microfilariae in the haemocele: the proportion of microfilariae that survive and develop to become infective larvae decreases as more microfilariae are ingested.[18] Conversely, *S. damnosum* s.s. and *S. sirbanum* may be able to maintain transmission even when skin microfilarial densities are low. Because of this phenomenon, one would expect the impact of mass ivermectin treatments on the transmission of the parasite to be limited in areas where onchocerciasis is transmitted by these species. This phenomenon of limitation is lower among *S. yahense* as well as among other vectors in the forest regions of West Africa. The incidence of onchocerciasis can therefore be expected to decrease to a greater extent and more rapidly in the areas where onchocerciasis is not transmitted by *S. damnosum.* s.s. and *S. sirbanum.*

Thus, it seems that despite some unfavorable factors, the impact of repeated mass treatments with ivermectin on the transmission of onchocerciasis can be quite pronounced. This effect will be greater as the treatment area is expanded to include more communities in the surrounding area.

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Authors' addresses: M. Boussinesq, J. P. Chippaux. J. C. Ernould, and J. Prod'hon, Antenne ORSTOM Aupres du Centre Pasteur du Cameroun, PO Box 1274, Yaounde, Cameroon. D. Quillevere, Vector Control Unit of the World Health Organization Onchocerciasis Control Programme in West Africa, PO Box 549, Ouagadougou, Burkina-Faso.

Reprint requests: M. Boussinesq, Antenne ORSTOM aupres du Centre Pasteur du Cameroun, PO Box 1274, Yaounde, Cameroon.

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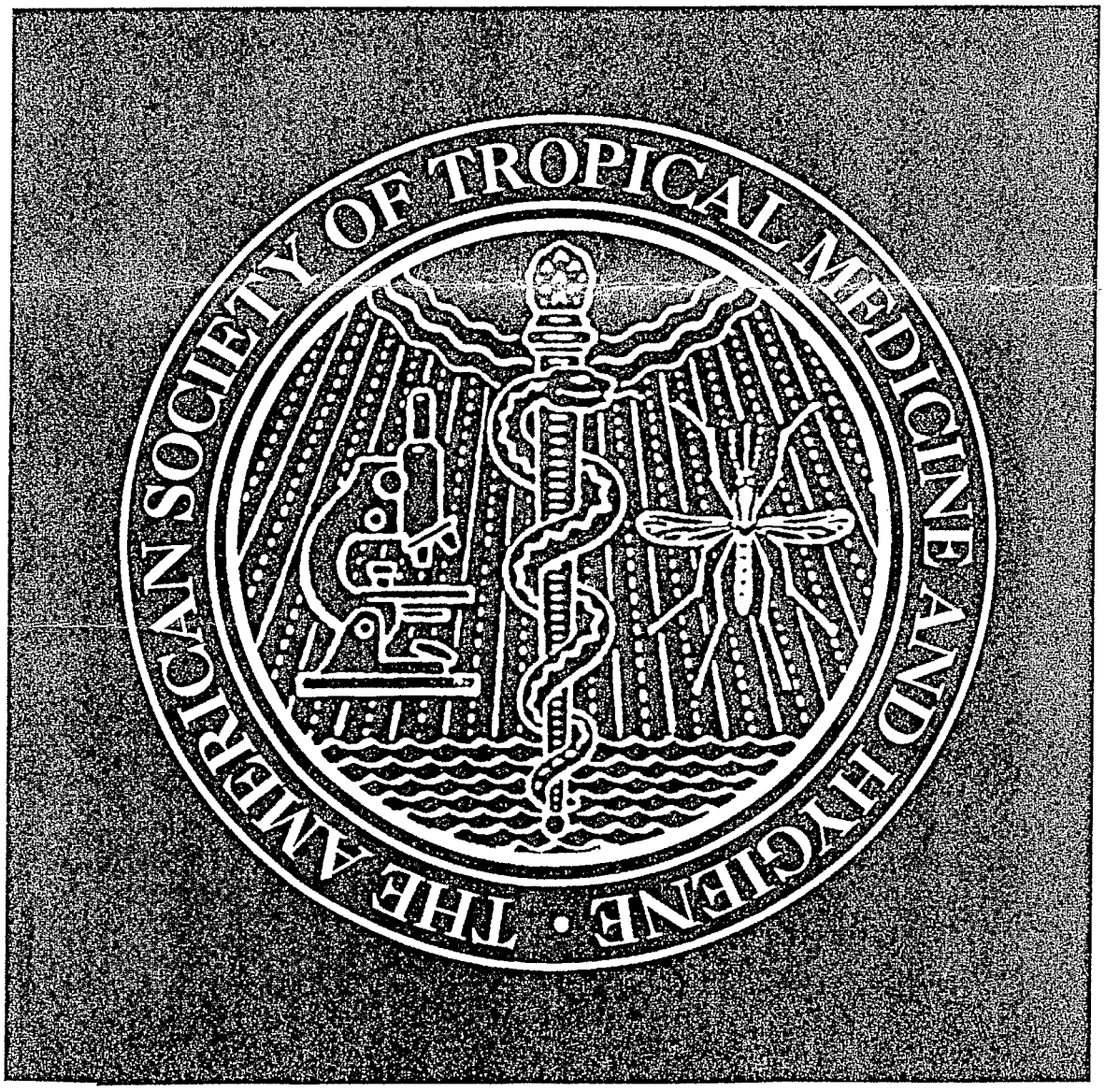

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