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The Use of Catalytic Models as Tools for Elucidating the Clinical and Epidemiological Features of Trachoma

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A change in the clinical pattern of trachoma from a grave to a milder form has been noted in several endemic areas in recent years and has been attributed to improvements in biophysical conditions, as well as to specific control measures. The disease, thus modified, frequently presents difficulty in diagnosis under field conditions, and equivocal cases, which are sometimes encountered in relatively large numbers, pose a problem in the assessment of over-all incidence, prevalence and relative gravity of trachoma in the area. The problem assumes particular importance in field studies, such as therapeutic and vaccination trials.

In an attempt to determine by epidemiological methods the true nature of these clinically equivocal cases, the data collected during a survey of the prevalence of trachoma in Taiwan have been subjected to an intensive study with the aid of catalytic models. The evidence is that most, if not all, of these cases are trachomatous.

INTRODUCTION

Two characteristic features of trachoma—granulations (follicles) and scarring of the conjunctiva—were recognized in Egypt in Pharaonic times. Corneal pannus was described in mediaeval manuals of the Greeks and Arabs. During the first half of the present century, when biomicroscopy came into use, refined clinical studies of trachoma carried out in the Middle East, North Africa, Europe and the United States of America confirmed the concept of a clear-cut disease entity with the three above-mentioned cardinal signs. Workers in these areas considered pannus a *sine qua non* in the diagnosis and there was almost universal acceptance that it occurred very early in the course of the disease.

In Japan, however, Ishihara (1941), Mitsui (1949) and Mitsui et al. (1962) claimed that experimental trachoma in human volunteers could run its course without pannus or cicatrization; moreover, they revived the hypothesis, first broached by Fritsch, Hofstätter & Lindner (1910) and supported by Jones (1961), that trachoma and inclusion conjunctivitis have a single etiologic agent. Jones (1961, 1964) further claimed that this agent is capable of producing a spectrum of disease entities, with typical trachoma at one end, typical inclusion conjunctivitis at the other, and a range of intermediate forms in between. This is still a subject of controversy among trachomatologists and intensive research is being directed towards clarifying the situation.

In the meantime, in the course of surveys carried out in other areas where trachoma is endemic (Australasia, Asia, Central and South Africa) many cases were encountered which on *macroscopic examination* [2] presented only one characteristic sign of trachoma.

The above considerations are reflected in the reports of the WHO Expert Committee on Trachoma (1952, 1956, 1962). The first report (1952) dealt, in the clinical section, almost exclusively with the classification of what may be called " classical " trachoma. In the second report (1956) the Committee " agreed that differences occur in the clinical and epidemiological picture of trachoma as found in different regions "; it recommended criteria for diagnosis (presence of *at least two* of four cardinal

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[2] The term " macroscopic examination " is used for convenience in this paper to cover the use of binocular and monocular loupes, simple focal illumination and other diagnostic devices applicable under field conditions, as distinct from examination with the major conventional biomicroscope. By " macroscopic pannus " is meant pannus that can be detected under field conditions (usually not less than 2.0 mm extension from the limbus). " Microscopic pannus " is minimal but definite neovascularization, which can be observed only with a biomicroscope.

signs) and discussed the differential diagnosis. The Committee's third report (1962) redefined the evolutive stages of trachoma and introduced a new clinical designation, namely, " ND " (diagnosis Not Determined), which covers those cases presenting only one cardinal sign. The Committee recommended that " such (ND) cases should be included in any routine treatment programme pending further clinical and laboratory studies but should be excluded from the appraisal of results ".

The frequency with which ND cases are encountered differs from one area to another. When they are met with infrequently in an area of high trachoma endemicity, as in North Africa, they are merely a source of academic interest and, for practical purposes, may be ignored. When they are seen in relatively large numbers in areas of moderate or low trachoma endemicity, as in Taiwan, they present a serious problem to the clinician and the epidemiologist.

The Taiwan survey, carried out in 1960-61 before large-scale treatment operations were commenced, covered a multistage stratified sample of the island's 11 million population. The sample comprised 36 731 persons in 6101 households. More than 99% (36 507 in 6092 households) of the sample was examined. Clinical examination, using simple focal illumination and a $\times$ 10 monocular loupe, disclosed 15 149 cases of frank (i.e., " two signs ") trachoma and 2378 cases of " one sign " trachoma (later relabelled " ND cases " in accordance with the Expert Committee's recommendation).

As far as the frank trachoma cases were concerned there was a direct correlation throughout between local prevalence rates and the relative gravity of the disease. The ratio between ND cases and frank trachoma varied directly with the prevalence of the latter, between 1 : 4 in areas of low prevalence ($<10\%$ active trachoma) and 1 : 15 in areas of high prevalence ($>35\%$ active trachoma). In the great majority of these ND cases the diagnostic sign that was missing (or undetectable by macroscopic examination) was pannus. However, some 20 ND cases encountered in a routine school inspection were examined with the biomicroscope by three experienced trachomatologists. In all but one case " microscopic " pannus was present. In some of the above cases the biomicroscope also revealed epithelial keratitis and/or very fine cicatricial changes that could not be detected with a simple loupe (Thygeson, Maxwell-Lyons & Chang—unpublished work, 1964). These epidemiological and clinical findings strongly suggest that, in Taiwan at least, a large proportion of ND cases are, in fact, mild cases of trachoma.

If, in the Taiwan findings, the ND cases are added to the frank trachoma cases the correlation between local prevalence rates and relative gravity becomes even more sharply defined. This would suggest that in some communities, favoured by environmental and other factors but in the absence of organized treatment, trachoma had been diminishing both quantitatively and qualitatively, whereas in other, less favoured communities, it had remained both prevalent and grave. This is an interesting " retrospeculation " for which it is difficult to produce any supporting evidence. The whole subject, however, is of great potential importance. It is likely that improvements in sanitation, mass-treatment operations and, perhaps, vaccination programmes will lead to the emergence of large numbers of " ND cases ", which, as has been seen, are notoriously difficult to interpret clinically under field conditions. Whether ND cases are classified as trachomatous or not will obviously affect the estimated incidence, prevalence, and cure rates of trachoma.

The study here presented attempts to assess changes in the epidemiology of the disease over the past 20 years; the material for the study is drawn from the epidemiological survey of trachoma carried out in Taiwan in 1960-61. The question whether or not to include ND cases in the age-specific trachoma prevalence rates is raised and an attempt is made to determine epidemiologically the true identity of these cases.

Catalytic models, as developed by Muench (1959), are applied to age-prevalence curves. Catalytic curves attempt to describe mathematically the rate of change of a variable as a function of time. The epidemiological situation under discussion is assumed to involve a " quantity " of trachoma cases that changes—by time—in direct relation to the " amount " of susceptibles that remains to be changed. This exponential relationship is considered as the manifestation of the interaction between infection and the population on which it acts, the rate of change being dependent on the " force of infection ", i.e., the magnitude of infection—presumed constant—per unit of population per unit of time. " Certainly such a force of infection contains variables associated with the nature of the host, his method of life, his previous experience of infection; the nature of the infective agent, its variability in virulence and mode of transmission;

together with a plethora of others, of many of which we may not even be dimly aware. Yet we are examining an *average* effect of this complex and, on the average, in a large enough group of similar persons, a corresponding complex will exercise similar effects and so can conveniently be regarded as a unit for certain purposes of comparison." (Muench, 1959; p. 2).

Simple mathematical models of epidemiological processes can be used:

(1) *To test a hypothesis*: a hypothesis that is in accord with the observed pattern of the disease helps in the better understanding of the characteristic under study. On the other hand, as Muench states, definite discrepancies between hypothesis and observations point to the inadequacy of the model and the need for the revision of concepts. The nature of such discrepancies may give a clue to the dimensions and direction of the revision. The model will thus provide clues as to the mode of action of the disease.

(2) *To measure a "force of infection"*: ". . . hypotheses whose results do fit observation allow for the rationalization and measurement of constants which have been included in the hypothesis. The estimate of size of the simple forces implicated in the model gives a means of direct comparison between different groups in terms of their exposure to infection. Moreover, this estimate can be made on the basis of spot surveys of a population without the need of lengthy observations of successive events. . . However, if the model is to be used as a tool for measuring a force of infection, the nature of the disease must be thoroughly understood so that the components of the model can be correctly interpreted in terms of the epidemiologic picture." (Muench, 1959; p. 6).

OBJECTIVES

The present study attempts, with the aid of catalytic models:

(1) to elucidate, epidemiologically, the clinical features of trachoma in a given community—Taiwan, and

(2) to assess changes in the risk of infection and in the disease picture with time.

The study, at the same time, provides a means for determining the value of catalytic models as tools for the better understanding of the epidemiology of the disease.

METHODS

Total and active trachoma age-prevalence histograms are constructed and simple and two-stage catalytic curves, respectively, are fitted to them.

In an attempt to investigate the identity of ND cases, histograms and catalytic curves are constructed as above for trachoma *plus* ND cases.

Because of the lack of a reasonably precise knowledge of the central point of the age-group 65 years and over, the age-prevalence histograms and the corresponding catalytic curves are restricted to the age-band 0-64 years.

In applying catalytic models to age-prevalence of total trachoma in Taiwan, the assumptions are simplified to give the over-all effects of a complex epidemiological situation. The basic assumptions are:

(1) that the population is exposed to a *constant* force of infection that has not varied greatly over the age-band under study, 0-64 years: the force is to be measured in terms of effective contacts per year, no matter how complex the chain of events leading up to these contacts, and

(2) that the evidence of effective contact is definite and remains so for life.

The equation for the simple catalytic curve is:

$$y = 1 - e^{-rt} \qquad (y = 0 \text{ at } t = 0)$$

where y is the fraction of the population diagnosed as having trachoma (or ND), e the base of natural logarithms, r the force of infection, in terms of effective contacts per year per unit of population (effective contact means a contact sufficient to produce infection if the subject is susceptible), and t = age (centre point of each age-group).

In fitting a two-stage catalytic curve to an active trachoma age-prevalence histogram, further assumptions are made—namely:

(1) that active trachoma passes into the healed stage at a definite rate and

(2) that healed trachoma does not revert to an active stage.

The equation for the two-stage catalytic curve is:

$$y = \frac{a}{a-b}(e^{-at} - e^{-bt}) \qquad (y = 0 \text{ at } t = 0)$$

where a is the force of infection, in terms of effective contacts per year per unit of population, and b the rate at which active trachoma passes into healed trachoma.

The nomograms provided by Muench (1959) have been used to obtain the constants r, a and b.

FINDINGS

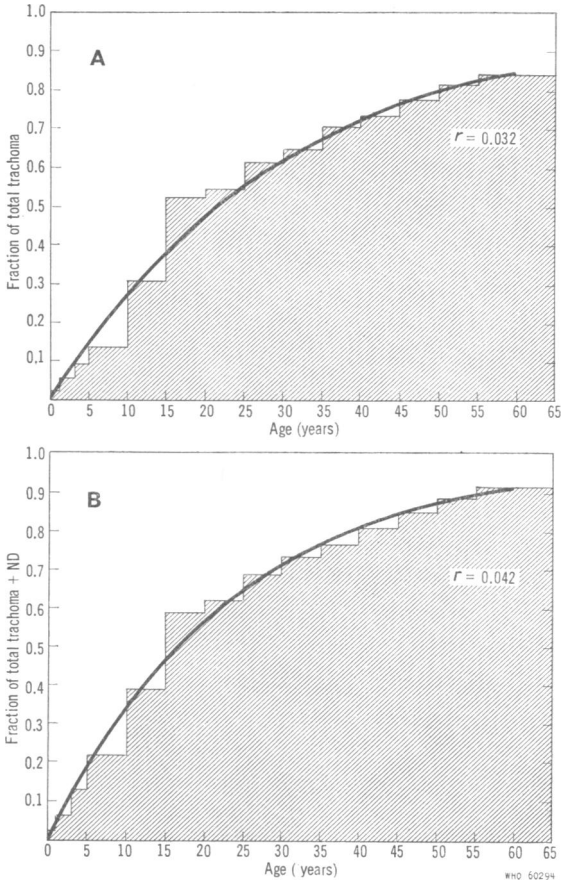
Age-prevalence of total (Stages I, II, III, IV) trachoma

The results obtained are shown in Table 1 and Fig. 1. The model indicates a " force of infection " of 0.032, i.e., an average of 32 effective contacts per year per 1000 susceptibles. A reasonably good fit is obtained between the simple catalytic curve and the histogram, although the latter shows markedly lower levels for the age-group 5-9 years and appreciably higher values for the age-group 15-19 years. Beyond the age of 20 years a remarkably close fit is obtained.

The incorporation of ND cases results in a better fit: the two age-groups 5-9 and 15-19 years maintain the characteristics noted above but to a lesser degree. Again a remarkably good fit is obtained beyond the age of 20 years. Introducing the ND cases increases the average number of effective contacts per year per 1000 susceptibles to 41.

FIG. 1

FITTING OF SIMPLE CATALYTIC CURVE TO AGE-PREVALENCE HISTOGRAM FOR (A) TOTAL TRACHOMA AND (B) TOTAL TRACHOMA + ND CASES



Age-prevalence of active (Stages I, II, III) trachoma

The results obtained are shown in Table 2 and Fig. 2. A two-stage catalytic curve gives a reasonably good fit. The same feature seen in the case of total trachoma is manifest: compared to the catalytic curve the histogram is appreciably lower in the age-group 5-9 years and markedly higher in the age-group 15-19 years. Again a remarkably good fit is obtained beyond the age of 20 years. The constants for the curve are:

annual effective contacts per 1000 susceptibles..... 40
annual rate of healing of active trachoma..... 6.8%.

The incorporation of ND cases improves the fit, mainly by lessening the difference between the histogram and the catalytic curve in the two above-

FIG. 2

FITTING OF TWO-STAGE CATALYTIC CURVE TO AGE-PREVALENCE HISTOGRAM FOR (A) ACTIVE TRACHOMA AND (B) ACTIVE TRACHOMA + ND CASES

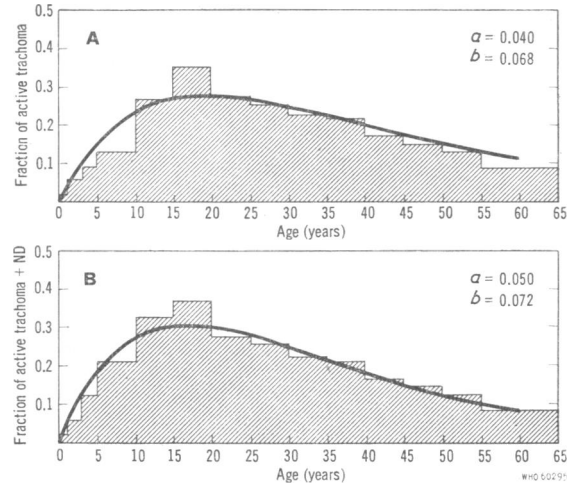


TABLE 1

AGE-PREVALENCE OF TOTAL TRACHOMA CASES AND TOTAL TRACHOMA + ND CASES IN EPIDEMIOLOGICAL STUDIES IN TAIWAN 1960-61

Age (years)	No. examined	Total trachoma			Total trachoma + ND		
		No. of cases	Fraction of no. examined		No. of cases	Fraction of no. examined	
			Measured	Estimated [a]		Measured	Estimated [a]
<1	1 265	24	0.019	0.015	25	0.020	0.020
1-2	2 930	161	0.055	0.061	177	0.060	0.078
3-4	2 733	254	0.093	0.119	345	0.126	0.151
5-9	6 609	899	0.136	0.212	1 439	0.218	0.266
10-14	4 469	1 373	0.307	0.330	1 734	0.388	0.402
15-19	2 800	1 461	0.522	0.428	1 652	0.590	0.513
20-24	2 312	1 257	0.544	0.513	1 435	0.621	0.604
25-29	2 402	1 473	0.613	0.585	1 657	0.690	0.678
30-34	2 288	1 486	0.649	0.646	1 684	0.736	0.738
35-39	1 898	1 320	0.695	0.699	1 458	0.768	0.786
40-44	1 657	1 216	0.734	0.743	1 344	0.811	0.826
45-49	1 408	1 093	0.776	0.781	1 195	0.849	0.859
50-54	1 286	1 049	0.816	0.813	1 143	0.889	0.885
55-64	1 510	1 276	0.845	0.853	1 384	0.916	0.916

[a] By fitting simple catalytic curve.

TABLE 2

AGE-PREVALENCE OF ACTIVE TRACHOMA CASES AND ACTIVE TRACHOMA + ND (ACTIVE LESIONS) CASES IN EPIDEMIOLOGICAL STUDIES IN TAIWAN 1960-61

Age (years)	No. examined	Active trachoma			Active trachoma + ND		
		No. of cases	Fraction of no. examined		No. of cases	Fraction of no. examined	
			Measured	Estimated [a]		Measured	Estimated [a]
<1	1 265	24	0.019	0.019	25	0.020	0.026
1-2	2 930	161	0.055	0.071	177	0.060	0.086
3-4	2 733	252	0.092	0.129	342	0.125	0.156
5-9	6 609	875	0.132	0.200	1 397	0.211	0.238
10-14	4 469	1 192	0.267	0.256	1 482	0.332	0.294
15-19	2 800	986	0.352	0.275	1 038	0.371	0.304
20-24	2 312	634	0.274	0.272	647	0.280	0.289
25-29	2 402	616	0.256	0.256	623	0.259	0.262
30-34	2 288	519	0.227	0.234	519	0.227	0.230
35-39	1 898	411	0.216	0.208	411	0.216	0.197
40-44	1 657	277	0.167	0.182	277	0.167	0.166
45-49	1 408	210	0.149	0.158	210	0.149	0.138
50-54	1 286	161	0.125	0.135	161	0.125	0.114
55-64	1 510	130	0.086	0.106	130	0.086	0.084

[a] By fitting two-stage catalytic curve.

mentioned age-groups; the close fit beyond the age of 20 years is maintained. The constants for the catalytic curve are:

annual effective contacts per 1000 susceptibles..... 50
annual rate of healing of active trachoma..... 7.2%.

DISCUSSION

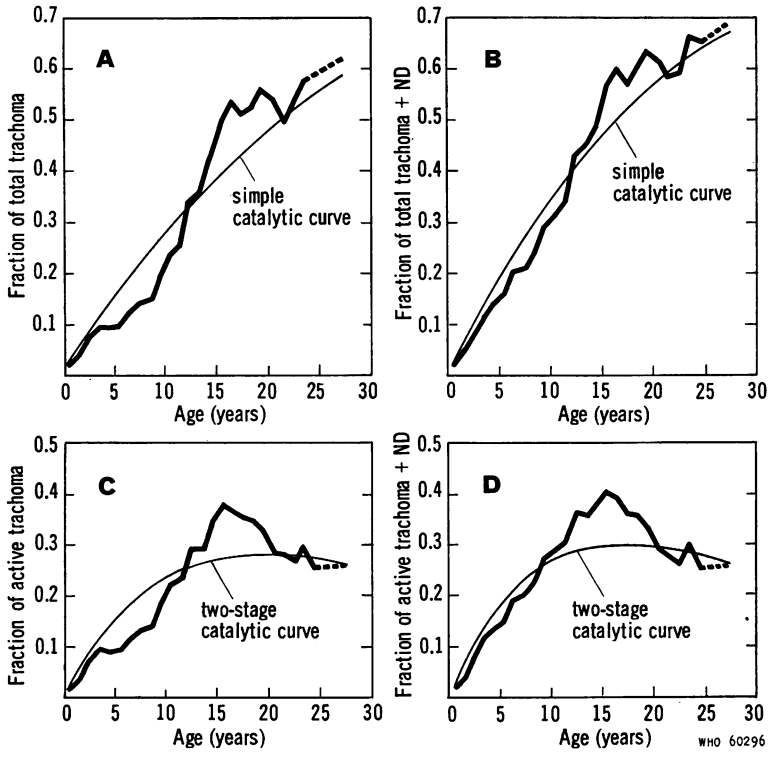
In applying deterministic models one deals with an assumed definite relationship between a given " force " and the population on which it acts; the factor of chance variation, which modifies the actual outcome observed in each case, is omitted. The object of a deterministic model is to measure a " force " in terms of its over-all action rather than to describe in detail the mode of its action. Provided that the assumptions are approximately valid, deterministic models have one distinct advantage over probabilistic models—namely, greater simplicity. Moreover, when the numbers are large, there is good agreement between stochastic and deterministic predictions (Bartholomay, 1964).

The histogram of Fig. 1A shows the following features with increase in age: a rapid rise in the first five years of life, a much less rapid increase during the ages of 5-9 years, a marked increase in the following two age-groups, particularly in the age-group 15-19 years, and a smooth steady rise thereafter. The true identity of the cases in the first five years is in doubt. It is always difficult, and often impossible under field conditions, to examine, even macroscopically, the upper limbus of very young children. The co-operation of the child and the possibility of examination, however, increase rapidly as the child grows older (Table 3).

TABLE 3
RELATIVE PROPORTIONS OF TRACHOMA AND ND CASES IN WHICH UPPER LIMBUS WAS EXAMINED AND OF TRACHOMA CASES IN WHICH IT COULD NOT BE

Age (years)	Total no. of trachoma and ND cases	Total trachoma		Upper limbus examined						Upper limbus not examined	
				Total		Trachoma		ND cases		Trachoma	
		No.	%	No.	%	No.	%	No.	%	No.	%
<1	25	24	96.0	1	4.0	—	—	1	4.0	24	96.0
1	57	52	91.2	9	15.8	4	7.0	5	8.8	48	84.2
2	120	109	90.8	24	20.0	13	10.8	11	9.2	96	80.0
1-2	177	161	91.0	33	18.6	17	9.6	16	9.0	144	81.4
3	146	120	82.2	48	32.9	22	15.1	26	17.8	98	67.1
4	199	134	67.3	114	57.3	49	24.6	65	32.7	85	42.7
3-4	345	254	73.6	162	47.0	71	20.6	91	26.4	183	53.0
5	216	130	60.2	154	71.3	68	31.5	86	39.8	62	28.7
6	275	161	58.5	237	86.2	123	44.7	114	41.4	38	13.8
7	267	176	65.9	245	91.8	154	57.7	91	34.1	22	8.2
8	306	186	60.8	300	98.0	180	58.8	120	39.2	6	2.0
9	375	246	65.6	369	98.4	240	64.0	129	34.4	6	1.6
5-9	1 439	899	62.5	1 305	90.7	765	53.2	540	37.5	134	9.3
10	343	258	75.2	340	99.1	255	74.3	85	24.8	3	0.9
11	344	255	74.1	344	100.0	255	74.1	89	25.9	—	—
12	399	319	79.9	395	99.0	315	78.9	80	20.0	4	1.0
13	344	278	80.8	344	100.0	278	80.8	66	19.2	—	—
14	304	263	86.5	304	100.0	263	86.5	41	13.5	—	—
10-14	1 734	1 373	79.2	1 727	99.6	1 366	78.8	361	20.8	7	0.4

FIG. 3
AGE-PREVALENCE LINE-GRAPHS (BY SINGLE YEAR OF AGE IN AGE-BAND 0-24 YEARS) FOR (A) TOTAL TRACHOMA, (B) TOTAL TRACHOMA + ND CASES, (C) ACTIVE TRACHOMA AND (D) ACTIVE TRACHOMA + ND CASES



With this in mind, the following plan was adopted in the Taiwan survey. Cases in which the upper limbus could not be examined and, for this reason, the presence of pannus could not either be confirmed or excluded, and in which only one of the other cardinal signs was present, were recorded as " one-sign trachoma " and provisionally included in the computation of the trachoma prevalence rates. The ratio of trachoma cases in which the limbus could not be examined to cases in which it was examined, by year of age in the age-group 0-4 years, is 24 : 0, 12 : 1, 7.4 : 1, 4.4 : 1, and 1.7 : 1. The ratio of total trachoma (whether the limbus is examined or not) to ND cases for the same ages is: 24 : 1, 10.4 : 1, 9.9 : 1, 4.6 : 1, and 2.1 : 1. Considering that, of the 108 (limbus-examined) ND cases in the 0-4 years age-group, 102 had conjunctival signs of trachoma but no pannus detectable macroscopically, it would seem probable that, had the upper limbus been examined in all cases in this group, a high proportion would have been labelled ND in the absence of macroscopic pannus. The trachoma prevalence histogram (Fig. 1A) would then have shown a lower level at this age.

Fitting a simple catalytic curve to the histogram (and considering the above argument relating to trachoma prevalence in the early years of life) brings out the basic characteristics of the histogram. While there are evident irregularities in the histogram in the first 20 years of life—and hence a marked discrepancy between the histogram and the catalytic curve—the histogram runs a course beyond this age that conforms with the assumptions on which the catalytic curve is built. There are two possible explanations. One is based on the concept of a change in the disease picture with time, i.e., that trachoma in Taiwan ran a definite course until 20 years before the time of the study (1960-61) and that since then changes in the disease pattern have set in. The alternative explanation is that factors that result in a differential risk of infection have always been operating on those in the age-group 0-19 years.

Plotting a line-graph for total trachoma prevalence by year of age for the first 24 years of life and re-fitting the corresponding part of the catalytic curve (Table 4, Fig. 3A) shows that the upward rise of the line-graph beyond the catalytic curve starts

TABLE 4. PREVALENCE RATES OF TRACHOMA AND TRACHOMA PLUS ND CASES BY EVOLUTIVE STAGE (AND BY SINGLE YEARS OF LIFE IN AGE-BAND 0-24 YEARS)

Age (years)	No. examined	Trachoma												Trachoma + ND cases											
		Total		Tr I		Tr II		Tr III		Total active		Tr IV		Total		Tr I		Tr II		Tr III		Total active		Tr IV	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<1	1 265	24	1.9	24	1.9	—	—	—	—	24	1.9	—	—	25	2.0	25	2.0	—	—	—	—	25	2.0	—	—
1	1 435	52	3.6	47	3.3	5	0.3	—	—	52	3.6	—	—	57	4.0	51	3.6	6	0.4	—	—	57	4.0	—	—
2	1 495	109	7.3	92	6.2	15	1.0	2	0.1	109	7.3	—	—	120	8.0	101	6.8	16	1.1	3	0.2	120	8.0	—	—
3	1 277	120	9.4	103	8.1	17	1.3	—	—	120	9.4	—	—	146	11.4	120	9.4	23	1.8	3	0.2	146	11.4	—	—
4	1 456	134	9.2	91	6.2	37	2.5	4	0.3	132	9.1	2	0.1	199	13.7	136	9.3	54	3.7	6	0.4	196	13.5	3	0.2
5	1 368	130	9.5	87	6.4	30	2.2	12	0.9	129	9.4	1	0.1	216	15.8	149	10.9	51	3.7	15	1.1	215	15.7	1	0.1
6	1 375	161	11.7	93	6.8	46	3.3	19	1.4	158	11.5	3	0.2	275	20.0	178	12.9	68	4.9	24	1.7	270	19.6	5	0.4
7	1 283	176	13.7	89	6.9	48	3.7	36	2.8	173	13.5	3	0.2	267	20.8	155	12.1	67	5.2	42	3.3	264	20.6	3	0.2
8	1 286	186	14.5	75	5.8	51	4.0	54	4.2	180	14.0	6	0.5	306	23.8	150	11.7	78	6.1	65	5.1	293	22.8	13	1.0
9	1 297	246	19.0	93	7.2	65	5.0	77	5.9	235	18.1	11	0.8	375	28.9	172	13.3	90	6.9	93	7.2	355	27.4	20	1.5
10	1 112	258	23.2	87	7.8	63	5.7	90	8.1	240	21.6	18	1.6	343	30.8	132	11.9	85	7.6	102	9.2	319	28.7	24	2.2
11	1 015	255	25.1	68	6.7	42	4.1	124	12.2	234	23.0	21	2.1	344	33.9	102	10.0	72	7.1	132	13.0	306	30.1	38	3.7
12	941	319	33.9	74	7.9	42	4.5	160	17.0	276	29.3	43	4.6	399	42.4	113	12.0	60	6.4	167	17.7	340	36.1	59	6.3
13	776	278	35.8	55	7.1	35	4.5	139	17.9	229	29.5	49	6.3	344	44.3	82	10.6	52	6.7	145	18.7	279	36.0	65	8.4
14	625	263	42.1	33	5.3	24	3.8	156	25.0	213	34.1	50	8.0	304	48.6	46	7.4	32	5.1	160	25.6	238	38.1	66	10.6
15	528	262	49.6	22	4.2	19	3.6	158	29.9	199	37.7	63	11.9	297	56.2	31	5.9	25	4.7	159	30.1	215	40.7	82	15.5
16	571	303	53.1	14	2.5	20	3.5	174	30.5	208	36.4	95	16.6	341	59.7	19	3.3	27	4.7	176	30.8	222	38.9	119	20.8
17	578	294	50.9	15	2.6	12	2.1	176	30.4	203	35.1	91	15.7	326	56.4	18	3.1	16	2.8	176	30.4	210	36.3	116	20.1
18	535	278	52.0	10	1.9	14	2.6	161	30.1	185	34.6	93	17.4	318	59.4	17	3.2	16	3.0	161	30.1	194	36.3	124	23.2
19	588	324	55.1	12	2.0	9	1.5	170	28.9	191	32.5	133	22.6	370	62.9	13	2.2	13	2.2	171	29.1	197	33.5	173	29.4
20	545	289	53.0	4	0.7	3	0.6	146	26.8	153	28.1	136	25.0	334	61.3	8	1.5	5	0.9	146	26.8	159	29.2	175	32.1
21	410	201	49.0	4	1.0	3	0.7	105	25.6	112	27.3	89	21.7	239	58.3	7	1.7	4	1.0	105	25.6	116	28.3	123	30.0
22	373	199	53.4	2	0.6	9	2.4	87	23.3	98	26.3	101	27.1	220	59.0	2	0.5	9	2.4	87	23.3	98	26.3	122	32.7
23	475	271	57.0	6	1.3	2	0.4	132	27.8	140	29.5	131	27.6	313	65.9	7	1.5	3	0.6	133	28.0	143	30.1	170	35.8
24	509	297	58.3	1	0.2	4	0.8	126	24.8	131	25.7	166	32.6	329	64.6	1	0.2	4	0.8	126	24.8	131	25.7	198	38.9
25-29	2 402	1 473	61.3	11	0.4	7	0.3	598	24.9	616	25.6	857	35.7	1 657	69.0	17	0.7	8	0.3	598	24.9	623	25.9	1 034	43.0
30-34	2 288	1 486	64.9	8	0.3	7	0.3	504	22.0	519	22.7	967	42.3	1 684	73.6	8	0.3	7	0.3	504	22.0	519	22.7	1 165	50.9
35-39	1 898	1 320	69.5	2	0.1	5	0.3	404	21.3	411	21.6	909	47.9	1 458	76.8	2	0.1	5	0.3	404	21.3	411	21.6	1 047	55.2
40-44	1 657	1 216	73.4	1	0.1	—	—	276	16.7	277	16.7	939	56.7	1 344	81.1	1	0.1	—	—	276	16.6	277	16.7	1 067	64.4
45-49	1 408	1 093	77.6	1	0.1	2	0.1	207	14.7	210	14.9	883	62.7	1 195	84.9	1	0.1	2	0.1	207	14.7	210	14.9	985	70.0
50-54	1 286	1 049	81.6	—	—	—	—	161	12.5	161	12.5	888	69.0	1 143	88.9	—	—	—	-	161	12.5	161	12.5	982	76.4
55-64	1 510	1 276	84.5	—	—	—	—	130	8.6	130	8.6	1 146	75.9	1 384	91.6	—	—	—	—	130	8.6	130	8.6	1 254	83.0

at an earlier age than 15 years and corresponds more or less to the age of withdrawal from primary school. Since the school trachoma-control campaign [1] is limited to primary schools all over the island, it is possible that the apparent discrepancy between the catalytic curve and the prevalence line-graph in the school-age region is a direct consequence of this compaign. However, ascribing the effect to the school campaign will not account for the lower-than-expected rates in the pre-school children (provided that the argument concerning the identity of trachoma cases in these ages is accepted), unless it is assumed that the school campaign actually reduces the source of infection. This assumption is not consistent with the steady rise in the later years of school age and the markedly high prevalence beyond the primary school age—unless one speculates that the reduction in infection in the school-age children results in the accumulation of a heavy load of susceptibles who are no longer protected once they leave school, with the result that a " retarded " high rate of infection sets in, tapering off when a balance between susceptibles and infection is reached, presumably by the age of 20-24 years.

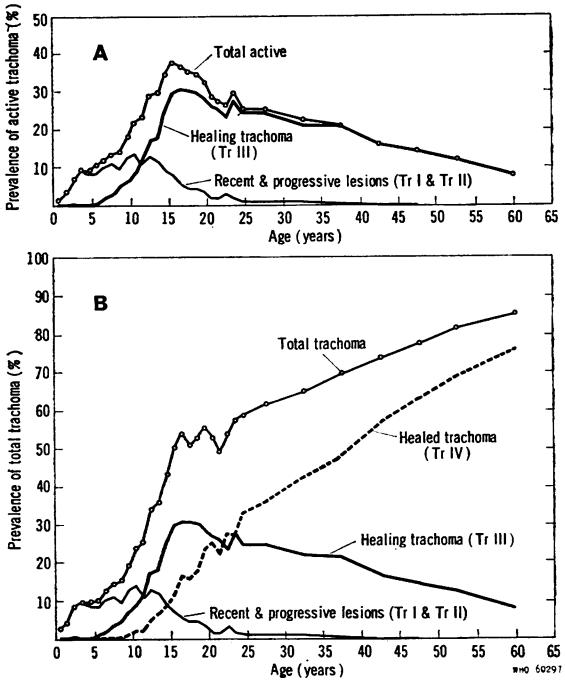
A study of the active-trachoma age-prevalence histogram (Fig. 2A) indicates a markedly high prevalence in the age-group 15-19 years. Fitting a two-stage catalytic curve to the histogram, on the assumption that active trachoma passes into healed trachoma at a definite rate, again indicates that the discrepancies between the observed prevalence and the mathematical model are limited to the first 20 years of life, which accords with the above-mentioned observations (Fig. 2A). Moreover, it would seem that the discrepancies in the total-trachoma picture in these ages reflect the prevalence of active trachoma.

A line-graph of active-trachoma prevalence by single years of age (Fig. 3C) again indicates that the markedly high prevalence rate seen in the histogram in the age-group 15-19 years actually starts at an earlier age, corresponding more or less to the age of withdrawal from primary school. Moreover, it provides a new feature—a sharp decline in the prevalence of active trachoma beyond the age of 15 years. This age heralds the withdrawal from the gregarious life of childhood and early adolescence: although 52.7% of children in the age-group 12-14 years attend school (junior high), only 16.4% in the age-group 15-19 do (senior high). Moreover, 58.0% of males in the age-group 12-14 who fail to attend school are gainfully employed, but this figure increases to 91.8% in the age-group 15-19 years. For females the age of 15 years heralds withdrawal into the household in anticipation of marriage. The picture would therefore favour the assumption of epidemiological factors at present in operation and producing the observed pattern of trachoma prevalence.

Dividing active trachoma into its components Tr I + Tr II, denoting recent and progressive lesions, and Tr III, representing healing trachoma (WHO Expert Committee on Trachoma, 1962), and plotting the corresponding age-prevalence line-graphs, indicates that active trachoma in the age-group 15-19 years is formed in the main part of Tr III (Fig. 4A). The proportionate distribution of

FIG. 4

AGE PREVALENCE OF EVOLUTIVE STAGES OF TRACHOMA (BY SINGLE YEAR OF AGE IN AGE-BAND 0-24 YEARS) FOR (A) ACTIVE TRACHOMA AND (B) TOTAL TRACHOMA



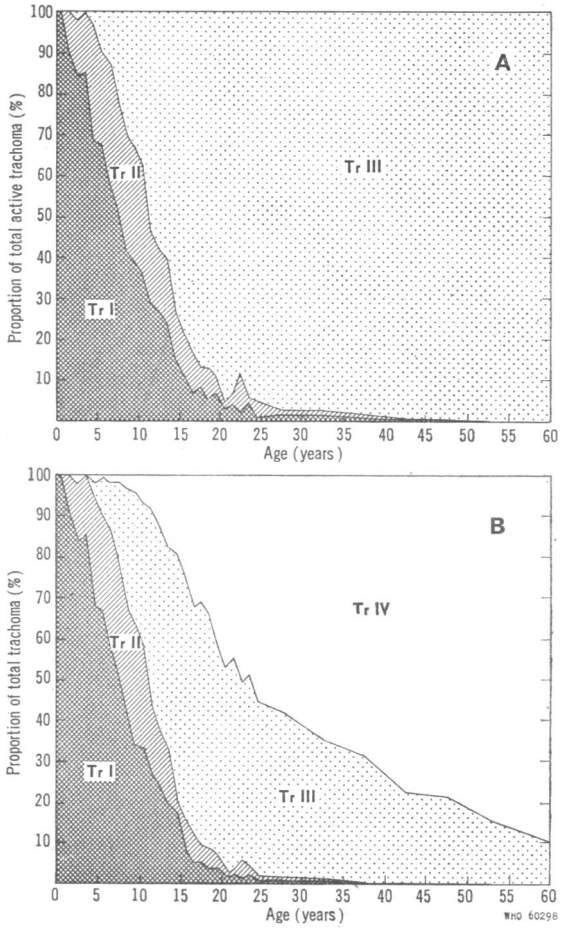
[1] The school control campaign entailed case-finding among all the new entrants in primary schools throughout Taiwan, followed by collective treatment of all those found to be suffering from trachoma or conjunctivitis or both. Follow-up examinations were carried out at the beginning of each school-year, while in the sixth (final) year a case-finding examination covering all children was again conducted. Children showing active signs of either disease were treated.

the evolutive stages (Fig. 5) shows clearly the steady decline of the proportion of Tr I and Tr II with age until the age-group 15-19 years is reached, when the steep decline levels off before fading away as age further increases. On the other hand, the prevalence of recent and progressive lesions (Fig. 4A) starts to decline at an age more or less coinciding with the age of withdrawal from school.

Superposing the age-prevalence line-graphs for healed and total trachoma (Fig. 4B) shows that healed trachoma traces an expected exponential course running in its first part parallel to the rising limb of the healing-trachoma line-graph. On the other hand, the exponential formation of the total-trachoma line-graph is distorted by a hump corresponding to the peak prevalence of Tr III in the age-group 15-19 years. It would therefore seem imperative for the understanding of the pattern of both active and total trachoma in the first twenty years of life to study the sequence of events determining the passage of recent and progressive trachoma into healing trachoma. According to the recommendations in the third report of the WHO Expert Committee on Trachoma (1962), Tr III may be diagnosed in the absence of corneal lesions (two cardinal signs, follicles and scars, furnishing sufficient criteria for diagnosis), whereas earlier stages require the presence of pannus for their diagnosis. ND cases form a sizable group in Taiwan (Table 5) and are formed mainly of cases in whom, under field conditions, pannus could not be detected.[1]

FIG. 5

PROPORTIONATE DISTRIBUTION OF EVOLUTIVE STAGES OF TRACHOMA (BY SINGLE YEAR OF AGE IN AGE-BAND 0-24 YEARS) FOR (A) ACTIVE AND (B) TOTAL TRACHOMA



These cases, passing into the healing stages, would give rise to Tr III without pannus. In fact, in Taiwan, out of 4588 Tr III cases (in the age-band 0-64 years), pannus could not be seen in 439. It would therefore seem probable that Tr III is formed in some of the ND cases in the healing stage, and a better understanding of the healing process would therefore require the addition of ND cases to the earlier stages of trachoma. The incorporation of ND cases in the line-graphs for recent and progressive, healing, and total active trachoma gives a definitely clearer picture of the relationship between the three line-graphs and it furthermore introduces the concept of cohorts moving along time, the Tr III line-graph following, at a fixed distance (in time) the course charted by the recent and progressive lesions (Fig. 6A).

However, Tr III reaches a peak higher than would be projected from the line-graph for Tr I and Tr II. A two-stage catalytic curve (Fig. 2B and 3D) shows a closer fit along the entire course of the line-graph (or the histogram), except for the ages 12-19 years (age-groups 10-14 and 15-19, especially the latter, in the histogram). The fit, closer than that obtained with the same graphs but with ND cases excluded, is due mainly to the filling of the gap between the line-graph and the catalytic curve in the ages 4-11 years. This is a reflection of the divergence of the two line-graphs in the area where Tr I and Tr II

[1] Some ND cases are diagnosed on the evidence of active limbal changes alone. This group poses several problems, ranging from the accuracy of clinical diagnosis of minimal limbal changes (most of these cases have approximately 0.5 mm of neovascularization) under field conditions to the stage of the disease to which they would correspond. They would seem to fit best in healing, if not actually healed, stages.

TABLE 5

PREVALENCE OF ND CASES BY TYPE OF LESION DETECTED AND BY AGE

Age (years)	Total no. of ND cases	Active lesions								Healed lesions					
		Total		Pannus		Immature follicles		Mature follicles		Total		Pannus		Conj. scars	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
<1	1	1	...	—	—	1	...	—	—	—	—	—	—	—	—
1	5	5	100.0	—	—	4	80.0	1	20.0	—	—	—	—	—	—
2	11	11	100.0	1	9.1	9	81.8	1	9.1	—	—	—	—	—	—
3	26	26	100.0	3	11.5	17	65.4	6	23.1	—	—	—	—	—	—
4	65	64	98.5	2	3.1	45	69.2	17	26.2	1	1.5	—	—	1	1.5
5	86	86	100.0	3	3.5	62	72.1	21	24.4	—	—	—	—	—	—
6	114	112	98.2	5	4.4	85	74.6	22	19.3	2	1.8	1	0.9	1	0.9
7	91	91	100.0	6	6.6	66	72.5	19	20.9	—	—	—	—	—	—
8	120	113	94.2	11	9.2	75	62.5	27	22.5	7	5.8	3	2.5	4	3.3
9	129	120	93.0	16	12.4	79	61.2	25	19.4	9	7.0	1	0.8	8	6.2
10	85	79	92.9	12	14.1	45	52.9	22	25.9	6	7.0	2	2.4	4	4.7
11	89	72	80.9	8	9.0	34	38.2	30	33.7	17	19.1	4	4.5	13	14.6
12	80	64	80.0	7	8.8	39	48.8	18	22.5	16	20.0	6	7.5	10	12.5
13	66	50	75.8	6	9.1	27	40.9	17	25.8	16	24.2	5	7.6	11	16.7
14	41	25	61.0	4	9.8	13	31.7	8	19.5	16	39.0	4	9.8	12	29.3
15	35	16	45.7	1	2.8	9	25.7	6	17.1	19	54.3	1 0	28.6	9	25.7
16	38	14	36.8	2	5.3	5	13.2	7	18.4	24	63.2	6	15.8	18	47.4
17	32	7	21.9	—	—	3	9.4	4	12.5	25	78.1	8	25.0	17	53.1
18	40	9	22.5	—	—	7	17.5	2	5.0	31	77.5	11	27.5	20	50.0
19	46	6	13.0	1	2.2	1	2.2	4	8.7	40	87.0	10	21.7	30	65.2
20	45	6	13.3	—	—	4	8.9	2	4.4	39	86.7	10	22.2	29	64.4
21	38	4	10.5	—	—	3	7.9	1	2.6	34	89.5	4	10.5	30	78.9
22	21	—	—	—	—	—	—	—	—	21	100.0	4	19.0	17	81.0
23	42	3	7.1	1	2.4	1	2.4	1	2.4	39	92.8	9	21.4	30	71.4
24	32	—	—	—	—	—	—	—	—	32	100.0	10	31.2	22	68.8
25-29	184	7	3.8	—	—	6	3.3	1	0.5	177	96.2	51	27.7	126	68.5
30-34	198	—	—	—	—	—	—	—	—	198	100.0	60	30.3	138	69.7
35-39	138	—	—	—	—	—	—	—	—	138	100.0	38	27.5	100	72.5
40-44	128	—	—	—	—	—	—	—	—	128	100.0	34	26.6	94	73.4
45-49	102	—	—	—	—	—	—	—	—	102	100.0	18	17.6	84	82.4
50-54	94	—	—	—	—	—	—	—	—	94	100.0	19	20.2	75	79.8
55-54	108	—	—	—	—	—	—	—	—	108	100.0	11	10.2	97	89.8
65 +	48									48	100.0	1	2.1	47	97.9
Total	2 378	991	41.7	89	3.7	640	26.9	262	11.0	1 387	58.3	340	14.3	1 047	44.0

form a sizable proportion of active trachoma (Fig. 7).

The addition of ND cases to healed and total trachoma (Fig. 1B and 6B) has little effect on the exponential rise of Tr IV beyond a general rise in magnitude. This can be attributed to a trend of healing of ND cases consistent with the general trend for trachoma cases. On the other hand, the exponential rise of total trachoma is more manifest, and the difference between the catalytic curve and the line-graph (or histogram) in the age-group 15-20 years is much reduced. This would therefore suggest that, in Taiwan, ND cases actually form part of trachoma.

In support of this is the fact, mentioned earlier, that in a limited study of ND cases in schoolchildren, biomicroscopy revealed minimal but definite corneal neovascularization in the great majority of cases. The exclusion of ND cases would tend to accentuate unduly trends in the disease picture, while their inclusion as trachoma cases tends to help in evaluating and explaining these trends. The relationship that the healing-trachoma line-graph bears to the line for recent and progressive lesions would suggest that healing trachoma belongs to a cohort that has experienced a higher infection rate than would be expected at present. As the changes are limited to the past 20 years, the following factors may have affected the trachoma picture over this period:

(1) disruption of social and biophysical environment as a consequence of war,

(2) introduction of the school trachoma-control campaign in 1954, and

(3) a general improvement in socio-economic conditions and in the standard of living.

The age-group 15-19 years (which has a particularly high rate of trachoma) would accordingly represent the cohort that was either born or had passed through early childhood during the war years and had gone through primary school largely untouched by the trachoma-control campaign. The tendency for lower prevalence rates in the younger age-groups would reflect the effect of the general rise in the standard of living and the introduction of the school campaign. The load of recent and progressive lesions is predominantly in the preschool and school-age groups (Fig. 8), the drop in their prevalence coinciding with the age of withdrawal from primary school (Fig. 6). There is, however, no visible discontinuity in the entire course of the line-graph that would reflect a direct effect of the institution or withdrawal of the school campaign.

FIG. 7

PREVALENCE RATES OF TRACHOMA AND TRACHOMA + ND CASES

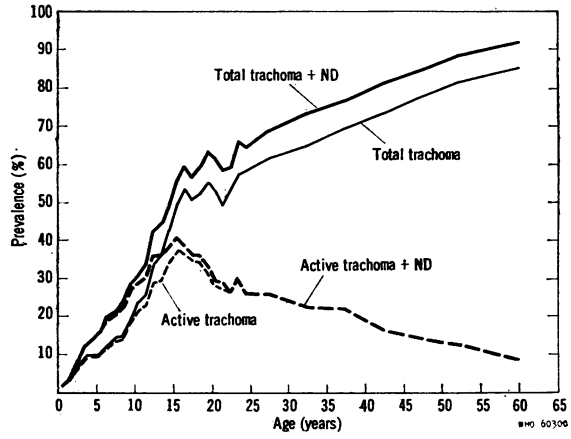


FIG. 6

AGE PREVALENCE OF EVOLUTIVE STAGES OF TRACHOMA + ND CASES (BY SINGLE YEAR OF AGE IN AGE-BAND 0-24 YEARS) FOR (A) ACTIVE STAGES AND (B) TOTAL CASES

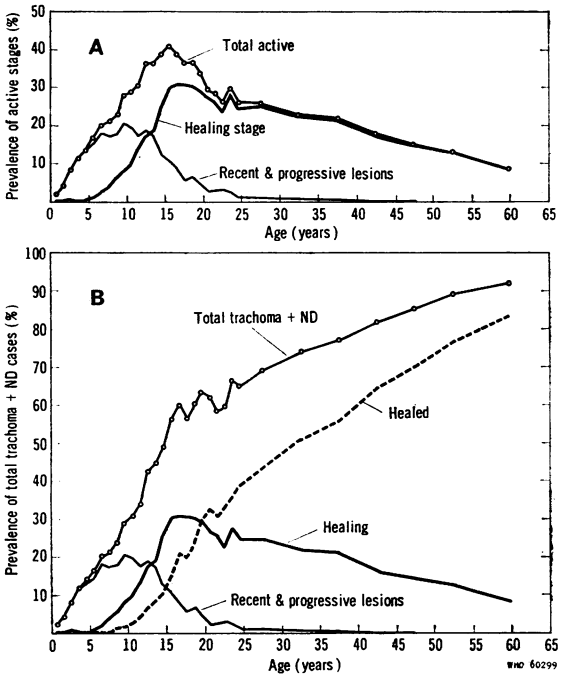
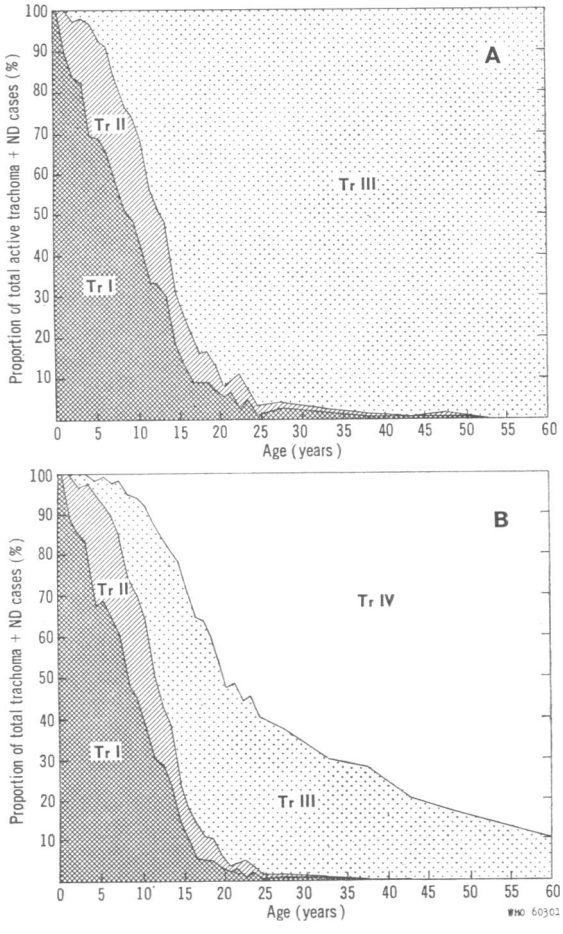


FIG. 8

PROPORTIONATE DISTRIBUTION OF EVOLUTIVE STAGES OF TRACHOMA + ND CASES (BY SINGLE YEAR OF AGE IN AGE-BAND 0-24 YEARS) FOR (A) ACTIVE STAGES AND (B) TOTAL CASES



Similarly, there is no apparent interruption of the line-graph of healing trachoma on withdrawal from the school campaign.

It would therefore seem that the most likely interpretation of trachoma prevalence in Taiwan is as follows:

(1) The prevalence of trachoma increased exponentially with age until 20 years prior to the present study (1960-61), when factors affecting the disease pattern were introduced.

(2) The cohort born or passing its infancy and early childhood during the war years, and largely escaping the possible effect of the school campaign, has suffered a higher rate of infection than has been experienced before the war or since.

(3) Trachoma is contracted as early as the first year of life and throughout the preschool and primary school years. The hardly interrupted smooth drop of the prevalence of recent and progressive infections beyond the primary-school age reflects the effect of the factors mentioned earlier and resulting from a gradual withdrawal from the gregarious life of childhood and early adolescence.

(4) The general reduction in the infection rate in recent years is primarily due to a rise in the general standard of living; the school campaign may be a contributing factor.

The above argument suggests that trachoma in Taiwan has been subject to changes during the past 20 years. These changes have been induced by factors that have since ceased to exist, as well as by factors that are still in operation. In addition, the argument indicates that ND cases are actually an integral part of trachoma. Their exclusion, when dealing with a stable trachoma picture formed of healing and healed trachoma, i.e., in the older age-groups, would lower the prevalence and healing rates. Their omission when dealing with trachoma in the younger age-groups, formed mainly of recent and progressive lesions, would seriously bias the reported incidence and prevalence of the disease. This may assume great importance when changes in the disease picture induced by direct intervention or occurring independently of specific control measures are assessed.

In applying catalytic curves to total and active trachoma age-prevalence curves, certain assumptions were made. These assumptions overlook various features of the disease that fail to show in a spot-prevalence survey, but the presence of which is deduced from the follow-up of a number of trachoma and ND cases, as well as Tr 0 persons [1]—namely:

(1) There is evidence that a proportion of trachoma cases, and particularly of ND cases, resolve

[1] In a separate study 484 definite trachoma cases, 477 ND cases and 511 Tr 0 children, all in the first to the fourth primary-school grades (roughly 6-10 years of age) were followed for a period of two years, from October 1962 to November 1964. Although the study is of a very limited nature and scope (limited numbers of limited ages in purposely selected areas followed up for a very limited time), yet the results would indicate that in Taiwan there is probably a high rate of infection, a high rate of spontaneous cure and a high rate of reinfection or relapse. The study provided evidence that cases can lose their identity as trachoma to become ND cases through healing by losing all but one cardinal sign of trachoma.

without leaving signs of healed trachoma (i.e., inactive pannus and cicatrization) detectable under field conditions.

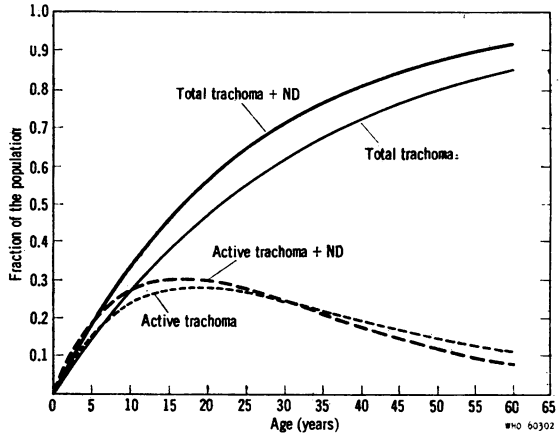
(2) There is reason to believe that there is a rather high rate of reinfection (or relapse) among Tr IV cases.

It would seem that these are the factors responsible for the difference between the " infection force " given by the simple and by the two-stage catalytic curves, and causing the overlap in the earlier course of these two curves (Fig. 9). The discrepancy in the mode and rate of healing between trachoma and ND cases is apparently a factor in the observed difference between the two two-stage catalytic curves in their later parts, the curve for active trachoma plus ND cases assuming a lower level than that for active trachoma alone.

On the other hand, in spite of the inaccuracies in the assumptions, the catalytic curves provide a close enough fit to permit their use as mathematical models of trachoma infection in Taiwan.

FIG. 9

SIMPLE AND TWO-STAGE CATALYTIC CURVES FOR TOTAL AND ACTIVE TRACHOMA, WITH AND WITHOUT ADDITION OF ND CASES



CONCLUSION

Notwithstanding the oversimplification of the assumptions on which they are derived, the catalytic curves provide valuable tools (*a*) for delineating changes in the trachoma picture and (*b*) for indicating the probable identity of ND cases; the factors effecting the changes and the assessment of the clinical identity of ND cases have been considered in an analysis of the available information. As a measure of a " force of infection ", the catalytic curves would presumably be of value in assessing changes in the disease picture with time. It is expected that a limited survey will be conducted in Taiwan in 1966 and that a full survey (similar to that of 1960-61) will be carried out in 1968. These surveys will determine the value of catalytic models as tools for comparative study; they will, moreover, provide the real test for the interpretation of the epidemiology of trachoma here presented.

RÉSUMÉ

Pour préciser l'ampleur du problème du trachome à Taïwan et établir des méthodes de lutte appropriées, une enquête sur échantillon de la population totale de l'île a été effectuée en 1960-1961; 36 507 personnes ont été examinées. Au cours de cette enquête, les auteurs ont trouvé un assez grand nombre de cas pour lesquels les méthodes de diagnostic applicables sur le terrain ne permettaient de mettre en évidence qu'un seul des signes cardinaux du trachome. Ces cas furent étiquetés « non déterminés » ou « ND », en accord avec les recommandations du Comité OMS d'experts du Trachome qui exige la présence d'au moins deux signes cardinaux pour affirmer le diagnostic. A Taïwan, si les cas ND étaient présents à tous les âges, le rapport de leur nombre à celui des trachomes avérés a été d'autant plus élevé que l'âge était plus bas. On a trouvé des cas semblables dans d'autres zones d'endémie trachomateuse et on les a attribués à une évolution de la maladie clinique vers des formes d'une moindre gravité. L'apparition de ces cas douteux en nombre appréciable pose un grave problème lorsqu'il s'agit *a*) de déterminer la prévalence et la gravité relative de la maladie dans une collectivité donnée et *b*) de mesurer les effets de mesures spécifiques de lutte. Pour cette raison, les informations obtenues au cours de l'enquête sur la prévalence du trachome à Taïwan ont été soumises à une étude approfondie pour essayer de déterminer par des méthodes épidémiologiques la véritable nature de ces cas, en utilisant des modèles catalytiques créés par Hugo Muench. Des courbes catalytiques simples et à deux degrés ont été adaptées respectivement aux histogrammes décrivant la prévalence et la répartition par âge du trachome avéré, total (stades I-IV) et actif (stades I-III). Une concordance étroite a été obtenue pour les âges supérieurs à 20 ans mais non pour les plus jeunes. Des courbes semblables ont été adaptées

aux histogrammes du trachome total et actif en ajoutant les cas ND correspondants. De cette façon, la concordance obtenue a été meilleure — observation qui soutient l'hypothèse selon laquelle la majorité sinon tous les cas ND sont des cas bénins de trachome. Cependant on notait encore une faible distorsion dans les groupes d'âge 5-9 et 15-19 ans. Une étude de la progression de la maladie au cours de ses stades évolutifs a mis en évidence des facteurs qui pourraient sans doute être responsables des écarts constatés.

Il est à prévoir que des méthodes épidémiologiques comportant l'emploi de modèles catalytiques seront de plus en plus appliquées dans l'avenir, en particulier dans le domaine des essais de traitement et de vaccination.

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