THE ROLE OF EPIDEMIOLOGY IN STUDIES OF THE PATHOGENESIS OF TROPICAL DISEASES

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This paper attempts to show the links that tie together epidemiology and pathology in research concerned with tropical diseases. On first sight, a discussion of links between these two different disciplines may be viewed as an arduous, factitious exercise. However, on closer examination it becomes apparent that epidemiology and pathology cover some common grounds which are of great relevance for future studies of tropical diseases.

According to modern concepts, epidemiology is defined as a discipline that is ultimately concerned with studies of aetiological factors and of determinants in the pathogenesis of disease. Although these new definitions (Paul, 1958; MacMahon *et al.*, 1960; Barker, 1973; Lowe and Kostrzewski, 1973; Lilienfeld, 1976) are broader than the older ones, they have not changed the traditional role and basic function of epidemiology to study the distribution and dynamics of disease in human populations.

There is a common bond between epidemiology and pathology: both disciplines aim to integrate medical findings (Sartwell, 1972). Pathologists refer to the field of "geographical pathology" which is close to what epidemiologists mean by "geographical epidemiology". One of the oldest descriptions of what August Hirsch in 1883 called the "Geographical and Historical Pathology" is almost identical with modern definitions of epidemiology. As Hirsch stated, it is: "Aetiological inquiry, climate and medical anthropology; geographical and historical pathology is the knowledge of the distribution of disease in time and space, and of the causal connexion between them and the human environment".

A new trend of research is that of multidisciplinary teams in which epidemiologists collaborate with clinicians, pathologists, biologists, biostaticians and specialists of many other disciplines. As a result of such cooperation, the role of epidemiology has extended to aiding clinicians in the identification of disease syndromes and of their causes, including the factors that are responsible for variations of the clinical picture of the same disease as may be observed in different populations and in different geographical areas.

The methods used in modern epidemiology are uniquely suited to identify and quantify the factors that interact in the complex causation of tropical diseases and nutrition, and that are involved in the pathogenesis of chronic parasitic diseases. They can also help in making a distinction between the relative contributions of different potential causes of disease on the clinical picture. In many rural areas of developing countries in the tropics, endemic parasitic infections are often found together with a host of other infectious and non-infectious diseases and health conditions. Moreover, many of these infections involve agents of only facultative pathogenicity, causing diseases that may lack pathognomonic significance even in their advanced stages. These features of tropical parasitoses are usually combined with a lack of medical facilities in the areas and populations affected. Together, these factors are responsible for the considerable deficiencies that still exist in the recognition and reporting of tropical

diseases. Without such information, adequate surveillance and disease control are not possible.

Under field conditions, many of the parasitic infections and diseases remain unrecognized and are often lumped together with other ill-defined conditions in the anonymous pool of undiagnosed and often undiagnosable illness. To solve questions arising from the complex aetiology of illnesses in tropical villages and to study the interactions between different causes of disease, close co-operation between epidemiologists and pathologists is essential.

The uses of epidemiology and the sequence of studies needed in a research programme of tropical diseases may be summarized as follows: At first the prevalence and distribution of infections and related diseases must be determined. Thereafter, information on the dynamics of infection and disease should be obtained by determining their incidence, relapse, reversion and, if possible, disease-specific death rates in a carefully selected population sample. Further studies of the patterns of infections and disease in different geographical areas using standardized methods of measurement will often lead to the identification of those factors or contributing causes that determine the final outcome of a disease in a given area. This applies especially to the study of chronic parasitic diseases. The clues may then be used to develop a hypothesis about the essential factors involved in disease causation. This hypothesis can be tested by examining the characteristics of the affected individuals in relation to other persons in the group from which the cases are drawn. Finally, the validity of the conclusions about causation can be studied in greater detail by controlling one or more of the specific disease determinants either by geographic comparison or by experimental design.

Before presenting the outline of a research strategy for the epidemiology of tropical diseases as it is now being developed by the UNDP-WHO Special Programme for Research and Training in Tropical Diseases, presented herein are examples that illustrate different uses of epidemiology in studies of selected tropical diseases that have involved the collaboration of pathologists.

The first example deals with the case of an unexpected clinical finding made in the course of routine field studies in a village of the African savannah. The unexpected finding in that study was the detection of numerous microfilariae of *Onchocerca volvulus* in the urine of a sizeable proportion of the village population. The steps that were subsequently taken to examine the clinical and epidemiological significance of this finding and to elucidate the pathogenesis of microfilaruria in onchocerciasis, are shown in Table 1.

Table 1

Observation of "new" clinical manifestations of a disease (Example: microfilaruria in onchocerciasis).

1. Assessment of its frequency and distribution in a sample of the general population.
2. Confirmation that manifestation occurs in other endemic areas.
3. Search for associations between occurrence of the "new" sign and other factors.
4. Development of a hypothesis on the pathogenesis of the "new" manifestation.
5. Examination of the validity of the conclusions.
6. Studies of its clinical and epidemiological significance.

The results of the epidemiological studies showed that microfilaruria occurred in both sexes and in all age groups but that it was closely associated with the intensity of infection as determined by counts of microfilariae from routinely taken skin biopsies

(Table 2). As our own (Buck *et al.* 1971,1973, 1977) and other research teams extended their studies of onchocercal microfilaruria to other endemic areas of the disease in Africa and Central America, it rapidly became evident that this "new" manifestation was a common complication of onchocerciasis and that it had been overlooked and did not fit into the contemporary concepts of the disease.

Table 2

Onchocerca volvulus skin counts and prevalence of microfilaruria.

Microfilarial count in skin snip	Number in group	With microfilaruria	
		Number	Per cent
0	13	3	23.1
1-20	27	7	25.9
21-50	23	6	26.1
51-100	56	18	32.1
200+	17	9	52.9
Total	136	43	31.6

A systematic search for associations between various host factors revealed that, in addition to the already mentioned close association between microfilaruria and infection intensity, there was also a correlation with low titres (Fig. 1) in indirect haemagglutination tests with *O. volvulus* and *Dirofilaria immitis* antigens, respectively; with double infections of *Loa loa* and *Dipetalonema perstans;* and with elevated transaminase levels in serum specimens (Fig. 2). Consequently, the hypothesis of onchocerciasis occurring as a systemic disease with microfilaruria as one of its manifestations, was tested and onfirmed by parasitological, clinical and pathological studies. This conclusion has been strengthened by further investigations which included the use of diethylcarbamazine in

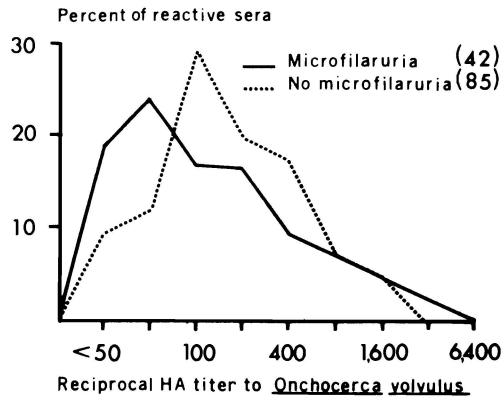

Fig. 1—IHA tests showing low titres.

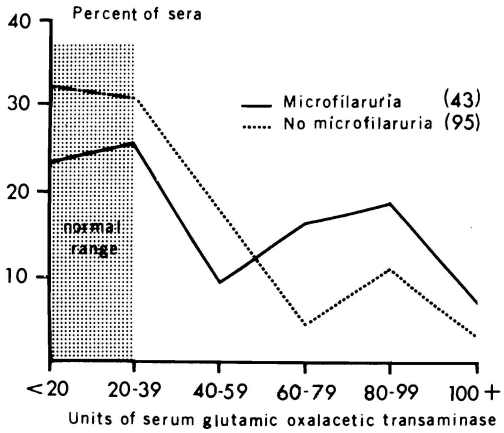

Fig. 2—GOT levels in serum specimens.

provocative tests to mobilize microfilariae (Table 3). The clinical and epidemiological significance of the urinary complications of onchocerciasis has not yet fully determined.

However, there are clues that microfilaruria may be associated with pathological changes of the kidney as shown in Fig. 3 of a retrograde pyelography of a 40-year-old woman with microfilaruria, showing calyceal distortion in the middle and lower system; and backflow of contrast material from the lower calyces into the renal papillae on the left side. The radiographic changes are com-

Table 3

Mean number of microfilariae *(O. volvulus)* in urine, blood and sputum of onchocerciasis patients before and after 50 mg of diethylcarbamazine and placebo.

Medication	Before treatment	After treatment			
	Urine	Urine		Blood	Sputum
		3 hours	18-24 hours	3 hours	18-24 hours
DEC (10 pts.)	1 ± 0.3 (0 - 5)	28 ± 22.9 (0 - 187)	79.4 ± 45 (1 - 416)	22.5 ± 10.5 (0 - 104)	140.9 ± 63.8 (0 - 367)
Placebo (Vit. C) (4 pts.)	53 ± 4.0 (0 - 17)	2.0 ± 1 (0 - 6)	1.0 ± 6 (0 - 3)	9.0 ± 4.5 (0 - 28)	6.0 ± 0 (6)

Table 4

Relationships between age and organ distribution of *P. westermani* (143 cases, including 3 autopsies).

Age group (year)	Total No.	Lungs	Pleura	Brain	Abdomen	Skin	Kidneys	Spermatic cord	Testicles	Extrathoracic	Extrapulmonary
5-9	9	9	0	1	0	0	0	0	0	1	1
10-14	39	37	2	2	1	0	0	0	2	5	7
15-24	50	45	10	5	1	1	0	0	0	7	17
25-34	27	25	7	4	1	0	1	1	1	8	15
35-44	14	14	3	0	0	0	1	0	0	1	4
45 +	4	4	0	0	0	0	0	0	0	0	0
Total	143	134	22	12	3	1	2	1	3	22	44

Fig. 3—A retrograde pyelography showing pathological changes.

patible with chronic infection and suggest focal papillary necrosis.

As a second example of the contributions epidemiological studies can make to the interpretation of disease phenomena, is a case study of combined epidemiological and clinical investigations of paragonimiasis in a village of South Korea in which virtually the entire population had been examined for clinical signs of this chronic infection (Sadun and Buck, 1960). The various steps taken in sequence, to define the range of the signs and symptoms of paragonimiasis in that area, are summarized in Table 5. As a result of these efforts, the frequency distribution of the various clinical manifestations of the disease, alone and in combination, could be determined (Table 4).

Scientists should take cognizance of the problems caused by multiple infections and multiple disease states as they present so often in rural areas of developing countries in the tropics. In this unexplored field, much needs to be done. Our present knowledge about the

Table 5

Definition of the range of signs and symptoms of a disease (paragonimiasis).

1. Determination of prevalence and distribution of infection in a community.
2. Clinical examination of all infected persons to determine types and frequency of all (specific and non-specific) signs and symptoms.
3. Clinical evaluation.
4. Frequency distribution of clinically inapparent and overt infections by types of manifestations.

influences of disease interaction on the clinical picture is rudimentary. This point may be illustrated by the frequency and size of hepatosplenomegaly as a physical sign of choice for both the malariologist and specialist of schistosomiasis to appraise endemicity levels and the frequency of morbidity caused by either one of these two infections. The steps to be taken for adequate examination of the problem are outlined in Table 6. A comparison of the prevalence of splenomegaly and hepatomegaly between African villages with uncontrolled hyperendemic malaria and with and without schistosomiasis *(Schistosoma haematobium* and *S. mansoni)*, is shown in Fig. 4. In this figure, the frequency and size of each splenomegaly and hepatomegaly are combined into a single index which facilitates making quantitative comparisons between localities and populations. The graphs indicate that malaria and *S. mansoni* infections, but not malaria and *S. haematobium*, produce combined effects on the liver and spleen that have resulted in measurable increases of both the prevalence and the size of hepatosplenomegaly. Further definitive studies of the pathological and clinical significance of this interaction must be carried out by specialists in close co-operation with epidemiological field teams.

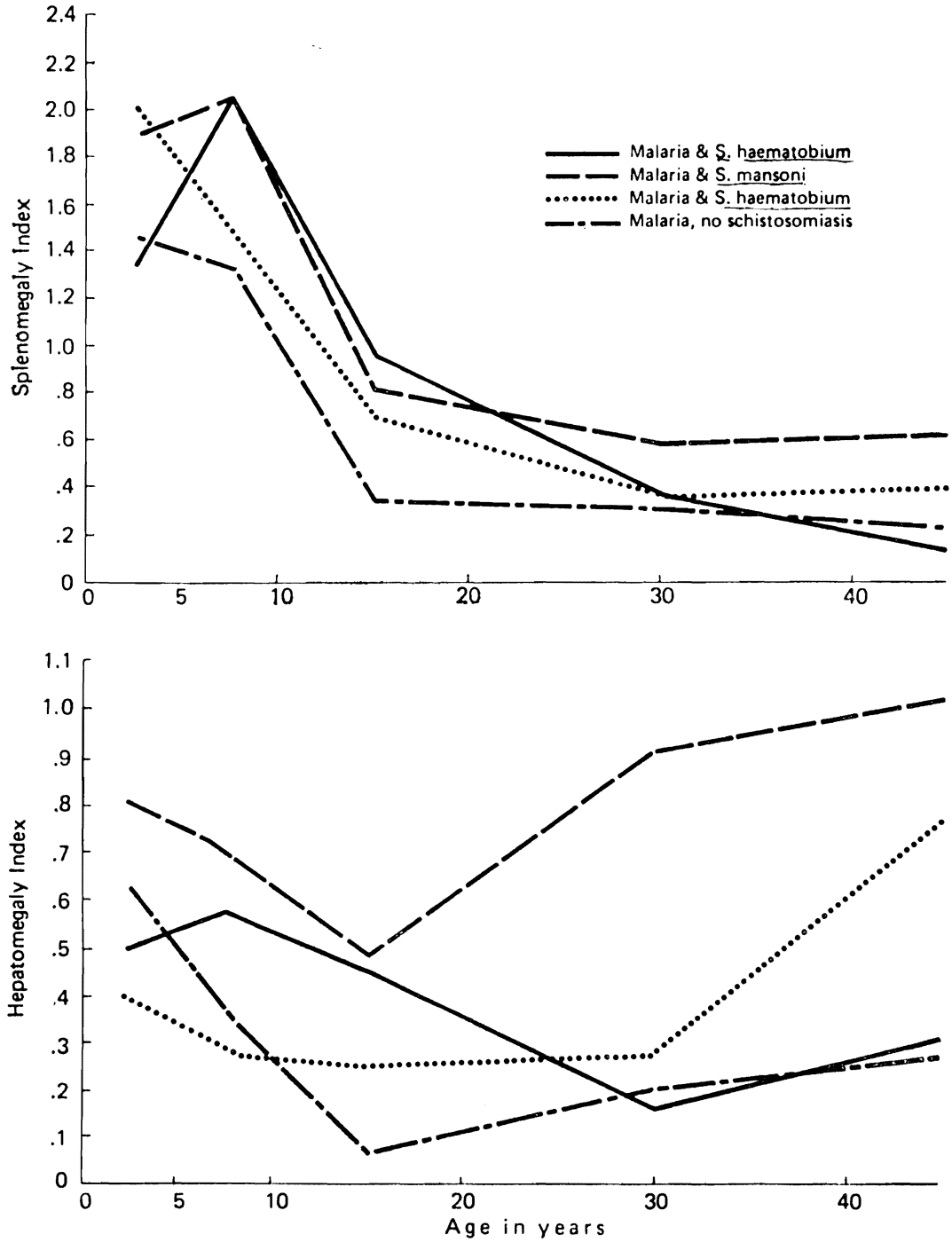

Fig. 4—Splenomegaly and hepatomegaly index* in African villages with or without schistosomiasis (*S.haematobium* and *S.mansoni*) by age.

*Index = $\frac{\text{prevalence (\%)} \times \text{size.}}{100}$ sizes are scored from 1-4.

Table 6

Disease interactions in endemic areas with polyparasitism and other multiple infections and conditions (Hepatosplenomegaly).

1. Measure endemicity level and distribution of each disease in the same community.
2. Determine the state of the infections in each individual.
3. Compare the relative frequency and severity of the condition(s) between persons with and without single or multiple infections.
4. Establish quantitative correlations between infections, their intensity, age, sex and other important host factors.
5. Clinical evaluation of findings.
6. Pathological evaluation of findings.

Perspectives and priorities for epidemiological research of tropical diseases were analyzed by expert members of a Scientific Working Group on Epidemiology convened in June 1977 under the auspices of the UNDP-WHO Special Programme for Research and Training in Tropical Diseases. In its recommendations, this Group laid emphasis on the following tasks:

1. To establish the need for a unifying epidemiological methodology to cover as many of the tropical parasitic diseases as possible;
2. To formulate the concepts and logistics behind such methodology as an alternative to the vertical epidemiological approach, which is wasteful of manpower as well as of resources and is inadequate as a basis for formulating a rational operation of control programmes;
3. To put methods to the test in a multidisciplinary research programme, initially to be established at the Tropical Disease Research Centre in Ndola, Zambia;
4. To provide a training base for such a multidisciplinary and multifactorial research.

The Group considered that epidemiological research had an important contribution to make in studies of morbidity and mortality caused by chronic parasitic diseases. In such studies quantitative assessments have remained difficult for a number of reasons, among others, the low pathognomonicity of many clinical manifestations of these diseases; the frequency of multiple infections of the same persons; the often vague constitutional character of symptoms that are not easy to elicit accurately; the lack of any specific symptoms or signs of ill-health in the majority of the infected persons; and the usually inadequate medical facilities in the areas where the diseases are most abundant. Linking again epidemiology and pathology, it was felt that there was a dearth of information concerning the morbid anatomy of the chronic parasitic diseases of the tropics as they occur in different parts of the world. For this reason, close co-operation between epidemiological teams and pathologists would be essential for detailed studies on the pathology and pathogenesis of these chronic parasitic infections. It was recommended that autopsies should be carried out whenever possible and that biopsy material be sent to appropriate laboratories and reference centres that participate in the Special Programme. The initial research combining epidemiology, clinical and, hopeful, pathological studies will commence at the WHO Tropical Disease Research Centre in Ndola, Zambia, where the preparations have proceeded well and are now in their final stage.

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