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COMMUNICATIONS

THE AETIOLOGY OF PHLYCTENULAR
OPHTHALMIA*

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(Conclusion)

3.—Personal Investigations

The investigations recorded here were all carried out at White Oak Hospital, a hospital-school of 364 beds under the control of the London County Council, serving children with eye affections requiring prolonged treatment. The upper age limit for admission is sixteen years, and admission is obtained by reference from hospitals, school clinics and school medical inspectors. Though serving London primarily, the hospital is open to children from other parts of the country. Established in 1897 it served originally for the isolation and schooling of children with trachoma in the Poor Law schools of the Metropolis, and having proved singularly successful in eradicating this affection (Sorsby, 1937), the accommodation became available for the treatment of children suffering from other chronic eye disease. Since 1921 an increasing number

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of admissions have concerned such affections as blepharitis, interstitial keratitis and phlyctenular ophthalmia, admissions for trachoma gradually diminishing to insignificant numbers of late years. In the present study, which covers mainly the cases admitted between July 1935 to December 1940, free use was made of statistical data extracted from the records of the writer's predecessors in the office of Visiting Ophthalmologist, the late E. Treacher Collins (1901-1927) and the late M. S. Mayou (1927-1935), and of the interim reports published in 1936 and 1938 (Sorsby, Hamburger and Benham, 1936; Sorsby, Hamburger, Coveney and Nevin, 1938).

(A) *Sex Distribution of Phlyctenular Ophthalmia*

During the sixteen years 1925-1940, 1,392 children with phlyctenular ophthalmia were admitted to the hospital, boys making up 39.1 per cent. and girls 60.9 per cent. of the total number. This distribution differs markedly from that seen in 2,646 cases of other affections (mainly blepharitis and chronic conjunctivitis) in which the corresponding percentages were 53.7 per cent. and 46.3 per cent. Cases of interstitial keratitis were analysed separately, as a heavy preponderance of this affection on girls is a well-established fact. Trachoma cases were likewise treated separately owing to the fact that an artificial sex distinction is liable to be introduced in this group, seeing that the condition is infectious and that on

TABLE VI
*Sex incidence of the main groups of affection in children
admitted 1925-1940*

	Total Number	Boys	Girls	Percentage Distribution	
				Boys	Girls
Phlyctenular Ophthalmia...	1,392	544	848	39.1	60.9
Interstitial Keratitis ...	—	104	160	—	—
Trachoma ...	—	187	223	—	—
Others—mainly Blepharitis and Chronic Conjunctivitis	2,646	1,422	1,224	53.7	46.3

several occasions large numbers from a boys' or girls' residential school were admitted following a minor epidemic in local schools. It is clear from Table VI that whilst there is no marked difference in sex incidence in the total admissions to the hospital, there is a significant preponderance of girls in the phlyctenular group—a finding that agrees with that of other observers.

(B) *The significance of the state of nutrition, pediculosis capitis, focal sepsis, and of protein allergens in phlyctenular ophthalmia*

(1) The state of nutrition.

Records of weight on admission and of progress during treatment are kept in all cases. The statistics department of the London County Council have evaluated these data for an unselected group of children with phlyctenular ophthalmia in comparison to a similar blepharitis group amongst those admitted during 1936 and 1937. The statistical evaluation is shown in the subjoined tables (Tables VIIa and VIIb) from which it is seen that no tangible difference in the state of nutrition is apparent as between the two groups.

TABLE VIIA

Age and sex of patients on admission according to condition treated

Age Groups	1936						1937					
	Blepharitis			Phlyctenular ophthalmia			Blepharitis			Phlyctenular ophthalmia		
	M	F	Total	M	F	Total	M	F	Total	M	F	Total
1-2 years ...	3	2	5	4	2	6	1	4	5	2	7	9
3-4 years ...	5	3	8	5	10	15	6	4	10	3	7	10
5-7 years ...	15	12	27	8	8	16	20	18	38	5	17	22
8-11 years ...	12	17	29	5	6	11	30	20	50	4	10	14
12-15 years...	2	1	3	1	4	5	13	7	20	4	3	7
16 years ...	—	—	—	—	—	—	—	—	—	—	—	—
Total cases...	37	35	72	23	30	53	70	53	123	18	44	62
Mean age (in years and months) ...	7·4	7·11	7·8	6·3	7·1	6·9	9·1	8·3	8·9	8·0	6·8	7·1

TABLE VII B

Comparison between variation from normal weight for age on admission, normal expected increase in weight, and actual increase in weight at end of first quarter; all figures having been corrected to correspond with the age-group distribution of the 1936—Blepharitis—Males—Group.

	1936				1937			
	Blepharitis		Phlyctenular ophthalmia		Blepharitis		Phlyctenular ophthalmia	
	Males lbs. oz.	Females lbs. oz.	Males lbs. oz.	Females lbs. oz.	Males lbs. oz.	Females lbs. oz.	Males lbs. oz.	Females lbs. oz.
Mean variation from normal weight for age on admission (+ over normal, - under)	-0 9	-0 6	-2 11	-0 7	-0 7	+1 6	+0 15	+0 10
Mean increase in weight at end of the first quarter ...	6 0	6 5	6 1	5 11	5 6	6 1	5 12	7 4
Mean normal expected increase in weight per quarter ...	1 5	1 5	1 5	1 5	1 5	1 5	1 5	1 5

(2) Frequency of pediculosis capitis.

Data were extracted from the registers for the six years 1930-1935, giving a total of 397 cases of phlyctenular ophthalmia and 1,195 cases of various other affections. These data are shown in Table VIII set out according to sex.

TABLE VIII

Incidence of pediculosis capitis in children admitted during 1930-35 inclusive.

	Phlyctenular Ophthalmia			Other Affections		
	Boys	Girls	Total	Boys	Girls	Total
Number admitted ...	145	252	397	632	563	1,195
Number found affected with pediculosis...	26	77	103	151	178	329
Percentage affected...	17·9	30·6	26·0	23·9	31·6	29·2

In both groups it will be seen that girls are more frequently affected with pediculosis, and such differences as were noted in the incidence of pediculosis for boys and girls were in favour of the phlycten group.

(3) Tonsillar sepsis.

During 1936-1938 184 cases of phlyctenular ophthalmia and 414 cases of other affections were examined for evidence of a difference in incidence of naso-pharyngeal sepsis. The findings are presented in Table IX.

TABLE IX

Incidence of tonsillar sepsis in phlyctenular ophthalmia and control groups

	Phlyctenular Ophthalmia	Blepharitis	Interstitial keratitis	Trachoma
Number of children seen ...	184	320	47	47
Recommended for removal of tonsils and adenoids...	14	20	5	3
Antral washouts ...	4	1	1	2
Tonsillectomy performed before admission ...	21	29	5	8

The 184 cases of phlyctenular ophthalmia, therefore, showed 35 instances of tonsillar sepsis against 70 in the control group of 414 cases, *i.e.*, 19 per cent. and 16.9 per cent. respectively. It should be added that in the tonsils removed in 20 phlyctenular children tubercle bacilli could not be detected. (No serial sections were made.)

(4) Non-bacterial allergens.

In an earlier investigation (Sorsby and Benham, 1936) an account was given of the response obtained with tests to various food and plant allergens in some chronic eye affections. Here it is only necessary to recall that 60 cases of phlyctenular ophthalmia all responded negatively to the following groups of allergens: unguatae extracts, derivatives of milk and egg, house dust, dandruff type, tree pollens, grass pollens, graminaceae, and a composite group consisting of substances like kapok, flock and feathers.

(C) *Evidence of Tuberculous Infection and
Tuberculous Disease*

(1) *Tuberculin reaction.*—All children admitted since July 1935 have been tested to tuberculin. In children over 6 years of age the Mantoux test is done as a routine: in those under six the Moro test is applied, Mantoux testing being done where there is some doubt as to the result. In all 592 cases of phlyctenular ophthalmia and 900 cases of blepharitis have been submitted to tuberculin testing. Table X shows the results classified for both these series in age groups.

TABLE X

*Results of tuberculin tests in 592 cases of phlyctenular ophthalmia
(July, 1935—December, 1940) and 900 cases of blepharitis
(July, 1935—August, 1939).*

Age in years	Phlyctenular Ophthalmia		Blepharitis	
	Positive	Negative	Positive	Negative
0-1	0	0	0	0
1-2	18	6	2	6
2-3	40	8	2	18
3-4	49	10	3	38
4-5	41	11	0	67
5-6	40	7	11	78
	188=81·7 per cent.		18=8·0 per cent.	
	42=18·3 per cent.		207=92·0 per cent.	
6-7	47	12	9	73
7-8	38	14	14	97
8-9	57	4	17	78
9-10	29	7	17	72
10-11	46	5	22	70
11-12	31	4	8	59
12-13	27	2	14	58
13-14	20	1	16	34
14-15	8	0	3	13
15-16	9	0	0	1
16-17	1	0	0	0
	313=86·4 per cent.		120=17·7 per cent.	
	49=13·6 per cent.		555=82·3 per cent.	
	501=84·8 per cent.		138=15·3 per cent.	
	91=15·2 per cent.		762=84·7 per cent.	

The difference in the results in the two groups is striking. The phlyctenular cases gave a positive incidence of 84·8 per cent. against an incidence of 15·3 per cent. in the blepharitis group. If only the children up to the age of six are considered the incidence of positive results for the blepharitis group is reduced by almost half—8·0 per cent. instead of 15·3 per cent.—but the incidence for the phlycten group is almost the same—81·7 per cent. instead of 84·8 per cent.

The high incidence of positive reaction in the whole of the phlycten group is in itself significant, and this significance is

emphasised by the fact that the incidence is practically identical for both the younger and the older children.

(2) *Radiological examination of the chest.*—From July 1935 until the outbreak of the War all children with phlyctenular ophthalmia were examined radiologically as a routine. The reading of the plates was done in all instances by the late Professor Richard Hamburger. As controls 87 unselected cases of blepharitis and 70 tuberculin positives amongst blepharitis cases were used. The results obtained are summarised in Table XI.

TABLE XI

Radiological chest findings in 510 cases of phlyctenular ophthalmia (July, 1935—August, 1939) compared with findings in 87 unselected cases of blepharitis and 70 tuberculin positive cases in a series of 429 children with blepharitis.

	Total Number	Tuberculosis of chest as shown by X-rays	In this number are included cases in which activity is to be suspected	Indefinite X-ray findings	Definitely negative
Phlyctenular Ophthalmia	510	368=72.2 per cent.	100=19.6 per cent.	82=16.1 per cent.	60=11.7 per cent.
Blepharitis					
(a) unselected	87	14=16.1 per cent.	3=3.4 per cent.	23=26.4 per cent.	50=57.5 per cent.
(b) Tuberculin posi- tives in a series of 429	70	36=51.4 per cent.	4=5.7 per cent.	28=40.0 per cent.	6=8.6 per cent.

The high incidence of positive radiological findings in the phlycten group as compared to 87 unselected cases of blepharitis stresses the significance of a tuberculous lesion in the aetiology of phlyctenular ophthalmia, whilst the significance of positive tuberculin reactions in phlyctenular children is emphasised by the considerable percentage of positive radiological findings in the 70 blepharitis cases who reacted positively to tuberculin. As a further comparison of the phlycten group with the blepharitis group, the following computation, given with some reserve, is perhaps admissible: if it assumed that, in the group of 429 blepharitis cases, the 359 who responded negatively to tuberculin show no radiological evidence of chest tuberculosis, then the incidence of radiological tuberculosis for the whole blepharitis group is 8.4 per cent. including 0.9 per cent. in which activity is to be suspected, as against 72.2 per cent. and 19.0 per cent. respectively for the phlycten group of 510 cases.

(3) *Clinical tuberculosis.*—A number of cases of tuberculous disease sufficiently definite to be notified were observed among

the 592 children with phlyctenular ophthalmia admitted between July 1935 and December 1940. The diagnoses were made by either the late Dr. Hamburger or Dr. S. A. Owen, the consulting paediatricist to the hospital, and in most instances agreed upon by both these physicians. No case of clinical tuberculosis was seen in the blepharitis group. The distribution of lesions is shown in the subjoined table.

TABLE XII

Clinical tuberculosis observed in 592 cases of phlyctenular ophthalmia and 900 cases of blepharitis (July, 1935—December, 1940)

	Phlyctenular Ophthalmia	Blepharitis
Chest	26	0
Cervical glands ...	6	0
Spine	2	0
Hip	2	0
Elbow	1	0
Meninges (fatal) ...	1	0
	38 = 6·4 per cent.	0

(4) *Family history of tuberculosis.*—A series of 263 successive cases of phlyctenular ophthalmia were submitted for information on the family history to the Tuberculosis department of the London County Council, who in turn sought this information from the medical officers of health of the various London boroughs. The necessary data were obtained from the tuberculosis registers of the boroughs supplemented in many cases by home visits. Table XIII summarises the returns obtained.

TABLE XIII

Family history of tuberculosis in 263 cases of phlyctenular ophthalmia (June, 1937—August, 1939)

Number of cases investigated	Family history negative	Family history positive	
		with contact of a case of tuberculosis	without contact
263	187 = 71·1 per cent.	59 = 22·4 per cent.	17 = 6·5 per cent.
		76 = 28·9 per cent.	

No comparative data for the blepharitis children were established and only indirect evidence on the frequency of positive family histories in the normal school child population is available. Bentley (1931) computed that in 1929 the incidence of a notified case of tuberculosis in the families of the school child population was 3·7 per cent. It is probably lower now, but in any case an

incidence of positive family history of tuberculosis about 8 times as heavy for the phlycten case in comparison to the normal child is suggestive.

(5) *Sedimentation rate.*—The sedimentation rate was determined in 254 cases of phlyctenular ophthalmia and in a control group of 256 cases of blepharitis. Generally speaking the quiescent phlyctenular cases showed normal rates, whilst the active phlyctenular cases showed a high rate (over 10mm., 1 hr.), as can be seen from the subjoined table.

TABLE XIV

Sedimentation rate in 254 cases of phlyctenular ophthalmia and in a control group of 256 cases of blepharitis

Phlyctenular ophthalmia: total number examined: 254			{ 124 active 130 quiescent	
		Active Cases	Quiescent Cases	
Sedimentation rate normal (up to 10 mm. 1 hr.)...	...	25 (20.2 per cent.)	121 (93.1 per cent.)	
Sedimentation rate raised (over 10 mm. 1 hr.)...	...	99 (79.8 per cent.)	9 (6.9 per cent.)	
Blepharitis: Total number examined			256	
Sedimentation rate normal ...			219 = 85.5 per cent.	
Sedimentation rate raised ...			37 = 14.5 per cent.	

No detailed investigations have been carried out on the course of sedimentation rates during the progress of the affection. The fact that quiescent cases show predominantly normal rates does in itself suggest that a return to normal occurs with progress towards subsidence. This is borne out by the few cases on which repeated observations were made. As examples the following may be given:

(1) Rate at the height of activity, 20mm., 1 hr.; two months later the eyes were quiet and rate had declined to 6mm.

(2) Rate at the height of activity 23mm., 1 hr.; six months later, though the eyes were quiet the rate was still 15mm., but this declined to 8 within another fortnight.

An increase in the rate from 17mm. to 22mm. within six weeks has been observed whilst the child was under treatment. The phlyctenular lesion had remained active during that time.

(6) *Absence of tubercle bacilli in stomach washings and in extirpated tonsils.*

(a) *Stomach washings.*

Fifty of the younger children under the age of 8 years with phlyctenular keratitis—some showing negative Mantoux reactions—had stomach lavage done, and the washings were examined, both bacteriologically and by guinea-pig inoculation, for the presence of the tubercle bacillus. All these 50 cases, as also 8 control cases of blepharitis were negative.

(b) As already noted, a search for tubercle bacilli in excised tonsils in 20 cases of phlyctenular ophthalmia gave negative results. (Serial sections were not made.)

(7) *The after-history as to clinical tuberculosis of 754 cases of phlyctenular ophthalmia and comparison with 526 cases of blepharitis and 498 cases of conjunctivitis treated at White Oak Hospital 1921-1931.*—The names of children admitted for phlyctenular ophthalmia for the 11 years between 1921-1931, and who at the time of admission had London addresses, were submitted in 1936-1937 to the Tuberculosis Department of the London County Council, who have a record of all notified cases of tuberculosis in their administrative area. In this way information was obtained on the after-history as to tuberculosis in this group of children. For controls the names of 526 cases of blepharitis and 498 cases of chronic conjunctivitis were also submitted. The subjoined tables summarise the data obtained.

TABLE XVA
Incidence of notified tuberculosis in 754 phlyctenular cases admitted to White Oak Hospital, 1921-1931

	Number of cases followed up	Number of cases showing tuberculosis	Age on admission and sex	Type of tuberculosis	Time noted in relation to admission
1921	75	2	(1) 6 M (2) 9 F	Lupus of skin and mucosa of nose Lungs	6 years later 3 years later
1922	87	3	(1) 12 F (2) 12 F (3) 12 F	Lungs Lungs Lungs	On admission. Died 16 months later 6 months before admission; had been under treatment for eye condition since age of 4 4 years later. Died 2 years subsequently
1923	63	1	15 F	Sclerokeratitis	4 years later
1924	51	2	(1) 7 F (2) 11 F	Renal Pleura	11 years later 3 years before
1925	74	5	(1) 12 M (2) 5 F (3) 7 F (4) 11 F (5) 3 M	(a) Ankle (b) Lungs Spine Lungs Cervical glands Spine	(a) 8 years before (amputation, 1916) (b) 4 years before 1 year later 9 years later 1 year later On admission

TABLE XVA—*continued*

	Number of cases followed up	Number of cases showing tuberculosis	Age on admission and sex	Type of tuberculosis	Time noted in relation to admission
1926	71	5	(1) 3 M (2) 13 M (3) 4 F (4) 10 F (5) 12 M	Lungs Lungs Lupus of Cheek (a) Kidney (b) Cystitis (c) Lungs Lungs	9 years later On admission 1 year later (a) 8 years later (b) 10 years later (c) 10 years later 6 years later. Died 2 years subsequently
1927	69	4	(1) 6 F (2) 2 F (3) 5 F (4) 12 M	Knee (a) Lungs (b) Hip Cervical Adenitis Lungs	Noted at Swanley (a) 2 years later (b) 7 years later 5 years later 4 years later
1928	79	5	(1) 12 M (2) 11 F (3) 5 F (4) 7 M (5) 2 F	Os calcis Lungs Bronchial adenitis Cervical Adenitis Lungs	1 year later 5 years later (Died within a year) Before admission 4 years before 6 years later. Died the same year
1929	60	6	(1) 11 M (2) 3 F (3) 4 F (4) 4 F (5) 9 F (6) 9 M	Ankle Cervical Adenitis Lungs Adenitis: neck, axilla and groin Cervical Adenitis ? knee (father and mother died of tuberculosis) Cervical Adenitis	2 years before 3 years later 2 years before (reported cured 1935) 3 years later 2 years later 6 years later
1930	63	4	(1) 6 F (2) 3 F (3) 10 M (4) 8 M	Tuberculous abscess, neck Spine Lungs Lungs	4 years later At White Oak 6 months before admission 6 years later
1931	62	3	(1) 8 M (2) 11 M (3) 13 F	Cervical glands Lungs Lungs	3 years later 1 year later 4 years later. Died 2 years subsequently
	754	40 = 5.3 per cent.			

TABLE XVb

Incidence of notified tuberculosis in 526 cases of Blepharitis admitted to White Oak Hospital, 1921-1931

	Number of cases followed up	Number of cases of notified tuberculosis	Age on admission and sex	Type of tuberculosis	Time noted in relation to admission
1921	46	1	(1) 7 F	Lungs	13 years later. Died the same year
1922	58	2	(1) 13 M (2) 9 M	Lungs Lungs	12 years later 13 years later
1923	43	0	—	—	—
1924	39	0	—	—	—
1925	31	2	(1) 5 M (2) 11 F	Adenitis Lungs	3 years later 11 years later
1926	48	0	—	—	—
1927	46	0	—	—	—
1928	46	0	—	—	—
1929	56	0	—	—	—
1930	69	0	—	—	—
1931	44	0	—	—	—
	526	5=0.95 per cent.			

TABLE XVc

Incidence of notified tuberculosis in 498 cases of conjunctivitis admitted to White Oak Hospital 1921-31

	Number of cases followed up	Number of cases of notified tuberculosis	Age on admission and sex	Type of tuberculosis	Time noted in relation to admission
1921	48	1	10 F	Lungs	10 years later
1922	41	0	—	—	—
1923	39	0	—	—	—
1924	60	0	—	—	—

TABLE XVC—continued

	Number of cases followed up	Number of cases of notified tuberculosis	Age on admission and sex	Type of tuberculosis	Time noted in relation to admission
1925	58	0	—	—	—
1926	112	0	—	—	—
1927	40	1	10 F	Lungs	9 years later
1928	27	0	—	—	—
1929	24	1	9 M	Tarsus	3 years before. (Still under supervision, 1937)
1930	31	0	—	—	—
1931	18	0	—	—	—
	498	3=0·60 per cent.			

The difference in the incidence of notifiable tuberculosis in the phlycten group and in the two control groups appears to be significant: against an incidence of 5·3 per cent. (40 cases out of 754) in the phlycten group, the blepharitis group gave 0·95 per cent. (5 cases out of 526) and the conjunctivitis group 0·60 per cent. (3 cases out of 498), or 0·8 per cent. if the two control groups are treated as one. The incidence of tuberculosis in the phlycten group followed up over a period of six to sixteen years is therefore about seven times as high as in the control group. The type of tuberculosis seen in these erstwhile phlycten cases is frequently of considerable gravity. The distribution of lesions in these forty cases was: tuberculosis of lungs, 18; bone and joints, 9; glands, 9; kidney, 2; skin and mucosa, 2; eye, pleura, bladder and abscess of neck, 1 each. It is also worth noting that against 1 (0·1 per cent.) death from tuberculosis in the control group there were 6 (0·8 per cent.) in the phlycten group, and that whilst the fatality in the control group occurred 13 years after admission for blepharitis, the deaths in the phlycten group all occurred within 2 years (in two instances within a year and, in four, within two years).

4.—Discussion

(1) *The nature of the phlycten.*—Valuable as it is the experimental work on phlyctenular ophthalmia has not solved the problem of its aetiology. It has eliminated the possibility of the

phlycten being a reaction of the conjunctiva and cornea to microbial infection and it has stressed the significance of a sensitised soil. Beyond that, the evidence gives no guidance to the phlyctenulosis as a clinical problem. The experimental evidence fits in well with the findings that the phlycten is histologically and biologically sterile and unspecific in structure. The core of epithelioid cells amongst which are interspersed some polymorphs is the picture of a non-specific allergic reaction. It is true that the phlycten may show considerable histological variation: giant cells (but no caseation) may be present but this only indicates chronicity; a considerable mononuclear and polymorph reaction may be seen but this occurs with ulceration and secondary infection of the ulcerated phlycten.

The non-specificity of the phlyctenular reaction is clearly reflected in the clinical findings, which, whilst indicating the occurrence of the phlycten in a great variety of affections leave room for the clinical entity which goes under the name of phlyctenular ophthalmia. It is on the aetiology of this clinical entity that no clear guidance is given by experimental and histological studies beyond the suggestion that this must be sought in the interaction of an exogenous or endogenous exciting factor with a sensitised soil. The problem still remains whether clinically the sensitisation is always of the same character and whether the exciting agent must be specific or non-specific. The solution to this clinical problem lies largely, if not entirely, in clinical studies.

(2) *Possible aetiological factors.*—If the phlycten is regarded as a non-specific allergic reaction, there is no *a priori* reason why most of the numerous causal factors that have been suggested in phlyctenular ophthalmia could not be incriminated on theoretical grounds. On such grounds, anomalies in the carbohydrate metabolism could well be the cause of phlyctenulosis, in view of the work on the hapten particle of organisms as a source of sensitisation; given such a sensitisation from infection by a hapten-bearing organism, carbohydrate abuse might precipitate a phlyctenular reaction. Focal sepsis and non-bacterial allergy could equally be causes and pediculosis might well be a cause if it is assumed that a toxin is first absorbed into the system. In all such assumptions, specificity is taken for granted, though there is some experimental evidence that the exciting agent need not necessarily be specific. If it is granted that, with a sensitised soil, a non-specific exciting factor is effective, the theoretical case for faulty carbohydrate metabolism, focal sepsis and pediculosis becomes even less open to criticism. But all these discussions deal with hypotheses. The task remains, in the first place, to establish the nature of the sensitisation seen in patients with phlyctenulosis.

(3) *The nature of the sensitisation seen in phlyctenulosis.*—

From the review of the literature and the evidence brought out in the personal investigations, it is clear that whilst malnutrition, pediculosis and focal sepsis and non-bacterial allergy are seen in cases of phlyctenular ophthalmia, there is no tangible evidence that these conditions occur with greater frequency in such patients compared to the normal child population, and no evidence whatever that any one of these factors could explain the occurrence of phlyctenulosis in the mass. The available data do, however, indicate tuberculous infection as a dominant feature. Briefly this evidence may be summarised as:

(i) Positive tuberculin reaction: this was noted in 752 (78.3 per cent.) out of 960 children under the age of 6 years reported in the literature and in 188 (81.7 per cent.) of a series of 230 reported in the present study.

(ii) Radiological evidence of tuberculosis: a heavy incidence is reported by many observers. In the present series it was found in 72.2 per cent. (368 cases out of 510).

(iii) Clinical tuberculosis: noted in 6.4 per cent. (38 cases out of 592) in the present series against no cases in a larger control group.

(iv) Family history of tuberculosis: observed in 28.9 per cent. in a series of 263 cases.

(v) Sedimentation rate: in 124 cases of active phlyctenular ophthalmia, 99 (79.8 per cent.) showed a rate of over 10mm., 1 hr.

(vi) After history of children with phlyctenular ophthalmia: in a series of 367 cases Ajo found the subsequent mortality rate from tuberculosis practically twice that of the normal population; tuberculous disease had developed in 39 out of 100 (somewhat selected) cases, who could be examined clinically. In the present study 754 cases gave 40 cases (5.3 per cent.) of tuberculous disease against 8 cases (0.8 per cent.) in 1,024 controls; there was a mortality rate from tuberculosis of 0.8 per cent. in the phlycten group against 0.1 per cent. in the control group.

The personal experience of F. Hamburger (1923) is rather illuminating. His eldest son had become infected with tuberculosis at the age of 15 years. For five months the four remaining children had shown no evidence of infection as revealed by repeated tuberculin tests. Then, within the space of two days, three of these four children developed transient conjunctivitis, the youngest showing a typical phlyctenular reaction (with two subsequent recurrences). Tuberculin reactions now proved positive in all the four children. Hamburger traced the source of infection to a maid who had been employed in the household for two years and had been found healthy when first engaged. She was now suffering from open pulmonary tuberculosis.

The trend of the following case history from the records of White Oak Hospital is not an isolated instance. A boy, aged 1 year, was admitted for active phlyctenular ophthalmia. The Moro test was positive. Radiographs showed marked right hilar shadows and a wide mediastinal shadow, suggestive of tuberculous infection of the right middle and lower lobes. Clinically, the lungs gave an impaired note over the right paravertebral region. (Dr. Helen Mackay.) The child did not do well and was taken away by the parents against advice, after seven months' stay at the hospital. The family history had been negative. The child was readmitted seven months later with a severe relapse. In the meantime the mother had been notified as a case of pulmonary tuberculosis.

If it is accepted that tuberculous sensitisation is the underlying condition necessary for the development of phlyctenulosis, the question still remains what are the factors necessary to excite the reaction. Not all tuberculous-infected children develop phlyctenulae, and phlyctenular ophthalmia shows a difference in sex incidence and a seasonal variation which cannot be explained without a fuller understanding of both the basic sensitisation and the added exciting factors.

(4) *Seasonal variation and sex incidence in relation to the aetiology of phlyctenulosis.*—Seasonal variation in the incidence of phlyctenulosis with its peak in spring led to the suggestion that sunlight acts as an exciting agent and to the contrary supposition that the phlycten is the end-result of months of lack of sunshine. Rohrschneider (1935) has sought to explain the spring incidence by establishing a relationship between the month of maximum incidence of phlyctenulosis in various centres to the amount of sunshine available in these different centres at the particular time. He concluded that the highest incidence of phlyctenulosis occurs when the sun is at 45° , and holds that the amount of ultra-violet radiation present has some bearing on the outbreak of phlyctenulosis. A detailed study by Urbanek and Roschkott (1939) of meteorological conditions for Vienna in relation to the monthly incidence of phlyctenulosis was rather inconclusive. They found that over a number of years, when the peak incidence of phlyctenulosis was in March, there was sunny weather during that month; with a cold March the maximum incidence of phlyctenulosis came later in the year. Maximum incidence did not, however, necessarily occur with warm months; in 1928-1932 April was exceptionally sunny, yet the maximum incidence of phlyctenulosis did not occur till May. The secondary peak in incidence observable in autumn was sometimes, but not invariably, associated with a warm autumn month.

The spring peak may perhaps also be connected with the accumulating vitamin A deficiency during the winter months. The

absence of fresh vegetables during winter and the low vitamin A content of milk during the winter months may lead to a lowering of the vitamin A of the blood—a possibility that is suggested by the finding of Frominopoulos that some of his patients had a distinctly subnormal vitamin A content.

Whatever be the explanation, the greater incidence of phlyctenulosis during spring has clinical parallels, both, with tuberculin reactions, and erythema nodosum. The incidence of positive tuberculin reactions is greater in spring and reactions are apt to be more marked during those months (lit. in Peyer, 1921). Erythema nodosum—generally regarded as a tuberculous manifestation—has a seasonal distribution similar to phlyctenular ophthalmia (lit. in Walgren, 1930) and this is of interest both in relation to the more ready reaction of the skin to tuberculin during spring and the readier appearance of phlyctenulae during these months.

The *sex incidence* of phlyctenulosis with the heavier affection of girls is probably an expression of both a greater incidence of tuberculous sensitisation and a greater exposure to possible exciting factors. There is some evidence that tuberculous infection is more frequent in girls.

In London Dow and Lloyd (1931) carried out Mantoux reactions in 576 boys and 427 girls aged 0-15 years. The percentage of positive reactors was consistently higher for girls: 46.1 per cent. against 40.8 per cent. for the two groups as a whole, and for the age groups 0-5 years, 5-10 years, 10-15 years, the incidence was respectively 25.0 per cent., 41.7 per cent. and 60 per cent. for girls against 21.8 per cent., 37.1 per cent. and 56.8 per cent. for boys. Data for Paris are given by Nobécourt and Briskas (1936); 2,093 boys aged 6-15 years and 1,672 girls of the same ages were tested to tuberculin between 1921 and 1935. The age groups 6-9 gave 49.1 per cent. of positive reactors in girls against 43 per cent. in boys; the age groups 10-15 gave corresponding incidences of 67.5 per cent. and 63.3 per cent. A heavier incidence for girls is also reported for New York by Drolet (1934). In a group of 6,080 children aged 0-15 years he found 14.9 per cent. positive reactors among girls, against 12.7 per cent. for boys. The higher incidence for girls was shown consistently in the subsidiary age groups 0-5, 5-10, 10-15 years, the respective percentages for girls being 10, 20.9 and 30.5 against 8.8, 17.4 and 28.1 for boys. In San Francisco Dickey and Seitz (1931) found for children aged 1-14 years in 1925, girls gave 24.3 per cent. positive reactors (in a series of 1,601) and boys 22.9 per cent. (in a series of 1,899). At Philadelphia Hetherington, McPhedran, Landis and Opie (1929) in a series of 2,029 girls aged 3-20 years found 75.1 per cent. positive reactors, against 72 per cent. in a corresponding series of 2,078 boys. Further data of a similar kind are available but it must be pointed

out that evidence of an opposite character has also been reported, and there is apparently no agreement on this issue.

The greater frequency of phlyctenulosis in girls may be due to a greater frequency of tuberculous infections in them, or to other factors such as the greater likelihood of young girls of tuberculous households being more confined to the home than boys and thus more exposed to superinfection. The greater frequency of pediculosis in girls may also be a factor—if it is accepted that pediculosis is an exciting agent of phlyctenulosis in a sensitised soil. (It is also conceivable that pediculosis in a tuberculous household may produce the necessary breach in the skin for tuberculous infection to occur.) Finally, it is possible that girls react more readily to any foreign protein, as Weekers (1929) suggested on a study by Dujardin who reported that 50 per cent. of women against only 10 per cent. of men give strong reactions to the intradermal injection of 2 c.c. horse serum.

(5) *The outbreak of phlyctenulosis.*—Granted that tuberculous infection is the basic condition for the occurrence of phlyctenulosis, it must be admitted that little is known of the actual mechanism which precipitates the phlycten. There is some validity in the argument that the seasonal variation and the difference in sex incidence of phlyctenulosis are primarily aspects of tuberculous infection rather than of the phlycten problem. Again, the age of incidence of phlyctenulosis may be regarded as evidence not of a special predilection that children have for phlyctenulae, but as evidence that the phlycten is a manifestation of the stage of tuberculous invasion rather than of the later development of tuberculous localisation at definite organs (second and third stages in Ranke's classification.) All such conceptions lead to a study of the reaction of the body to tuberculous infection and the mass of experimental and clinical observations on this aspect has, as yet, not been reduced to clear cut fundamentals. The fact that, in established tuberculous disease, the Mantoux reaction is not infrequently negative and that, in the earlier stage of invasion, tuberculin tests are almost always positive, leads to the suggestion that the body (or at any rate the skin) is hyperallergic in the invasive stage. On such a view phlyctenulosis is an expression not only of tuberculous infection but of tuberculous hyperallergy. The allergic states of the body are, of course, not static phenomena. They constantly vary in intensity and an hyperallergic phase may be precipitated by measles, or any other debilitating condition. One aspect of the mechanism of the production of the phlycten may therefore be tuberculous infection, concurrent with an hyperallergic phase. Poverty, malnutrition and overcrowding, so often associated with tuberculosis, may be the factors largely responsible

for the development of the special degree of hyperallergy postulated as necessary for the appearance of a phlycten. On the experimental side Kuniya (1935) has advanced some evidence showing that the ease with which phlyctenulae can be excited in a tuberculous-sensitised animal varies directly with the degree of phagocytosis against the tubercle bacillus.

The nature of the factors that precipitate a phlycten in the hyperallergic is unknown. If it is believed that only a specific agent will precipitate a phlycten, then this must be sought in liberated tubercle bacilli or their products within the child's body, or in tubercle bacilli in the child's environment. If non-specific irritants are capable of inducing a phlycten then any of the endless exogenous factors that have been suggested as responsible for phlyctenulosis may be involved. On this issue there is no evidence on which to base any valid conclusions.

The subjoined diagram is given with considerable reserve and is not to be taken as a summary of established facts but as an indication of the likely mechanism in the production of phlyctenulosis.

(6) *The significance of phlyctenulosis.*

(a) Aetiological considerations.

If it is urged that the tuberculous nature of an affection is proved only by the demonstration of tubercle bacilli in the lesion, all the available evidence clearly excludes phlyctenular ophthalmia. The affection is also excluded if there is insistence on the demonstration of tubercle bacilli elsewhere in the body apart from the actual phlycten, for blood cultures have given negative results (other than those obtained by the Loewenstein technique); stomach washings, as reported in the present investigations, have also been negative, and the evidence for tubercle bacilli in the tonsils is not extensive. The case for the tuberculous nature of phlyctenular ophthalmia rests on less direct evidence.

That evidence—and it is strikingly similar to that advanced for the tuberculous nature of erythema nodosum—has been questioned, not indeed as to its accuracy, but on the interpretation which has been given to it. It is argued that positive tuberculin tests indicate a non-specific allergic skin reaction, and Loddoni has shown that

acute phlycten cases respond positively to horse serum as well as to tuberculin. Such an objection overlooks the facts that the response to tuberculin is not transient (as is a positive result to horse serum) but a permanent characteristic of the patient, and that the positive skin reaction is not an isolated finding in such a patient. The heavy incidence of radiologically demonstrable tuberculosis cannot be overlooked; nor can the considerable incidence of clinical tuberculosis in the course of phlyctenular ophthalmia be dismissed. The after history of phlycten patients revealing not only a heavy incidence of tuberculosis, but also a considerable mortality, cannot be without significance.

Those who question the tuberculous nature of phlyctenular ophthalmia stress the fact that this affection is rare in sanatoria. It may be doubted whether this is strictly true, for many cases of phlyctenular ophthalmia are transient in character and easily overlooked. Moreover, evidence of past phlyctenulosis in patients with established tuberculous disease is not infrequent. It may be granted that phlyctenulosis is not commonly seen in adults with tuberculosis, but this only indicates that the phlycten is not a feature of that stage of tuberculosis which is manifested by the localisation of the disease into specific organs, but of the earlier stage of invasion which is accompanied by allergy induced by the invasion.

In strict logic it may be admitted that the phlycten is not a manifestation of tuberculosis, but the evidence that it is a manifestation of the altered state of the body following the invasion of the tubercle bacillus appears to be incontrovertible.

This conclusion is subject to an important qualification. In some 10-15 per cent. of cases there is no evidence for tuberculous infection. These cases illustrate the non-specificity of the phlycten reaction and experience at White Oak Hospital has shown that non-tuberculous phlyctenular ophthalmia tends to run a distinct clinical course. The disease is much more protracted, the response to treatment is poor, and there is a marked tendency towards massive scarring of the cornea which shows facette-formation rather than the localised opacities seen in the more usual type.

(b) Prognostic considerations.

Phlyctenular ophthalmia is not a minor malady, either from the ophthalmological, or from the general aspect. Though not an important cause of blindness, it may result in considerable impairment of vision. But its general significance overshadows the purely ophthalmological aspects. At its best the occurrence of phlyctenular ophthalmia in a child indicates tuberculous infection, and its significance is that of a spontaneous Calmette reaction; in a young child this in itself is a serious matter. The phlycten is, however, more than a spontaneous tuberculin reaction.

The raised sedimentation rate that is seen in active phlyctenular ophthalmia is in itself suggestive. It is an open question whether this raised rate reflects an underlying general disturbance of which the phlycten is the expression, or whether the phlycten represents the local point at which a superinfection has occurred. Either reading carries considerable prognostic significance. It is true that most cases of tuberculous infection, whether accompanied by phlyctenulae or not, subside without developing into clinical tuberculosis, but the occurrence of a phlycten seems to indicate a check to that favourable outcome. This is also brought out by the two studies available on the after-history of large series of cases of phlyctenular ophthalmia. Both Ajo's series and the study reported here indicate a heavy incidence of tuberculous disease in later life with a not inconsiderable mortality. There is certainly no evidence for believing, as is generally done in the case of tuberculous adenitis in children, that the affection is protective against the development of severe tuberculosis in adult life. It would therefore appear that it is not enough to regard the child with phlyctenular ophthalmia as infected with tuberculosis; there is strong presumptive evidence that the child must also be regarded as hyperallergic and devoid of a proportionate increase in immunity. The phlycten is thus more than a sign of tuberculous infection; it is a danger signal of possible tuberculous disease. The frequent relapses seen in the course of phlyctenular ophthalmia are not so much an ophthalmological problem as part of the larger issue which deals with the factors that determine whether a tuberculous infection will become quiescent or evolve into tuberculous disease.

(7) *Outstanding problems.*—The conception of phlyctenulosis as a manifestation of an hyperallergic phase in tuberculous infection requires clarification, and the problem resolves itself into a study of objective evidence for such a phase. A more detailed investigation of sedimentation rates in phlyctenulosis may bring further light on the underlying general reactions. Obscure as these aspects of phlyctenulosis are, there is much greater obscurity on the exciting factors operative on the sensitised soil. The fundamental problem whether such factors are largely endogenous or exogenous has hardly been explored at all. No valid interpretation of photophobia—a striking feature in phlyctenulosis—appears to be available, nor is there conclusive evidence that the heavier incidence of phlyctenulosis in girls is indeed due to a heavier incidence of tuberculous infection in them.

The final and most fundamental question is whether the phlycten is to be regarded as a protective reaction by which the body eliminates the toxins of the tubercle bacillus and of other breakdown products foreign to the body, or whether it is the incidental manifestation of tissue damage produced by tuberculous infection under suitable conditions.

Summary

I.

A review of the literature reveals that :

1. The phlycten is not a specific lesion. It has been described in conjunctival and corneal reactions in a variety of aetiologically distinct conditions. The mass of phlyctenular ophthalmia does, however, constitute a clear-cut clinical entity.

2. Excepting the period 1914-18 and its aftermath when there was a sharp increase in the incidence of the affection on the Continent, phlyctenular ophthalmia has become much less frequent during the past 40 years.

3. The disease falls heavily on childhood but young adults are frequently affected.

4. Girls are more frequently affected than boys, the ratio being about 6 to 4.

5. There is a seasonal variation in incidence, the affection being commonest in spring.

6. There is no valid evidence incriminating nutritional deficiencies, focal sepsis, pediculosis and endocrine disturbances as causal factors.

7. A mass of evidence points to tuberculous infection as the underlying cause of phlyctenular ophthalmia. This evidence consists of (1) a high incidence of positive tuberculin reactions; (2) a high incidence of radiologically demonstrable tuberculous chest lesions; (3) the finding of tubercle bacilli in the tonsils of phlycten patients; (4) a considerable incidence of a personal history of tuberculous disease; (5) a considerable incidence of a family history of tuberculosis; (6) an unfavourable after-history in many cases; (7) the clinical similarity of phlyctenular ophthalmia to the sequence of the ophthalmo-reaction of Calmette in tuberculous patients; (8) a significant incidence of previous phlyctenulosis in adults suffering from tuberculosis.

8. Experimental studies implicate a sensitised soil as well as an exciting factor in the development of the phlycten. Sensitisation can be induced by a variety of agents, tuberculous infection being one. The exciting factor is best, but not necessarily the specific sensitising agent.

II.

An analysis was made of the data on cases of phlyctenular ophthalmia treated at White Oak Hospital during 1921-1940, and detailed investigations are recorded on the cases treated between June 1935 and December 1940. Each point investigated was

checked in control material obtained largely from the children treated for blepharitis at that hospital. These data show that :

1. The heavier incidence of the affection on girls is confirmed.
2. There is no evidence that malnutrition, focal sepsis and pediculosis are seen more frequently in phlyctenular ophthalmia than in blepharitis.
3. Non-bacterial allergy is not a causal factor in phlyctenulosis.
4. Positive tuberculin reactions were obtained in 84.8 per cent. of all phlycten cases and in 81.7 per cent. in phlycten cases under the age of 6 years. The corresponding incidences in blepharitis cases were 15.3 per cent. and 8.0 per cent.
5. Radiological evidence of tuberculosis was present in 72.2 per cent. of phlycten cases against 8.4-16.1 per cent. for controls.
6. Clinical tuberculosis was seen in 6.4 per cent. of phlycten cases against no cases in the control series.
7. A family history of tuberculosis was present in 28.9 per cent. of phlycten cases against a computed incidence of 3.7 per cent. for the normal school child population.
8. The sedimentation rate was raised in 79.8 per cent. of cases with active phlyctenular ophthalmia. Quiescent phlyctenular ophthalmia and blepharitis gave normal rates.
9. Tubercle bacilli could not be recovered in the stomach washings of 50 cases, nor in the excised tonsils of 20 others.
10. The after history of cases treated between 1921 and 1931 revealed an incidence of 5.3 per cent. of clinical tuberculosis and a mortality rate of 0.8 per cent. in the phlycten against 0.8 per cent. and 0.1 per cent. respectively for the controls.

III.

It is concluded that phlyctenular ophthalmia is a manifestation, not of tuberculous disease, but of tuberculous infection, the phlycten making its appearance only when a hyperallergic phase is present and there is a suitable (? specific) exciting factor of endogenous or exogenous origin. It is suggested that the age distribution, sex-incidence and seasonal variation seen in phlyctenulosis are best explained on the assumption that the affection is tuberculous in character. The prognostic significance of the phlycten is graver than that of a positive tuberculin reaction in a child; this is borne out by the subsequent incidence of tuberculosis and mortality from it in children previously affected with phlyctenulosis.

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REFERENCES

- AJO (1938).—*Acta Ophthal.*, Suppl. XV.
 ATTIAH (1935).—*Bull. Ophthal. Soc. Egypt*, Vol. XXVIII, p. 73.
 D'AYREX (1910).—*Bull. et Mém. Soc. Franç. d'Ophthal.*, Vol. XXVII, p. 237.
 BAKKER.—Quoted by Boen-Lian (1930).
 BALLANTYNE (1936).—*Trans. Ophthal. Soc. U.K.*, Vol. LVI, p. 82.
 BARRETT (1938).—*Austral. and New Zealand Jl. Surg.*, Vol. VIII, p. 239.
 BEDNARSKI (1911).—*Klin. Monatsbl. f. Augenheilk.*, Vol. XLIX, p. 521.
 BEER (1813).—*Lehre der Augenheilkunde*, Vienna, Vol. I, p. 588.
 BELENSKY-RASKIN (1913).—*Zeitschr. f. Augenheilk.*, Vol. XXIX, p. 503.
 BENTLEY (1932).—*Lancet*, Vol. I, p. 689.
 BICKERTON (1936).—*Trans. Ophthal. Soc. U.K.*, Vol. LVI, p. 84.
 BLAIR (1924).—*Trans. Amer. Acad. Ophthal. and Otolaryn.*, Vol. XXIX, p. 195.
 BOEN LIAN (1930).—*Klin. Monatsbl. f. Augenheilk.*, Vol. LXXXIV, p. 360.
 BRACCI-TORSI (1935).—*Ann. di Ottal. e Clin. Ocul.*, Vol. LXIII, p. 359.
 BRUCKNER (1929).—*Ann. d'Ocul.*, Vol. CLXVI, p. 804.
 BRUNS (1904).—*Arch. f. Ophthal.*, Vol. LVIII, p. 439.
 ——— (1912).—*Jl. Amer. Med. Assoc.*, Vol. LIX, p. 1002.
 BÜCKLERS (1935).—*Klin. Monatsbl. f. Augenheilk.*, Vol. XCIV, p. 109.
 BURGIN and HIGGINS (1938).—*Amer. Jl. Dis. Childr.*, Vol. LVI, p. 239.
 BYWATER (1911).—Thesis. Ref. *Ophthalmoscope*, Vol. IX, p. 670.
 CARVILL (1929).—*Trans. Amer. Ophthal. Soc.*, Vol. XXVII, p. 314.
 CASPARIS (1927).—*Amer. Jl. Dis. Childr.*, Vol. XXXIV, p. 779.
 CERCHEZ (1934).—Ref. *Centralb. f. Ophthal.*, Vol. XXXI, p. 741.
 CERZA (1935).—Ref. *Centralb. f. Ophthal.*, Vol. XXXV, p. 627.
 CHAMS (1930).—*Arch. d'Ophthal.*, Vol. XLVII, p. 38.
 CHOU.—In Kwan (q.v.).
 COHEN (1909).—*Klin. Monatsbl. f. Augenheilk.*, Vols. XLVII, I, p. 405.
 COLUMBA (1935).—*Ann. di Ottal. e Clin. Ocul.*, Vol. LXIII, p. 437.
 CONNERTH (1926).—*Deut. Med. Wochenschr.*, Vol. I, p. 533.
 COSULCHI.—Quoted by Puscariu and Lazarescu.
 CREMER (1929).—*Arch. f. Augenheilk.*, Vols. C-CI, p. 729.
 ——— (1931).—*Münch. Med. Wochenschr.*, p. 1223.
 CURTIN (1914).—*Jl. Amer. Med. Assoc.*, Vol. LXIII, p. 571.
 DAVIS and VAUGHAN (1912).—*Ophthal. Rec.*, Vol. XXI, p. 476.
 DERBY (1908).—*Arch. of Ophthal.*, Vol. XXXVII, p. 515.

- DICKEY and SEITZ (1931).—*Amer. Rev. Tuberc.*, Vol. XXIII, p. 13.
- DOW and LLOYD (1931).—*Brit. Med. J.*, Vol. II, p. 183.
- DROLET (1934).—*Amer. Rev. Tuberc.*, Vol. XXX, p. 1.
- EDLER (1931).—*Prakt. Tuberkulosebl.*, Vol. V, p. 120.
- EOCHE-DUVAL (1934).—La Kératoconjonctivite pustuleuse de l'enfant et les affections du rhino-pharynx. Thesis. Paris.
- ESCOLAN (1934).—Traitement endocrinien . . . de kérato-conjonctivite phlycténulaire. Thesis. Paris.
- ESSEN-MÖLLER (1936).—*Acta Ophthalm.*, Vol. XIV, p. 414.
- FONTANA (1933).—*Boll. d'Ocul.*, Vol. XII, p. 598.
- FOSTER (1936).—*Proc. Roy. Soc. Med.*, Vol. XXIX, p. 755.
- FRANCESCHETTI and GUGGENHEIM (1929).—*Klin. Monatsbl. f. Augenheilk.*, Vol. LXXXII, p. 1.
- FROMINOPOULOS (1940).—*Klin. Monatsbl. f. Augenheilk.*, Vol. CIV, p. 1.
- FUNAISHI (1923).—*Klin. Monatsbl. f. Augenheilk.*, Vol. LXXI, p. 141.
- (1925).—*Amer. J. Ophthalm.*, Vol. VIII, p. 618.
- GARCIA MONTES and SILVA (1938).—*Rev. Cub. Oto.-Neuro.-Oftal.*, Vol. VII, p. 46.
- GIALLOMBARDO (1924).—*Boll. d'Ocul.*, Vol. III, p. 93. (Quoted by Rohrschneider, 1935).
- GIBSON (1918).—*Amer. J. Dis. Childr.*, Vol. XV, p. 81.
- GOLDBACH (1917).—*Jl. Amer. Med. Assoc.*, Vol. LXIX, p. 102.
- GOLDENBERG (1917).—*Jl. Amer. Med. Assoc.*, Vol. LXIX, p. 104.
- (1930).—*Amer. J. Ophthalm.*, Vol. XIII, p. 699.
- GOLDSTEIN and WOOD (1934).—*Amer. J. Dis. Childr.*, Vol. XLVII, p. 171.
- GOULDEN (1936).—*Trans. Ophthalm. Soc. U.K.*, Vol. LVI, p. 80.
- GRENET and LANGLOIS (1934).—*Bull. Soc. Pédiatr. Paris*, Vol. XXXII, p. 96.
- GRONHOLM (1928).—*Acta Ophthalm.*, Vol. VI, p. 297.
- GUILERY (1921).—*Münch. Med. Wochenschr.*, p. 201.
- GUTTMANN (1898).—*Deut. Med. Wochenschr.*, Vol. XXIV, p. 535.
- GUTZEIT (1922).—*Zeitschr. f. Augenheilk.*, Vol. XLVI, I, p. 100.
- HAMBURGER (1923).—*Münch. Med. Wochenschr.*, Vol. LXX, p. 54.
- HARMAN (1925).—*Brit. Med. J.*, (II), p. 379.
- HAYASHI (1909).—*Klin. Monatsbl. f. Augenheilk.*, Vol. XLVII (ii), p. 557.
- HEINONEN (1936).—*Acta Ophthalm.*, Vol. XIV, p. 187.
- HETHERINGTON, MCPHEDRAN, LANDIS and OPIE (1929).—*Amer. Rev. Tuberc.* Vol. XX, p. 421.
- HIGASHI (1930).—*Ref. Centralb. f. Ophthalm.*, Vol. XXIII, p. 768.
- HINRICHS (1935).—*Zeitschr. f. Augenheilk.*, Vol. LXXXVI, p. 269.
- HIRD (1918).—*Brit. J. Ophthalm.*, Vol. II, p. 215.
- HIRSCHBERG (1904 and 1905).—Geschichte der Augenheilkunde (in Graefe-Saemisch Handbuch der Ophthalmologie). Leipzig 2te Aufl., Vol. XII, p. 381, and Vol. XIII, p. 132.
- HORNER (1889).—In C. Gerhardt, "Handbuch der Kinderheilkunde," Tübingen, Vol. V, Abt. 2, p. 279.
- IANKU *et al.* (1935).—*Cluj. Med.*, Vol. XVI, p. 80.
- IGA (1930).—*Klin. Monatsbl. f. Augenheilk.*, Vol. LXXXIV, p. 449.
- IRGERSHEIMER (1910).—*Klin. Monatsbl. f. Augenheilk.*, Vol. XLVIII, II, p. 593.
- IRGERSHEIMER and PRINZ (1921).—*Arch. f. Ophthalm.*, Vol. CV, p. 640.
- IWANOFF (1869).—*Klin. Monatsbl. f. Augenheilk.*, Vol. VII, p. 462.
- JACQUET, THIEFFRY and HAU (1935).—*Bull. et Mem. Soc. Méd. d'hôp. Paris*, Vol. LI, p. 420.
- KAMEKE (1930).—*Prakt. Tuberkulosebl.*, Vol. IV, p. 122.
- KASSNER (1921).—*Arch. f. Ophthalm.*, Vol. CIV, p. 337.
- KATNELSON, KACHAN and YUFA (1939).—*Vestnik Oftal.*, Vol. XV, p. 3. (Ref. *Arch. of Ophthalm.*, Vol. XXV, p. 516).
- KINSEY (1932).—*Jl. Canad. Med. Assoc.*, Vol. XXVI, p. 298.
- KÖLLNER and FILBRY (1919).—*Arch. f. Augenheilk.*, Vol. LXXXIV, p. 11.
- KRASO (1925).—*Zeitschr. f. Kinderheilk.*, Vol. XXXIX, p. 448.
- KRUSE (1926).—*Zeitschr. f. Kinderheilk.*, Vol. XLII, p. 505.
- KUBOKI (1924 a).—Ref. *Klin. Monatsbl. f. Augenheilk.*, Vol. LXXXIII, p. 528. (b) Quoted by Funaishi.
- KUNIYA (1935).—*Acta Soc. Ophthalm. Japon.*, Vol. XXXIX, Suppl. 366. (German summary, *ibid.* p. 32).

- KWAN (1938).—*Chin. Med. Jl.*, Vol. LIV, p. 421.
- KYO-YOH (1936).—*Ref. Centralbl. f. Ophthal.*, Vol. XXXIII, p. 363.
- LASKY (1932).—*Amer. Jl. Ophthal.*, Vol. XV, p. 725.
- LAZARESCU and DAMIAN (1936).—*Klin. Monatsbl. f. Augenheilk.*, Vol. XCVII, p. 626.
- LEBER (1901).—*Ber. Deut. Ophthal. Gesellsch.*, Vol. XXIX, p. 66.
- (1909).—*Arch. f. Ophthal.* Vol. LXXIII, p. 55.
- LEMOINE (1929).—*Arch. of Ophthal.*, N.S.I., p. 706.
- LODDONI (1930).—*Ann. di Ottal. e Clin. Ocul.*, Vol. LVIII, p. 28.
- LOEWENSTEIN (1925).—*Med. Klin.*, Vol. XXI, p. 845.
- LUPINO (1926).—*Ann. di. Ottal. e Clin. Ocul.*, Vol. LIV, p. 1209.
- MAGGI.—Quoted in Ch. Gouffier, "Contribution à l'étude de l'étiologie de la kérato-conjonctivite phlycténulaire." Thesis. Paris. 1912-13.
- MAGITOT, TILLÉ and DUBOIS-POULSEN (1936).—*Ann. d'Ocul.*, Vol. CLXXIII, p. 1.
- MANN (1920).—*Arch. f. Laryng.*, Vol. XXXIII, p. 507.
- MARFAN (1928).—*Presse Méd.*, Vol. XXXVI, p. 1105.
- MAZZOLO (1929).—*Boll. d'Ocul.*, Vol. VIII, p. 1099.
- MORELLI (1924).—*Ann. di Ottal. e Clin. Ocul.*, Vol. LII, p. 766.
- MÜLLER (1901).—*Wien. Med. Presse*, Vol. XLII, pp. 489 and 542.
- NASSAU and ZWEIG (1925).—*Zeitschr. f. Kinderheilk.*, Vol. XXXIX, p. 484.
- NELSON (1923).—*Jl. Amer. Med. Assoc.*, Vol. LXXXI, p. 211.
- NEUMANN (1933).—*Med. Klin.*, Vol. XXIX, p. 1407.
- NOBÉCOURT and BRISKAS (1936).—*Presse Méd.*, Vol. XLIV, pp. 625 and 913.
- and DUCAS (1934).—*Presse Méd.*, Vol. XLII, p. 1241.
- NOWAK (1922).—*Ber. Deut. Ophthal. Gesellsch.*, Vol. XLIII, p. 117.
- PAGANI and GENNARO (1929).—*Boll. d'Ocul.*, Vol. VIII, p. 633.
- PAPAGNO (1935).—*Ann. di Ottal. e Clin. Ocul.*, Vol. LXIII, p. 288.
- PARKOVITS-BUGARSKY (1930).—*Klin. Monatsbl. f. Augenheilk.*, Vol. LXXXV, p. 528.
- (1931).—*Ann. d'Ocul.*, Vol. CLXVIII, p. 288.
- PASCHEFF (1937).—*Clin. Bulgar.*, Vol. IX, p. 129 (Ref. *Centralbl. f. Ophthal.*, Vol. XXXIX, p. 540, 1937).
- PAVIA (1936).—*Rev. Otol. etc. y Cer. Neur. Sud.-Amer.*, Vol. XI, p. 219.
- PEYRER (1922).—*Beitr. z. Klin. d. Tuberkul.*, Vol. XLVIII, p. 139.
- PIERRET, BRETON and LOISON (1933).—*Arch. de Méd. des Enf.*, Vol. XXXVI, p. 393.
- PILON.—Quoted by Boen-Lian.
- POLEV and SAWALSKY-FISSAN (1925).—*Krimsky Med. Arch.*, Vol. II, p. 132. (Ref. *Centralbl. f. Ophthal.*, Vol. XVI, p. 56, 1926).
- PRICE (1940).—*Irish Jl. Med. Sci.*, p. 327.
- PUSCARIU and LAZARESCU (1935).—*Boll. d'Ocul.*, Vol. XIV, p. 465.
- PYFER.—Quoted by Gibson.
- RAMSAY (1933).—*Brit. Med. Jl.*, (i), p. 266.
- REDDING (1935).—*Pennsylv. Med. Jl.*, Vol. XXXIX, p. 158.
- DE REZENDE (1933).—*Revista de Ophthal. de S. Paulo*, Vol. II, p. 103.
- RIEHM (1928).—*Arch. f. Augenheilk.*, Vol. XCIX, p. 438.
- (1932).—*Arch. f. Augenheilk.*, Vol. CV, p. 55.
- (1930).—*Arch. f. Ophthal.*, Vol. CXXIII, p. 361.
- (1930).—*Ber. Deut. Ophthal. Gesellsch.*, Vol. XLVIII, p. 217.
- (1932).—*Centralbl. f. Tuberk.-Forsch.*, Vol. XXXVI, p. 337.
- ROCHA T (1932).—*Maandschr. v. Kindergeneesk.*, Vol. I, p. 298. (Ref. *Centralbl. f. Ophthal.*, Vol. XXVII, p. 464, 1932).
- ROHRSCHEIDER (1935).—*Zeitschr. f. Augenheilk.*, Vol. LXXXVI, p. 281.
- ROJAS (1937).—La kérato-conjonctivite phlycténulaire dans le cadre des slades de l'infection tuberculeuse. Thesis. Paris.
- ROLET (1931).—*Klin. Monatsbl. f. Augenheilk.*, Vol. LXXXVII, p. 497.
- RÖMER (1922).—*Klin. Monatsbl. f. Augenheilk.*, Vol. LXIX, p. 128.
- RÖMMELT (1936).—*Zeitschr. f. Augenheilk.*, Vol. XC, p. 1.
- ROSENHAUCH (1910).—*Arch. f. Ophthal.*, Vol. LXXVI, p. 370.
- RUBERT (1912).—*Klin. Monatsbl. f. Augenheilk.*, Vol. I, (ii), p. 273.
- ST. YVES (1722).—*Nouveau Traité des Maladies des Yeux*. Paris. Pp. 183-4.
- SARGNON (1939).—*Rev. d'Oto.-Neuro.-Ophtal.*, Vol. XVII, p. 401.

- SAVIN and PRESTON (1925).—*Lancet*, (i), p. 965, and personal communications by L. H. Savin.
- SCHIECK.—Quoted by Stargardt, 1916.
- (1932).—(a) *Munch. Med. Wochenschr.*, Vol. LXXIX, p. 6.
- (1932).—(b) *Tuberkulöse Infektion und Augenleiden*, Leipzig. (No. 48 of *Tuberkulose-Bibliothek*)
- SCHLESINGER and HART (1930).—*Arch. Dis. Childr.*, Vol. V, p. 191.
- SCHMELZER (1930).—*Zeitschr. f. Augenheilk.*, Vol. LXX, p. 149.
- SCHREIBER (1916).—*Ber. Deut. Ophthal. Gesells.*, Vol. XL, p. 471.
- SCHÜTZ and VIDEKY (1908).—*Wien. Klin. Wochenschr.*, Vol. XXI, p. 1285.
- SCHWARZ.—Thesis Königsberg, 1937. (Ref. *Centralbl. f. Ophthal.*, Vol. XLIII, 1939, and in Frominopoulos, 1940).
- SIWE (1934).—*Acta Tuberc. Scandinav.*, Vol. VIII, p. 224.
- (1935).—*Acta Paediat.*, Vol. XVII, (Suppl. 1), p. 170.
- SORSBY (1937).—Annual Report for 1935, London County Council, Vol. IV, (iii), p. 69.
- and BENHAM (1936).—*Proc. Roy. Soc. Med.*, Vol. XXIX, p. 955.
- HAMBURGER and BENHAM (1936).—*Trans. Ophthal. Soc. U.K.*, Vol. LVI, p. 63.
- HAMBURGER, COVENEY and NEVIN (1938).—*Trans. Ophthal. Soc. U.K.*, Vol. LVIII, p. 173.
- STALDER (1926).—*Schweiz. Med. Wochenschr.*, Vol. LVI, p. 618.
- STARGARDT (1916).—*Ber. Deut. Ophthal. Gesellsch.*, Vol. XL, p. 462.
- STEPHENSON and JAMIESON (1910).—*Brit. Med. J.*, (i), p. 916.
- STOCK (1907).—*Arch. f. Ophthal.*, Vol. LXVI, p. 69.
- V. SZILY (1930).—*Ber. Deut. Ophthal. Gesellsch.*, Vol. XLVIII, p. 227.
- TERRIEN and GOULFIER (1927).—Quoted by Weekers.
- TEJEDA (1932).—*Arch. Oftal. Hisp.-Amer.*, Vol. XXXII, p. 219. (Ref. *Centralbl. f. Ophthal.*, Vol. XXVII, p. 636, 1932).
- TIERRY (1937).—*Acta Ophthal.*, Vol. XV, p. 355.
- TIVNEN (1911).—*Jl. Amer. Med. Assoc.*, Vol. LVII, p. 1886.
- V. TÓTH (1930).—*Zeitsch. f. Laryng.*, Vol. XX, p. 293.
- TOWBIN and RAVIC-SCERBO (1930).—*Arch. f. Ophthal.*, Vol. CXXIV, p. 154.
- URBANER and ROSCHKOTT (1939).—*Klin. Monatsbl. f. Augenheilk.*, Vol. CII, p. 668.
- VANNAS (1935).—*Klin. Monatsbl. f. Augenheilk.*, Vol. XCIV, p. 49.
- VEEDER and HEMPELMANN (1920).—*Arch. of Paediat.*, Vol. XXXVII, p. 396.
- WALGREN (1930).—In Engel and Pirquet, *Handbuch der Kindertuberkulose*, Vol. I, p. 809. Thieme. Leipzig.
- WALKER (1928).—*Proc. Roy. Soc. Med.*, Vol. XXII, p. 19.
- WANG (1934).—*Klin. Monatsbl. f. Augenheilk.*, Vol. XCIII, p. 505.
- WARDROP.—*Essays on the Morbid Anatomy of the Human Eye*. London. Vol. I, Pl. 1, Fig. 3, 1808.
- DE WEEKERS (1909).—*Arch. d'Ophtal.* Vol. XXIX, p. 294.
- (1927).—*Arch. d'Ophtal.*, Vol. XLIV, p. 343.
- (1930).—*Arch. d'Ophtal.* Vol. XLVII, p. 13.
- (1909).—*Bull. de l'Acad. Roy. de Méd. de Belgique*, Vol. XXIII, p. 577.
- (1910).—*Ibid.*, Vol. XXIV, p. 435.
- (1929).—*Trans. XIII Internat. Congress of Ophthal.* Amsterdam. Vol. II, p. 458.
- and COLMANT (1922).—*Arch. d'Ophtal.*, Vol. XXXIX, p. 66.
- WERNER (1928).—*Acta Ophthal.*, Vol. VI, p. 138.
- WESSELY (1919).—*Jahreskurse Aertz. Fortbild.*, Vol. X, Heft II, p. 3. (Ref. *Munch. M. d. Wochenschr.*, Vol. LVII, p. 30, 1920).
- WHITTINGTON (1925-6).—Metropolitan Asylums Board Report, p. 333
- WIESE (1925).—*Beit. Klin. Tuberkul.*, Vol. LX, p. 613.
- WILDER (1910).—*Jl. Amer. Med. Assoc.*, Vol. LV, p. 21.
- WOOD (1917).—*Amer. Encycl. of Ophthal.*, Chicago, Vol. XII, p. 9634.
- WOODS (1933).—Allergy and Immunity in Ophthalmology. Baltimore, p. 107.
- WORINGER (1931).—*Paris Méd.*, (ii), p. 398.
- YAMAGUCHI (1937).—*Ref. Centralbl. f. Ophthal.*, Vol. XXXIX, p. 685.