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Mosquito-borne infections in Fiji

III. Filariasis in northern Fiji: epidemiological evidence regarding the mechanisms of pathogenesis

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SUMMARY

During a filariasis survey conducted in northern Fiji in 1968–9 examinations were made for microfilaraemia, enlarged lymph nodes and elephantiasis. Analysis of the microfilarial densities at different ages and the number of anatomical sites showing lymph gland enlargement or elephantiasis have been used to provide evidence on the clustering of infections and pathogenesis.

Although there is no evidence of clustering of risk of infection, there is evidence favouring the clustering of adult filariae in individuals. Nevertheless the number of sites of lymph node enlargement do not correspond with this finding and statistical evidence suggests that lymph-node enlargement is not necessarily associated with the near presence in the body of adult filariae, whether dead or alive.

Males of Indian ethnic origin showed a higher prevalence of elephantiasis than males of Fijian ethnic origin, but women of either ethnic race showed prevalences lower than those of men.

The onset of elephantiasis at a site does not directly reflect the number of infections sustained in the local area, but it appears that filariasis first induces for a limited period a proneness to elephantiasis. During this period a random and discrete event may induce the onset of elephantiasis. The nature of the event is unknown, but it probably is not trauma.

INTRODUCTION

Acute lymphangitis and lymphadenitis, localized inflammation with or without abscess formation, were shown definitely to be associated with infection by the filarial nematode *Wuchereria bancrofti* (Lewis, 1875; Manson, 1875). In endemic areas it was found that enlarged lymph nodes often contained living or dead adult filariae (Bahr, 1912; O'Connor, 1932). Moreover, although there was at one time argument whether elephantiasis was in fact caused by *W. bancrofti* it is now generally accepted that these filariae play an important part in the induction of this affliction. Nevertheless there are still differences of opinion as to whether enlarged

lymph nodes and elephantiasis at a particular site are due to the local presence of adult filariae or are reactions resulting from the presence of filariae anywhere in the body (Lane, 1937; Wartman, 1947; Manson-Bahr, 1952; Nelson, 1966; Beaver, 1970). Likewise the pathogenesis of elephantiasis, including the influence of extraneous factors such as trauma (Selwyn-Clarke, 1961; Jordan, 1954), still awaits further clarification.

Recently there have been available laboratory models employing experimental animals representing the human picture (Schacher & Sahyoun, 1967). In order to compare these models with the human disease it will be necessary to a certain degree to compare what may be termed the dynamics of the pathogenesis; for example, the intensity, duration and internal localization of infections. With regard to human infections, a great deal of the required information could have been obtained by longitudinal surveys of many years duration, but for reasons of practicability they were not done in endemic areas. Now that drug treatment is available such longitudinal surveys are for ethical reasons virtually impossible. Hence information must be sought from the analysis of surveys made over a short period of time, but including individuals of different ages.

The more obvious factors likely to influence the development of lesions of filariasis are the duration of exposure (age), risk of acquiring an infection, clustering of infections within the individual, and rates of recovery. The incidence of extraneous factors such as trauma may also be considered, if they are known or indicated. The data from which the factors can be evaluated must be reliable and assessable in a numerical form. The presence of microfilaraemia, the presence of lesions, enlarged lymph nodes and elephantiasis, and the number of sites of the lesions on individuals are obtainable with relative ease and good accuracy. Figures of the prevalence among individuals of the memory of episodes of fever or lymphangitis have been used in the past, but we consider that figures based on the memory of self-diagnosed clinical conditions are open to too many interpretations for meaningful discussion.

We have analysed data on filarial lesions obtained during a filariasis survey in northern Fiji, 1968–9 (Mataika, Dando, Spears & Macnamara, 1971), in order to determine which different theories of pathogenesis might fit the observed epidemiological patterns of lesions.

METHODS

A survey of filariasis in northern Fiji on the islands of Vanua Levu, Taveuni and Koro was conducted in 1968 and 1969. The survey has been described in detail by Mataika *et al.* (1971) in regard to the examination for microfilaraemia of population samples. All persons examined for microfilaraemia also received the clinical examination described below. Additional to these persons, a high, but not specifically selected, proportion of the population of Taveuni and southern Vanua Levu were examined for enlarged lymph nodes. An attempt was made to examine and enumerate all individuals in Taveuni and southern Vanua Levu who were suffering from elephantiasis.

Clinical examination

On both sides of the body the epitrochlear, axillary, inguinal and popliteal lymph nodes were examined for enlargement. The criterion for enlargement was the presence at the site of examination of one or more distinctly palpable glands being at least 1·5 times the normal size. Small shotty glands were not considered enlarged.

The limbs, breasts and genitalia were examined for elephantiasis, which was accepted as being present if there were signs and symptoms of sustained oedematous swelling with chronic skin changes.

RESULTS

Prevalence of microfilaraemia

These results have been presented already by Mataika *et al.* (1971).

Intensity of microfilaraemia (microfilarial density)

The results of surveys among Fijians in Taveuni and southern Vanua Levu are shown in Table 1.

Table 1. *Microfilariae in 20 mm.³ blood (Mf. D.) of Fijian male carriers in two areas of northern Fiji*

Age (years)		Taveuni & Koro	Southern Vanua Levu Coastal villages
5–9	No. examined	11	10
	Mf. D.*	9	6
	S.D. *L*†	0·63	—
10–14	No. examined	12	5
	Mf. D.	10	5
	S.D. *L*	0·64	—
15–19	No. examined	10	9
	Mf. D.	14	3
	S.D. *L*	0·47	—
20–29	No. examined	34	27
	Mf. D.	22	9
	S.D. *L*	0·53	0·68
30–39	No. examined	23	41
	Mf. D.	15	25
	S.D. *L*	0·68	0·60
40–49	No. examined	12	26
	Mf. D.	36	12
	S.D. *L*	0·55	0·49
50–59	No. examined	18	14
	Mf. D.	8	17
	S.D. *L*	0·45	0·80
60+	No. examined	11	11
	Mf. D.	9	7
	S.D. *L*	0·51	0·77

* Mf. D. = Geometric mean number.

† S.D. *L* = standard deviation of $\log_{10}$ of individual Mf. D.

Among those harbouring microfilariae in every group or subgroup in which sufficient data were collected, it was observed that the distribution among individuals of the number of microfilariae per 20 mm³ of their blood approximated a log.-normal distribution. For the various groups the geometric mean number of microfilariae per 20 mm.³ blood has been calculated. The standard deviation has been calculated from the transformed figures:

$$\text{S.D. } L = \text{standard deviation of } y,$$

where $y = \log_{10}$ microfilariae per 20 mm.³ blood.

Enlarged lymph nodes

For individuals living in different areas and for different age-groups within these communities the prevalence of enlarged lymph nodes and the prevalence of microfilaraemia showed a moderate correlation among males, but among females the correlation was low. Hence the main analysis of prevalence of enlarged lymph nodes has been made in regard to males. The results are presented in Table 2.

The distribution of the number of anatomical sites showing lymph-node enlargement among Fijian males from three different areas and among 67 Fijian males

Table 2. *Prevalence of enlarged lymph nodes at one or more sites among Fijian males in three areas*

		Area		
			Vanua Levu	
Age (years)	Fijian Males*	Taveuni Koro	Southern coastal	Northern coastal
0–4	Ex	416	277	76
	%+	7·7	1·1	0·0
5–9	Ex	445	275	79
	%+	22·8	5·1	6·3
10–14	Ex	421	220	64
	%+	27·1	31·2	6·3
15–19	Ex	210	131	37
	%+	43·8	19·8	27·0
20–29	Ex	297	167	37
	%+	45·1	14·4	13·5
30–39	Ex	238	187	45
	%+	50·0	29·4	22·2
40–49	Ex	185	112	31
	%+	60·5	40·2	12·9
50–59	Ex	143	89	34
	%+	58·3	56·2	20·0
60+	Ex	84	91	16
	%+	71·4	54·9	37·5
All ages	Ex	2442	1549	419
	%+	34·7	19·1	12·2

* Ex = number examined. %+ = percentage with enlarged nodes.

Table 3. *Distribution and mean number of sites of lymph node enlargement among Fijian males*

Area	Description of population	Age (years)	No. exam.	% with enlargement at no. of sites equal to or more than:					Mean no. sites in cases with enlargement at one or more sites
				1	2	3	4	5	
Taveuni and Koro	Without Mf	⩾ 30	90	61	41	13	10	0	2·06
	With Mf	⩾ 30	62	32	25	6	3	0	2·06
	Unselected	⩾ 30	650	58·6	38·0	13·3	5·9	0·5	1·98
	Unselected	All ages	2442	34·6	19·0	5·3	2·0	0·1	1·77
Southern Vanua Levu coastal	Without Mf	⩾ 30	114	28	15	2	0	0	2·06
	With Mf	⩾ 30	89	37	9	1	0	0	1·27
	Unselected	⩾ 30	479	41·6	23·9	7·4	3·3	0·4	1·84
	Unselected	All ages	1549	19·1	9·9	2·4	1·0	0·1	1·71
All areas (limited survey)	Elephantiasis patients	⩾ 30	67	88·0	68·6	31·3	11·9	1·5	2·29

with elephantiasis observed in Taveuni and southern Vanua Levu are given in Table 3.

Also shown are data on individuals who were examined both for enlarged lymph glands and microfilaraemia. An analysis of data pertaining to males of all age-groups coming from Taveuni and southern Vanua Levu showed that in order to make the distribution of the number (x) of anatomical sites showing lymph-node enlargement one that is nearly normal, transformed figures (z) should be used where $z = x^{-0.867}$. The exponential is sufficiently near to 1·0 to indicate that the distribution is virtually arithmetic-normal (Taylor, 1961).

Elephantiasis

The population at the time of the survey has been estimated as that of the 1966 census (Zwart, 1968) with an additional natural increase of 5·5 %. From these estimates and the observed number of cases of elephantiasis, prevalences have been calculated for various population groups. Since some cases of elephantiasis may have been overlooked the prevalences given may be considered as the lowest estimates.

Table 4. *Minimum estimated prevalence of elephantiasis among the population of Taveuni, Koro and southern Vanua Levu*

	Fijians				Indians			
	Males		Females		Males		Females	
Age (years)	No.	%	No	%	No.	%	No.	%
0–9	0	0	0	0	0	0	0	0
10–14	1	0·1	1	0·1	0	0	0	0
15–19	1	0·1	2	0·2	0	0	0	0
20–29	5	0·3	5	0·2	2	0·6	4	1·2
30–39	20	1·2	20	1·2	6	2·8	6	3·2
40–49	29	2·5	20	1·9	10	6·8	2	1·9
50–59	54	6·8	33	4·5	9	11·3	1	1·5
60+	42	6·7	20	3·3	7	9·0	0	0
All ages	152	1·08	101	0·73	34	1·59	13	0·65

No. = number observed. % = percentage of population.

In Table 4 are shown for Fijians and Indians in Taveuni and southern Vanua Levu prevalences of elephantiasis according to age; and in Table 5 are shown for the same groups the distribution of the number of anatomical sites with elephantiasis among patients. At the foot of the table are given the percentages which are cumulative as the number of sites decreases. The percentage prevalence is reduced by a factor of about 2·6 for each additional site affected in males, and by a factor of about 3·2 in females.

Among Fijian males afflicted with elephantiasis at only one anatomical site the ratio of those with lesions in the right arm to those with lesions in the left arm was 1·2:1; and as regards legs the numbers were nearly equal; yet the number of

Table 5. *Distribution of number of anatomical sites affected with elephantiasis in Fijians (ref. also Table 4)*

Age (years)	Males: % with lesions at specified no. of sites				Males: Mean no. sites	Females: % with lesions at specified no. of sites				Females: Mean no. sites
	1	2	3	4		1	2	3	4	
0–9	0	0	0	0	—	0	0	0	0	—
10–14	(100)	0	0	0	1·00	(100)	0	0	0	1·00
15–19	(100)	0	0	0	1·00	(100)	0	0	0	1·00
20–29	(80)	0	(20)	0	1·40	(180)	0	(20)	0	1·40
30–39	85	10	5	0	1·25	90	10	0	0	1·10
40–49	69	17	14	0	1·45	85	15	0	0	1·25
50–59	57	26	11	6	1·65	61	27	6	6	1·58
60+	43	38	5	14	1·90	50	30	15	5	1·75
All ages	61	24	9	6	1·61	71	20	6	3	1·41
Cumulative % (all ages)	100	39	15	6	—	100	29	9	3	—

patients giving a history of severe trauma to the right arm were at least seven times greater than those giving histories related to the left arm. In regard to legs the ratio was 2 to 1.

DISCUSSION

In this discussion we shall consider the pathogenesis of the filarial infection uninfluenced by specific therapeutic drugs.

Ethnic and genetic susceptibility or tolerance to infection

The high prevalence of elephantiasis among Indian men suggests a true ethnic difference. To some extent the higher prevalence among Indian than among Fijian men under similar conditions of exposure to infection may be exaggerated by the slighter build of Indians, making minimal signs of elephantiasis more conspicuous and easily recognizable.

Sex differences in prevalences of enlarged glands and elephantiasis parallel those of differences in prevalence of microfilaraemia. Since it has been indicated by Mataika *et al.* (1971) that, among Fijians at least, the sex difference regarding microfilaraemia may be largely determined by recovery rate and not exposure risk, it is suggested that the same factor may influence the other manifestations.

Load of infection

Mataika *et al.* (1971), by observing age-prevalences of microfilaraemia in the population, indicated the risk of acquiring microfilaraemia. In a limited search, moreover, they were unable to show evidence of an appreciable clustering of risk of acquiring microfilaraemia. A clear distinction must be made, however, between a clustering of risk of infection and a clustering of the numbers of reproductively active filariae which survive in an individual and manifest their presence by liberating microfilariae. Hairston & Jachowski (1968) have indicated that such clustering within individuals occurs among the people of Samoa; and the rise of up to six times in the microfilarial densities between those of the younger and those of the older age-groups in our observations could be attributed to a similar clustering (Table 1). It was with a view towards elucidating the problem of clustering that the observations were made on the number of sites of lymph node enlargement (Table 3). The plan of the survey was based on the hypothesis that lymph-node enlargement at a site was due to the local presence of one or more adult filariae. The finding that the statistical distribution of the number of sites with enlargement is arithmetic-normal, but not approaching a Poissonian distribution if individuals without any enlargements are considered, indicates that enlarged nodes are not caused by the near presence of adult filariae, and cannot be used to evaluate clustering. The evidence for clustering is still based primarily on the work of Hairston & Jachowski with the supporting evidence of microfilarial densities. Clustering not being related to risk of infection could be due to host–parasite relationship, or interparasite effects producing either a synchronism of activity or a regression, if the clustering became too high.

Associated factors

There is unlikely to be much variation in the virulence of the parasite in the relatively uniform epidemiological situation in Fiji. The immune response is still too little understood to be discussed further.

The enlargement of lymph nodes is certainly associated with filarial infection, although in Fiji as elsewhere there are many other causes (O'Connor, 1932; Jordan, 1955). From our evidence it appears that in individuals with filarial infection there is a factor which almost regardless of the number of adult filariae induces enlargement of lymph nodes, at a random number of sites, but with a mean of one to two sites. Once enlargement has been induced regression is slow, so that subsequent infections may increase the mean number of sites. The presence of microfilariae in the blood and escaping into the tissue spaces could be a factor.

Although there are causes of elephantiasis other than filariasis, it may be assumed from the work of Bahr (1912) that in Fiji filariasis is the main predisposing factor. If elephantiasis resulted merely from an accumulation over the years of filarial infections then the incidence rate (the number of new cases arising per unit time) could be expected to show a gradual increase with age until finally it became equal to the incidence rate of filarial infection. Nevertheless we found that after the initial rapid rise in the age-prevalence percentage the percentage reaches a plateau or may fall (Table 4). Such a finding is not unique to Fiji (Hayashi, 1962; Wilson, 1961). Since recovery from elephantiasis is rare, we might account for the plateau of prevalence in the older age-groups by postulating an increased mortality among patients. Such a postulated mortality rate, however, would be unrealistically high. Hence a combination of a slightly increased mortality among cases and a rapidly diminishing incidence rate after the age of peak incidence is indicated. Such a situation could occur if susceptibility to the development of elephantiasis rose during the 35- to 50-year age period and was subsequently lost, not to be reacquired.

Elephantiasis is associated with enlarged lymph nodes in over 80 % of cases, a figure significantly higher than that of the remainder of the population of similar age (Table 3). The mean number of sites of lymph-node enlargement in elephantiasis patients is slightly higher than that of unaffected individuals, but, considering the unhealthy state of the elephantiasis skin, it is not greatly higher. The numerical distribution of the number of sites showing elephantiasis is different from the distribution of lymph-node enlargement. There is a constant proportion in the reduction of prevalence for each additional site affected. This evidence indicates that among individuals susceptible or prone to elephantiasis the lesion itself is induced at a site by a randomly discrete event. That trauma is not the discrete event (Selwyn-Clarke, 1961) is indicated by the comparative divisions of prevalence between right and left sides for histories of trauma and for lesions of elephantiasis. Sepsis could be a cause.

Although we have not been able on epidemiological evidence to show the exact cause of the lesions in filariasis, we have been able to indicate the patterns of pathology into which theories should fit and to point out where existing theories may be inadequate.

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