THE AETIOLOGY OF PHLYCTENULAR OPHTHALMIA*

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1.—Historical

WITH the giving way, during the eighteenth century, of the conception of external ophthalmia to more detailed clinical entities, a form of kerato-conjunctivitis emerged in which nodular reactions formed a prominent feature. This is clearly brought out by St. Yves in his classical text-book of 1722, and a phlycten is well shown in a plate in Wardrop's *Essays on the Morbid Anatomy of the Human Eye*, which appeared in 1808 and laid the basis of ocular pathology. Localised reactions in the conjunctiva and cornea did not, of course, escape notice by earlier observers: Hirschberg (1904, 1905) has drawn attention to the description of Paul of Aegina in the late Greek classics, and to the account by Ali ben Isa among the Arabians. When Beer attempted, in 1813, to give an aetiological classification of ocular disease, scrofulous ophthalmia came to stand for a variety of conditions, of which a scrofulous diathesis was assumed to be the cause. The return to the anatomical method introduced by Wardrop in the long run broke down this group—Hutchinson's differentiation of interstitial keratitis being an outstanding achievement in this direction. The conflict between the aetiological and the anatomical approach to eye disease led on the one hand to the histological studies of the phlycten by Iwanoff in 1869, and, on the other, to the assumption of diatheses other than scrofula as the cause of the affection. It is thus that eczema was suggested by Horner in 1880 as the cause of the eye condition. With the advent of bacteriology, emphasis on extraneous factors dominated medicine, and the concluding two decades of the nineteenth century saw much work devoted to isolating a hypothetical causative organism of phlyctenular kerato-conjunctivitis. Almost every one of the organisms commonly present in the conjunctival sac was incriminated, and for a time the *staphylococcus aureus* almost gained acceptance. Towards the end of the century, when the first phase of bacteriology had spent its force and the general feeling was once more turning towards endogenous factors as the cause of phlyctenular keratitis, the scrofulous diathesis once again came to the forefront. Meanwhile the conception of scrofula had itself undergone great changes; bacteriology had demonstrated that the

* Hunterian Lecture delivered at the Royal College of Surgeons, January 30, 1942.

scrofulous joint and scrofulous glands were tuberculous in origin. The assumption that scrofulous eye conditions were likewise tuberculous could not, however, be verified. Neither histological nor bacteriological evidence were such that they could convincingly prove the phlycten as tuberculous. The scrofulous nature of the phlycten remained, as hitherto, a pathologically unverified clinical conception. The conflict that supervened as to whether all scrofula was tuberculous or merely a predisposing condition for tuberculosis is still reflected—though in different terms—in present-day literature, for the problem still remains whether phlyctenular keratitis is a frankly tuberculous manifestation, or a condition which develops in children likely to fall victims to tuberculosis. The conflict, however, had spread beyond these bounds; a number of observers have left these contentions aside, and have advanced factors unrelated to tuberculosis or scrofula as the causative agents of the affection. The work done during recent years has gone far to reconcile all these apparently conflicting views; active tuberculosis, the manifestations of predisposition to active tuberculosis, and factors totally unconnected with tuberculosis, all seem to be accounted for in the pathological conception of phlyctenular keratitis that is emerging at the present day.

2.—Review of Literature

(A) *Natural History of Phlyctenulosis*

There is no *a priori* reason for the accuracy of the widespread assumption that the phlycten—a nodular reaction in the conjunctiva or cornea—must have only one exciting cause. In fact, localised reactions of the phlycten type occur against a background of generalised conjunctivitis in a number of aetiologically distinct conditions. They are met in Koch-Weeks conjunctivitis, and Morax-Axenfeld conjunctivitis, whilst the conjunctival reactions in acne rosacea and lichen scrofulosa bear, indeed, a very close anatomical resemblance to “phlyctenular conjunctivitis.” They have also been described in Leishmaniasis keratitis (Chams, 1930). Cerza (1934) reports the appearance of phlyctenulae in 21 sucklings and infants during an epidemic of impetigo; in all cases *staphylococcus aureus* was found in the phlyctenulae. Isolated instances of the occurrence of phlyctenulae in allergic conjunctivitis such as due to bark of the poplar tree (Bücklers, 1935) or to strawberry (Lemoine, 1929) have been reported. Schieck (1932) has described it in metastatic gonococcal conjunctivitis (but not in accidental gonococcal infection of the eye in an old-standing case of gonorrhoea, as is stated in two current ophthalmic reference books). The pseudo-phlyctens of tropical countries illustrate still further the non-specificity of the phlyctenular reaction.

(1) Incidence.

Within living memory phlyctenulosis has declined greatly. Clinical impressions to that effect are recorded by Walker (1928), Ballantyne (1936), and Goulden (1936) for this country, by Barrett (1938) for Australia, and by Goldenberg (1930) for the United States.

These impressions are substantiated by a small series of statistical studies recorded for the United States and for several European countries.

(a) United States:—Redding (1935) found a steady decline in the number of cases seen at four large American university clinics during the period 1912-32, whilst Burgin and Higgins (1938) report a continuous decline over a period of 25 years at the Massachusetts Eye and Ear Infirmary, where 384 cases were seen in 1910-14 and only 54 in 1930-34.

(b) Holland:—At the University Clinic of Groningen, Rochat (1932) found that the incidence of phlyctenular ophthalmia between 1914-30 had declined from constituting 8·7 per cent. of all cases to 1 per cent. A similar trend was observed at the clinic in Utrecht.

(c) Sweden:—Essen-Möller (1936) reports a steady decline at a Lund clinic; between 1909 and 1933 the percentage of phlycten cases fell from 9·5 per cent. to 1·5 per cent. of the total number of cases seen.

(d) Finland:—At Helsingfors, Werner (1928) found a progressive decline from 13·4 per cent. in 1901 to about 4·0 per cent. in the period 1923-26. At Abo, where there is a relatively stationary school child population of about 4,000 per year, Heinonen (1936) found a decline in incidence from 1·5 per cent. to 0·5 per cent. during the period 1928-34.

(e) Switzerland:—Rolet (1931) records that in the period 1906-10 phlyctenulosis was responsible for 8·2 per cent. of the total number of out-patients at the University clinic at Berne and for only 3·6 per cent. in 1926-30.

(f) Austria:—A graph published by Redding for the Vienna University Clinic (1912-33) shows a marked decline in the number of cases seen, the decline being particularly striking between 1925 and 1933, the numbers falling from about 575 in the first year to about 375 in the last year. At the Vienna municipal hospital at Lainz there was a decline from a total of over 400 cases in 1924 to about 40 in 1937, judging from a graph given by Fronimopoulos. At another Vienna clinic Urbanek and Roshkott (1939) saw a decline from 1,359 cases in 1920 to about 250 in 1935.

To this consistent decline, which cannot altogether be ascribed to the decline in the child population, there are two exceptions. One comes from the data of the Hôtel Dieu at Paris, where a practically continuous increase in the number of cases seen at that

hospital has been observed in the period 1912-32. The second and more important exception, is a consistently higher incidence reported in several centres during the 1914 war and its aftermath. In Holland, Rochat found that the steady decline in the incidence of phlyctenulosis did not apply for 1914-17, when the numbers remained stationary, and for 1918, when there was a slight increase. In Finland there was no decline during the period 1918-22; instead an increase was noted (Werner). Gutzeit observed the same tendency in Prussia, whilst Kassner (1921) records a rise from around 4 per cent. in pre-war years to 7 per cent. in 1919 of the total of out-patients in University clinic at Gottingen, where an increase in the severity of the course of the phlyctenulosis was also observed. A steep increase in the number of phlycten cases was observed in Vienna during the war and the famine years following it. This is clearly brought out by the data recorded by Redding, by Urbanek and Roshkott, and by Fronimopoulos. According to this latter observer, phlyctenular ophthalmia was responsible for 40 per cent. of all eye disease in Vienna in that period.

(2) Age distribution.

Several large series are available and show agreement on the fact that phlyctenulosis is essentially a disease affecting children and young adults. There is, however, no agreement as to whether the affection is commonest in the first or in the second decade of life.

The following summary table sets out the more significant findings, but it must be realised that some observers dealt with

TABLE I
Showing distribution in age groups in some of the larger series of phlyctenulosis

Author	Total Number	Percentage of total number in various age groups								
		0-4	5-9	10-14	15-19	20-24	25-29	30-49	50-59	Over 60
Guttman, 1898 ...	6,550	33·0	27·4	16·8	10·2	5·2			7·2	
Krasso, 1925* ...	1,283	8·2	15·4	17·5	20·2	12·8	7·0	9·2	1·5	0·6
Gronholm, 1926 ...	c.1,500	30	21	21	16	9	1	—	—	—
Weekers, 1929 ...	1,394	23·5	25·0	19·8	15·8	8	2·3	5·7	—	—
Rolet, 1931 ...	2,495	22·5	21·5	26·0	11·0	8·7	5·0	4·7	0·5	—
Essen-Möller, 1936	2,614	21·7	23·4	19·5	13·8	8·8	3·7	5·1	0·7	0·2
Frominopoulos, 1940	c.2,970	9·7	16·3	19·0	18·0	10·0	7·7	13·7	3·4	1·3

* Taken from Essen-Möller's evaluation of Krasso's graph.

cases seen only in children's hospitals. Moreover, the data are not always presented in comparable form and in some cases had to be deduced from graphs.

Krasso (1925) holds that there are two peak periods, one at 3 to 4 years of age, the other at 15 years. Rolet's data, those of Fronimopoulos and to some extent also those of Essen-Möller, point in the same direction. The series reported by Guttman (1898) and Gronholm (1926) do not support this view.

TABLE II

Sex incidence of phlyctenular ophthalmia as reported in series of over 300 cases

Author	Total Number	Percentage Males	Percentage Females	Remarks
Guttman, 1898 ...	(1) 6,550	32.5	67.5	(1) "eczematous kerato-conjunctivitis"
	(2) 3,873	30.8	69.2	(2) part of the previous series; cases with phlyctenulae
	(3) c.12,500	40	60	(3) collected data from other observers
Gronholm, 1928 ...	c.1,500	42	58	—
Carvill, 1929 ...	350	30.3	69.7	—
de Weekers, 1929 ...	1,850	29	71	—
Rolet, 1931 ...	(1) 1,549	32.6	67.4	(1) 1906-10
	(2) 762	39	61	(2) 1926-30
Rezende, 1933 ...	324	33	67	—
Cerchez, 1934 ...	3.6	38	62	—
Puscariu and Lazarescu, 1935...	684	47.1	52.9	—
Heinonen, 1936 ...	1,025	40.4	59.6	—
Essen-Möller, 1936	2,614	39.8	60.2	—
Ajo, 1938 ...	449	51	49	—
Burgin and Higgins, 1938 ...	502	40.4	59.6	—
Frominopoulos, 1940	c.2,740	39	61	—

(3) Sex distribution.

That the incidence of phlyctenular ophthalmia falls heavier on females than on males appears to have been well recognised by the older observers. Guttman in 1898 produced elaborate evidence and Cohen writing in 1909 speaks of the "well known fact that the affection is twice as common in females as in males." This knowledge seems, however, to have been forgotten, for in 1929 de Weekers in one of his excellent papers on phlyctenular ophthalmia could bring it forward as a new observation before an International Ophthalmic Congress. The considerable attention that has been paid to this aspect of phlyctenulosis since de Weekers' paper has resulted in a mass of new evidence.

Table II summarises the findings reported in some of the larger series observed.

Evidence that phlyctenulosis is much more frequent in women is thus present in all the reported series, except those of Puscariu and Lazarescu (1935) and of Ajo (1938).

Guttman held that a difference in sex incidence becomes apparent at about the fifth year, and the discrepancy in the sex incidence increases with age. De Weekers' findings were somewhat similar; in the age group 1-10 years females constituted 56

TABLE III
Showing seasonal distribution of phlyctenulosis
Incidence of phlyctenulosis in monthly percentages of total

Author	Peyer	Werner	Hinreichs	Essen-Möller	Urbanek and Roschkott
Place	Graz	Helsingfors	Greifswald	Lund	Vienna
Years	1915-20	1901-26	1923-32	1909-33	1919-35
Total Number	2,813	3,405	1,257	2,614	c.9,630
Month					
January ...	11·3	7·8	13·2	8·3	9·5
February ...	8·2	7·1	12·3	7·0	8·2
March ...	9·7	9·1	15·0	9·7	9·7
April ...	10·3	10·6	14·3	9·3	9·4
May ...	10·7	10·6	10·5	9·7	9·7
June ...	8·3	9·2	4·8	8·6	8·0
July ...	8·0	10·1	4·0	9·5	7·8
August ...	7·2	8·2	3·8	9·9	8·2
September ...	6·0	6·7	6·5	8·0	7·3
October ...	6·6	7·9	7·0	6·7	7·5
November ...	6·1	6·3	5·6	6·7	7·6
December ...	6·9	6·4	2·8	6·4	7·0

per cent. of the total number of cases, 76 per cent. in the age group 11-16 years and 79 per cent. in the age group 17-45 years. In a series of 121 cases of phlyctenulosis seen in patients over 15 years of age, Cohen gives the sex ratio as 37 to 63 males to females. De Weekers held that there was an increase in incidence in women at the climacteric; this could not be confirmed by Essen-Möller.

(4) Seasonal variation.

An increase in the incidence of phlyctenulosis in spring has been noted by a number of observers (Wessely 1919, Schwarz 1937). April-June are given as the months of maximum incidence by Kassner (1921), March-May by Savin and Preston (1925), January-April by Harman (1925) and Rolet, April by Carvill (1929), whilst Kinsey (1932) speaks of July-September as the months with the lowest incidence. In Italy the highest frequency is reached in January-March (Giallombardo, 1924). Only a small number of detailed studies are available. (A study by Schwarz [1937] was inaccessible.) These are summarised in Table III.

The month of maximum distribution varies with these different centres, the highest being January for Graz, April-May for Helsingfors, March for Greifswald, and March-May for Vienna. At Lund the highest month is August (9.9 per cent.), but the incidence for March-July is also high (9.7, 9.3, 9.7, 8.6 and 9.5 per cent. for each of the five months respectively). In all these centres a low level is reached towards the end of the calendar year.

(B) *Aetiological Considerations*

(1) The problem of the "pseudo-phlycten" of tropical countries.

Phlyctenulosis in tropical countries appears to have clinical and possibly also histological features that differ from those seen in Europe and the United States. In India, Herbert noted in 1898 that more than a third of a hundred cases observed occurred in patients over 20 years of age. In Japan, Kuboki (1924) found that the affection is predominantly seen in adults; Yamaguchi (1937) gives the peak age as 16-20 years; in the tropical parts of the country phlyctenulae which are often observed there as a complication of catarrhal conjunctivitis, appear to be smaller than those seen in the more temperate regions of Japan (Kyo-Yoh, 1936). In Egypt both the age distribution and the course differ from those seen in Europe, the affection being evanescent and falling mainly on adults (Attiah, 1935). In Shanghai, too, the affection falls heavily on adults, though it is also seen frequently in children (Wang, 1934; Kwan, 1938). In Dutch East India there also appears to be an adult preponderance (Boen-Lian, 1930). The

data for Shanghai show a considerably greater incidence on males; in one series (Wang) there were 1,180 males and 654 females, in another (Kwan) there were 288 males and 197 females. The possibility that this discrepancy is artificial, arising from the fact that Chinese women do not readily seek advice, has been suggested (Wang). There is, however, some histological evidence that the tropical phlycten tends to have an epithelioid structure (Boen-Lian, Wang), though this is disputed (Bakker, Pilon). Moreover, there does not appear to be any seasonal variation in the incidence of phlyctenulosis in Shanghai. The possibility that the "pseudo-phlycten" seen in India is a misdiagnosis for conjunctivitis ulcerosa (Straub) and conjunctivitis pustulosa (Fuchs) is suggested by Pilon.

(2) Nutritional deficiency.

Almost every possible fault in diet has been incriminated as the cause of phlyctenular ophthalmia, excess of starchy food (Ramsay, 1933) and various vitamin deficiencies (Löwenstein, 1925; Papagno, 1935; Foster, 1936) being particularly stressed. No valid evidence is available except for the suggestive finding by Fronimopoulos (1940) that the vitamin A concentration in the blood of phlycten patients is often—but not always—distinctly subnormal. This observer regards vitamin A deficiency as a precipitating factor in some cases. Such evidence as has been brought forward for intestinal intoxication (Columba, 1935; Papagno, 1935; and others) is based on the fallacious test of indicanuria. A deficiency in calcium has been suggested on the strength of therapeutic results from the administration of this metal (Cremer, 1929; Lazarescu and Damian, 1936).

The rather vague conceptions of exudative diathesis first suggested by Czerny in 1903 has repeatedly been brought forward in the literature (Schütz and Vidéky, 1908; Bracci-Torso, 1935) without any valid support. No substantial evidence for underweight or overweight was found by Burgin and Higgins (1938).

(3) Focal sepsis.

Enlarged and septic tonsils are regarded by some observers as causal factors. (Nelson, 1923; Eoche-Duval, 1934; Goulden, 1936; Magitot *et alia*, 1936; Sargnon, 1939.) Here too no controlled evidence is available.

(4) Pediculosis capitis.

An extensive but rather uncritical literature incriminates pediculosis capitis (Thierry, 1937, and many earlier observers). Whilst not altogether dismissing this hypothesis, Heinonen (1936) could not find any conclusive support for it in his own statistical material.

(5) Endocrine disturbances.

These too have been suggested as causal factors, largely because of therapeutic results (Pagani and Gennaro, 1929; Escolan, 1934).

(6) Tuberculosis.

A growing volume of elaborate evidence is available on the significance of tuberculosis as the cause of phlyctenular ophthalmia. In so far as the tubercle bacillus has not been found in phlyctenulae, and in that the implantation of the organism in the conjunctiva produces a tuberculous reaction and not a phlycten, the evidence is negative, but a mass of observations is available implicating tuberculous infection rather than tuberculous disease.

(1) Positive tuberculin reactions in phlyctenulosis.

Since the introduction of the von Pirquet test in 1907 and its subsequent modifications, a high percentage of positive tuberculin reactions has been consistently reported by a number of observers. Table IV sets out the results given. As the age of the patients is of paramount importance in assessing the significance of these tests, the findings reported in this table have been further analysed so as to cover only children under the age of 6. The results thus obtained are shown in Table V. It will be seen from Table IV, dealing with over 6,000 cases, that with the exception of the series reported by Burgin and Higgins (1938), the cases (? of pseudo-phlyctens) given by Boen-Lian (1930), the early series of Bruns (1912) and the small series of 27 cases reported by Edier (1931), no observer found an incidence of less than 70 per cent. positive reactions, whilst most give a higher percentage. These findings remain valid for the subseries of 960 cases of children under 6 years of age. Here the mean percentage is 78.3 and if the series of Burgin and Higgins who gave an incidence of 60 per cent. is excluded, the percentage of positive results ranges between 74 and 94—an incidence that is not only suggestive but statistically significant after due allowance is made for the variations in the comparable normal child population of the various centres to which these statistics refer.

(2) Radiological evidence of pulmonary tuberculosis in patients with phlyctenulosis.

The interpretation of radiographs of doubtful chest lesions is particularly subject to the personal factor of the interpreter. Reports concerning a series of phlyctenular cases are therefore

TABLE IV
Showing the Results of Tuberculin Tests in Cases of Phlyctenular Disease

Year	Author	Method	Ages	Total Number	Number of positive reactors	Percentage	Remarks
1907	Stock	v. Pirquet	1-33	23	20	87	—
1908	Derby	v. Pirquet	?	43	38	88	—
	Schutz and Vidéky	v. Pirquet	5-14	15	12	80	—
1909	Weekers	v. Pirquet	Under 15	56	49	87.5	—
	Leber	v. Pirquet	—	—	—	75-80	Incidental reference; no further details given
1910	D'Ayrenx	Mantoux	Under 15	143	128	89.6	—
	Bywater	v. Pirquet and Moro	3½-17	16	16	100	—
	Irgersheimer	v. Pirquet	Children	146	98	70	—
	Rosenhauch	Moro	Under 15	41	48	96	—
			15-24	9	20	100	—
	Stephenson and Jamieson	v. Pirquet	2-12	20	142	91	—
	Weekers	v. Pirquet	1-15	156	32	88.8	—
	Wilder	v. Pirquet	2-14	31	—	—	—
		v. Pirquet	15-21	5	—	—	—
1911	Bednarski	v. Pirquet	Up to 10	100	100	100	—
	Maggi	Calmette	?	110	108	98.2	—
		v. Pirquet	?	54	51	94.4	—
	Tivnen	v. Pirquet	1-56	50	46	92	—
1912	Bruns	v. Pirquet	Children	102	62	60.7	—
	Davis and Vaughan	v. Pirquet	1-47	40	28	70	—
	Pyfer	?	?	49	41	84	—
	Terrien and Goulfier	v. Pirquet	?	600	—	93.75	—
1913	Belensky-Raskin	v. Pirquet Moro	1-46	100	92	92	—
					86	86	—

TABLE IV—continued.

Year	Author	Method	Ages	Total Number	Number of positive reactors	Percentage	Remarks
1914	Curtin	—	—	—	—	80	Remark made in discussion. No further details given
1916	Schreiber	v. Pirquet	?	"About 200"	—	93	Remark made in discussion. No further details given
1917	Goldbach	v. Pirquet	1-30	39	32	82	—
1918	Gibson	v. Pirquet	Mainly under 14	92	90	97.8	—
	Hird	v. Pirquet	1-15	16	15	94.1	—
	Wood	v. Pirquet	Children	20	20	100	—
1919	Köllner and Filbry ...	v. Pirquet	Children	120	—	95	—
1920	Veeder and Hemplemann	v. Pirquet	Children	196	—	"Over 92"	—
1921	Peyrer	v. Pirquet	?	"Many"	"Almost all"	—	—
1924	Blair	v. Pirquet	1-14	305	—	88	—
1925	Savin and Preston ...	v. Pirquet	1-1	25	19	76	—
	Cosulchi	?	?	221	—	94.8	—
1926	Lupino	v. Pirquet	1-14	57	43	75.4	—
1927	Casparis	Mantoux	?	18? more	18	? 100	—
1929	Carville	v. Pirquet	1-14	234	168	71.7	—
	Lemoine	v. Pirquet	Children	8	8	100	—
1930	Boen-Lian	Mantoux	Mainly over 15	106	56	52.8	"? Pseudo-phlyctens"
	Kameke	Moro	School children	16	16	100	—
	Towbin and Rawic-Scerbo	Mantoux	10-45	30	30	100	—

TABLE IV—continued.

Year	Author	Method	Ages	Total Number	Number of positive reactors	Percentage	Remarks
1931	Edler Woringer	" Moro Cutti-reaction "	4-14 Children	27 67	17 57	63 85.1	— —
1932	Tejeda Kinsey Lasky	v. Pirquet Mantoux " Tuberculin test "	Children " average 10-12 " 2-15, majority under 10	100 131 15	86 98 14	86 74.8 93.3	— — —
1933	Pierret et alia	—	Children	24	23	95.8	—
1934	Goldstein and Wood Siwe... Cerchez Wang	Mantoux Mantoux Mantoux ?	1-12 1-13 ? ?	60 140 306 64	58 123 — 59	96.6 88 98 92	— — — ? Pseudo-phlyctens
1935	Columba Vannas	Mantoux v. Pirquet	? Army Conscripts	31 229	29 194	96.6 84.7	— 72.6 per cent. of 42,722 con- scripts examined gave a positive reaction
	Puscariu and Lazarescu...	?	?	314	270	86.0	—
1937	Pascheff	—	—	—	—	95.5	—
1938	Burgin and Higgins Chou	v. Pirquet and Mantoux ?	(a) 0-14 (b) ? ?	502 127 100	300 76 95	59.7 60 95	— — —
1939	Urbanek and Roschkott...	?	?	160	143	89.4	—
1940	Frominopoulos	?	?	41	41	100	—

Total over 9,150

TABLE V
Showing the Results of Tuberculin Tests in Phlyctenular Cases Under the Age of 6 (based on Table IV)

Year	Author	Method	Ages	Total Number	Number of positive reactors	Percentage	Remarks
1910	Irgersheimer Weekers	v. Pirquet v. Pirquet	Under 5 1-5	78 44	58 40	74.4 90.9	— —
1911	Tivnen	v. Pirquet	1-5	17	15	88.2	—
1912	Davis and Vaughan	v. Pirquet	1-5	19	15	78.9	—
1913	Belensky-Raskin	{ v. Pirquet Moro	Under 5	34	{ 29 27	85.3 79.4	— —
1918	Gibson	v. Pirquet	Up to 5	40	39	97.5	—
1924	Blair	v. Pirquet	1-2 3-4 5-6	41 86 56	31 70 42	76 81 75	— — —
1925	Savin and Preston	v. Pirquet	1-5	9	8	88.8	—
1929	Carvill	v. Pirquet	1-2 3-4 5-6	38 54 51	31 39 38	81 72 74	— — —
1934	Goldstein and Wood	Mantoux	0-2 2-6	8 35	7 34	87.5 97.0	— —
	Siwe	Mantoux	0-1 1-2 2-3 3-4 4-5	17 24 14 12 11	16 22 13 12 10	94.0	—
1938	Burgin and Higgins	v. Pirquet and Mantoux	0-1 1-2 2-3 3-4 4-5 5-6	35 72 47 38 44 36	23 43 30 15 24 21	65.7 59.7 63.8 39.4 54.5 58.3	10 13 17 20 21 20 } expected percentage

171

960 752
Lowest percentage 57.3; highest percentage 97.5; average percentage 78.3

to be treated with reserve unless accompanied by reports on a control series. With this reservation the following data are given :

In 1922 Weekers and Colmant reported on the radiological findings in 36 cases, and Römer in 50. The first series were given as all showing active tuberculosis, and the second as "practically all active." In 100 cases Stalder, in 1926, found 64 with active tuberculosis and only 6 were definitely negative. Carvill, in 1929, found activity in 48.5 per cent. of 350 cases, whilst Cremer, in 1931, in a series of 150 found evidence of tuberculosis in all cases, 31.8 per cent. showing fresh lung lesions and 68.2 per cent. inactive lesions. The most careful study comes from Siwe (1934, 1935), who records a high incidence in children under 4 and a decreasing incidence in the older children; in a series of 140 cases, active tuberculous lesions were found in 75 per cent. of the children under 4, in 50 per cent. in children aged 4 to 7, and in 26 per cent. in those aged 7 to 13.

The evidence presented by Burgin and Higgins (1938) shows a lower incidence of tuberculous infection, though from the data they present it is not clear whether clinical or radiological tuberculosis is considered. In 502 cases of phlyctenulosis they found 109 cases of "clinical tuberculosis," 94 of whom were cases of tuberculosis of the hilus, 11 of other glands, 2 of peritoneum (and meninges); dactylitis and epituberculosis were responsible for one case each. All these were cases of "primary" or "childhood" tuberculosis, "and, consequently, were not immediately serious. Only 3 patients were critically ill with tuberculosis."

Further data come from Columba (1935) who in a series of 31 cases, mostly adults of about 20 years of age, found radiological evidence in all cases, 7 showing inactive lesions and the remainder evidence of activity. Pascheff (1937) gives hilus changes in 91 per cent. of his cases. Urbanek and Roschkott (1939) in a series of 160 cases found that only 59 were negative both radiologically and clinically. In a series of 41 cases Fronimopoulos (1940) found radiological evidence of tuberculosis in 30 cases, 5 of which also showed clinical signs.

(3) Tuberculous lesions in tonsils and adenoids.

Two of the observers who have found tonsillectomy helpful in the treatment of phlyctenular ophthalmia have suggested that the operation acts by the removal of a sensitising tuberculous focus. Mann (1920) in reporting ten cases of phlyctenulosis favourably influenced by tonsillectomy and removal of adenoids notes that of four cases in which histological examination was carried out, the tonsils showed tuberculous lesions in one case, the adenoids in another and that in two remaining cases no tuberculosis could be found (no serial sections were made). Von Tóth (1930) reports favourably on the result of the operation in 88 cases; in four out of seven cases in which the tonsils were studied histologically,

tuberculous lesions were found. He stresses that better therapeutic results are to be expected for operations in cases of tonsillar inflammation than in simple hypertrophy. Tubercle bacilli in extirpated tonsils were observed by Goldbach (1917) six times in a series of 18 cases.

(4) Personal history of clinical tuberculosis.

Some observers (Goldenberg, 1917, 1930; Goulden, 1936) stress the absence of tuberculosis in patients with phlyctenular ophthalmia. Davis and Vaughan (1912) found none in a series of 40 cases, Savin and Preston (1935) one in 50 cases, and Harman (1925) 8 in a series of 242 cases. A considerably greater incidence is reported by a number of other observers, though the material is heterogeneous and often devoid of comparative value.

(a) Cohen (1909) in a series of 123 cases in adults found evidence of incipient pulmonary tuberculosis in 63.4 per cent. He regarded the phlycten as an initial stage of pulmonary tuberculosis.

(b) Rosenhauch (1910) observed clinical tuberculosis in 20 out of his 50 cases, the localisation being: chest, 13; bone, 6; and pleura, 1.

(c) Hird (1916) found tuberculosis in 23 out of 30 cases, the lesions including: lungs, 12 (including active and healed cases); lupus of face, 3; shoulder, wrist, hip and knee, 1 each.

(d) Goldbach (1917) in a series of 39 cases found pulmonary tuberculosis 7 times, tuberculosis of the wrist once, and of the hip once.

(e) Nowak (1922) reported that more than half of his group of 260 adults with phlyctenular ophthalmia had active lung tuberculosis.

(f) Stalder (1926) observed 47 cases of active pulmonary tuberculosis in his series of 100 examined radiologically.

(g) Whittington (1926), in the course of one year, noted 25 cases of phlyctenular ophthalmia in a hospital with 800 beds, two thirds of which were devoted to children with surgical tuberculosis (Queen Mary's Hospital, Carshalton); 22 of these 25 children had active tuberculous lesions, 14 being bone tuberculosis and 6 gland tuberculosis.

(h) Carvill (1929) records tuberculosis in 175 (48.5 per cent.) out of a series of 350 cases, with the following numerical distribution: lungs, 29; meninges, 2; spine, 5; hip, 1; heel, 1; skin, 1; cervical glands, 55; and peribronchial glands (shown radiologically), 79.

(i) Towbin and Ravic-Scerbo (1930) found active tuberculosis, sometimes mild, in 19 out of their 30 cases.

(k) Puscariu and Lazarescu (1935) give an incidence of 41.3 per cent. of tracheo-bronchial adenopathy, determined by auscultation, in a series of 684 cases. In 466 patients under the age of

20 years they found glandular tuberculosis in 220 cases, pulmonary affection in 13, bone tuberculosis in 7 and there were 4 cases each of skin and of joint tuberculosis.

(l) Siwe's (1935) group of 140 children included 8 cases of pleurisy, 6 of skin tuberculosis and 5 of brain or of meninges.

(m) Heinonen (1936) found bone, joint or pulmonary tuberculosis (not examined radiologically) in 22 of his 301 cases (7.3 per cent). In the 11,000 school children from which the phlycten group was extracted the corresponding percentage was 2.8. Cervical adenitis was present in 23.5 per cent. of the phlycten group against 10.1 per cent. in the control group.

(n) Rojas (1937) noted phlyctenulosis in 12 children treated for tuberculosis at a children's clinic.

(o) Urbanek and Roschkott (1939) in a series of 160 cases observed miliary tuberculosis twice and clinical (and radiological) tuberculosis of the lungs in 73 patients.

(p) Fronimopoulos (1940) similarly observed 5 cases of pulmonary tuberculosis in a series of 41.

A number of observers have reported the association of phlyctenular ophthalmia with erythema nodosum (Neumann, 1933; Nobécourt and Ducas, 1934; Jacquet *et al.*, 1935; and Garcia Montes and Silva, 1938). Grenet and Langlois (1934) describe the occurrence of phlyctenulosis in a child suffering from tuberculous ulceration of the skin and mucosa of the nose and pharynx. Römmelt (1936) observed phlyctenulae in a case of tuberculous conjunctivitis.

(5) Family history of tuberculosis.

Lack of uniformity in the standard employed as to what collateral branches are regarded as part of the family, renders comparative evaluation of the data of different authors difficult. Savin and Preston (1925), who found 24 deaths from tuberculosis and 9 cases of illness in the families of their 50 cases, did not consider that this represented an undue incidence as compared with the general population of a corresponding social status. Davis and Vaughan (1912) found tuberculosis in 17 per cent. of the members of the families of their 40 cases. Weekers (1910) reported a positive family history 88 times in 156 cases and Blair (1924) in 20 per cent. of 305 cases. Carvill (1929) found that 77 (22 per cent.) of his 350 cases had contact with tuberculosis patients (though 23 out of these 77 showed no evidence of personal tuberculosis). In 33 instances one parent had died from tuberculosis, in 2 instances both parents, and in 7 a sibling; active tuberculosis was present in 17 parents and 14 sibs. In 10 cases in which more than one member of a family was affected with phlyctenulosis, tuberculosis in the home was found in six instances. A family history of tuberculosis was noted by Burgin in 22 per cent. of their 502 cases. In

a small series of 20 cases Stephenson and Jamieson (1910) recorded a percentage of 75, and Cohen (1909) a percentage of 63 in 123 adults suffering from phlyctenulosis. Friedenwald and Robertson (quoted by Woods, 1933) found 20 instances of open tuberculosis in the social environment of 21 cases of phlyctenular ophthalmia.

(6) The after history of patients with phlyctenular ophthalmia.

On this aspect the literature is most sparse, and none too systematic. Irgersheimer and Prinz, in 1922, reported on 92 cases followed up for a period of 10 to 30 years: 12 cases (13 per cent.) were found to be tuberculous. Nassau and Zweig (1925) found 9 cases (14.3 per cent.) of tuberculosis among 63 patients followed up for 1 to 16 years. Carvill (1929) reports 3 (0.8 per cent.) deaths from tuberculosis in a series of 350 cases. Woringner (1931) reported 2 deaths, 1 from pulmonary tuberculosis and the other from tuberculous meningitis, amongst 29 cases; the remaining cases were doing well; patients with hilar gland infection examined after 2 years "showed with remarkable regularity well healed lesions."

A more extensive study by Ajo (1938) traces the after history of 449 cases seen at Helsinki during 1912-27. The ages of the patients ranged between 1 and 33 years. Information on 367 could be obtained: 55 (15 per cent.) had died, at an average period of 7.4 years after the onset of phlyctenular ophthalmia, death being due to tuberculosis in 35 (9.5 per cent.) and possibly in 39 (10.6 per cent.) patients. Statistically the total mortality (15 per cent.) in this group of 367 patients was only slightly higher than that obtaining in the normal population, but the mortality from tuberculosis was almost twice the normal rate. Clinical examination was possible in 89 patients who had been traced, and in 11 more recent data from hospital records were available. In this group of 100 cases, 39 showed evidence of tuberculosis, the distribution being: chest, 7; cervical adenitis, 9, including 6 in whom the condition was quiescent; bone, 1; lupus, 1; calcified hilar glands, 18; pleurisy, 2; visible interlobar streaks, 1. Ajo concludes that not only does phlyctenular ophthalmia fail to give immunity against the subsequent development of severe tuberculosis as Irgersheimer and Prinz (1921), Nassau and Zweig (1925), Connerth (1926) and Woringner (1931) suggested, but that it exercises an unfavourable effect, as shown by the high mortality rate in his series.

(7) Phlyctenulosis in the antecedents of patients with tuberculosis.

Nowak (1922) found that 15 (38.5 per cent.) out of 39 adults with tuberculosis showed evidence of previous phlyctenular ophthalmia. Kruse (1926) found 11 (13.6 per cent.) out of 80 children with open

pulmonary tuberculosis were suffering or had suffered from phlyctenulosis. In a series of 2,144 cases at a tuberculosis sanatorium, Irgersheimer and Prinz (1921) found the incidence of previous phlyctenular ophthalmia as 2.2 per cent. (47 cases).

(8) Phlyctenulosis in tuberculous infected children.

Interesting comparative data are given by Siwe as to the frequency of phlyctenulosis in Mantoux-negative and Mantoux-positive children. In a group of 3,065 Mantoux-negatives there were 8 cases showing phlyctenulosis, against 68 cases in 1,515 Mantoux-positives, the respective percentages being 0.26 and 4.5. Siwe further found that of 664 children treated for tuberculosis 44 (6.6 per cent.) had phlyctenulae, against 24 (2.8 per cent.) amongst 851 Mantoux-positive children treated for lesions other than tuberculosis.

(9) Phlyctenular ophthalmia precipitated by the ophthalmoreaction and by tuberculin treatment.

The application of the ophthalmoreaction test for tuberculosis introduced by Calmette and by Wolff-Eisner in 1907 led to a series of severe conjunctivitis and keratitis, clinically similar to phlyctenular ophthalmia. This similarity was noted by many observers (Hayashi 1909, Marfan 1928), and Weekers appears to have made this observation the starting point of his studies on the significance of tuberculosis in phlyctenular ophthalmia. Apart from the local effect of tuberculin on the eye, earlier observers had noted that phlyctenulae were apt to break out on treatment with subcutaneous injection of tuberculin, in the rather massive doses that were used towards the end of the last century (Schütz and Vidéky, 1908; Stargardt, 1916). The appearance of phlyctenulae after treatment with tuberculin was noted more recently by Irgersheimer and Prinz (1921), Köllner and Filbry (1919) and Wiese (1925), whilst in Römmelt's (1936) case of tuberculous conjunctivitis inducing phlyctenulae indicates the same tendency. In this connection Bickerton's (1936) observation of phlyctenulae appearing after the operative removal of caseating tuberculous cervical glands is of interest.

(10) Laboratory findings.

(a) Tubercle bacilli in bloodstream.—Positive findings are reported by Riehm (1931) and Urbanek and Roschkott (1939), the Loewenstein technique being employed, and the examinations being carried out by the originator of the technique. In Riehm's series 5 out of 9 children with fresh limbal phlyctens were found to have living bacilli in the bloodstream. In Urbanek's group the incidence was 5 out of 54. Urbanek also submitted 19 cases to

another investigator (Maresch) who found bacilli in 1 case out of 19.

(b) Tubercle bacilli in the phlycten.—No observer has recorded the presence of tubercle bacilli in the phlycten. Stargardt (1916) described the occurrence of Much granules in a phlycten, his observation being checked by Much. This finding of doubtful significance appears to be an isolated instance.

Bruckner's (1929) observations may have some bearing on this matter. Tubercle bacilli implanted into the conjunctiva of the rabbit and guinea pig undergo degenerative changes; after initial alterations in staining reactions they do not stain at all.

(c) Tubercle bacilli in the stomach.—Judging by the title of an inaccessible publication, Iancu *et al.* (1935) appear to have found the tubercle bacillus in the stomach washings of a child with phlyctenular ophthalmia.

(d) Sedimentation rate.—The evidence on the sedimentation rate in phlyctenular ophthalmia is not extensive and rather contradictory. Franceschetti and Guggenheim (1929) found a definitely raised rate in only 6 out of 58 cases of "scrophulous eye conditions"; in 8 cases the rate was slightly above normal. They regarded such increased rates as due to an associated active tuberculosis of other organs. Schmelzer (1930) in 50 cases of "scrophulous" disease of the eye, found a definitely raised rate in 9 and a slightly raised rate in another 9 patients, and noted that with clinical healing of the eye condition the raised sedimentation rate returned to normal. A clear prognostic value was attached to a raised rate by Parkovits-Bugarsky (1930) who in 56 cases of phlyctenular ophthalmia found only 6 with normal rates; in 22 instances the rate was slightly above normal and in 28 it was definitely increased; the raised rates were not to be explained by any associated general condition but reflected the activity of the affection in the eye—the rate becoming normal with subsidence of the affection, and when it remained high, recurrences were to be expected. Higachi (1929), too, found a raised rate in phlyctenular ophthalmia and a return to normal on the subsidence of symptoms. Fontana (1933) attaches importance to the underlying tuberculous infection as the responsible factor for a raised rate: in 14 of his 30 cases the rate was raised and there was evidence of tuberculosis, whilst in the remaining 16 the rate was normal and signs of tuberculosis were absent.

(C) *Experimental Investigations*

Just as the search for tubercle bacilli in the phlycten has proved vain, so attempts to produce tuberculous lesions by inoculation with the phlycten material have been fruitless. At the beginning

of the century both Leber (1901) and Müller (1901) failed to obtain tubercles on the iris of rabbits' eyes in the anterior chamber of which phlycten material had been introduced (though one of Müller's 20 experimental animals did develop a transient nodule on the iris and this particular animal died later of miliary tuberculosis). Wessely (1919) failed to obtain any tuberculous changes in the conjunctiva of apes into which he had repeatedly implanted phlycten material, and this in spite of the great susceptibility of monkeys to minimal quantities of tuberculous material. All this evidence suggests that the phlycten is not only histologically but also biologically sterile.

Rather more successful were experiments with the tubercle bacillus itself. Satisfied that the phlycten is not produced by the virulent or living tubercle bacillus, Leber (1901) attempted to obtain phlyctenulae by implanting into the cornea tubercle bacilli sterilised by heat. The resulting corneal reaction was essentially tuberculous; giant cells were present and, after 8 weeks, bacilli that stained could be recovered from the lesion. Bruns (1904) had rather similar results by using an emulsion of tubercle bacilli. He did obtain lesions clinically suggestive of phlyctenulae (but histologically different) by the injection of the emulsion into the jugular vein of the rabbit. The "phlyctenulae" approached a tubercle in histological structure. Schieck's observation (quoted by Stargardt, 1916) that phlyctenulae can be produced by the injection of living tubercle bacilli into the carotid artery, does not appear to have been substantiated. (Schieck, 1932, b.)

Following the introduction of the Calmette-Wolf-Eisner ophthalmic-reaction, the paramount significance of sensitisation came to be appreciated. Weekers (1910) and Rosenhauch (1910) obtained phlyctenulae of the histological structure seen in man by the use of two different methods both involving the previous tuberculous sensitisation of rabbits by infection with bovine tuberculosis. Following on tuberculous sensitisation, the first observer instilled tuberculin into the conjunctal sac and the second implanted staphylococcus aureus using either the living or dead organism. Weekers' procedure is of course an experimental counterpart of the Calmette reaction and has been repeatedly confirmed (Rubert, 1912; Stargardt, 1916; Gibson, 1918; Kuboki, 1924; Kuniya, 1935; and others), whilst it is generally agreed that Rosenhauch's procedure, though valid, is less certain in effect (Rubert; Funaishi, 1923; Polev and Sawalsky-Fissan, 1925; Kuniya, 1935).

That tuberculous sensitisation was not an essential condition was shown by a series of other observations. Still using tuberculin as the local exciting agent, it was seen that animals could be sensitised by diverse agents. Guillery (1921) found proteolytic ferments (ferments of *B. prodigiosus* and *B. subtilis*; trypsin, etc.)

effective, whilst Loddoni (1930) obtained results with sensitisation by horse serum and Kuniya by sensitisation with staphylococci.

In further work neither tuberculous sensitisation nor tuberculin as the local exciting factor played any part. Sensitisation was induced by organisms like staphylococci (Funaishi, 1923), biological products like horse-serum (Riehm, 1928), chemicals like tyramine, cocaine (Funaishi) or calcium caseinate or a milk ferment, *Moya Bulgarea* (Morelli, 1924); once the animal was sensitised phlyctenulae could be excited by the instillation of the specific sensitising agent into the conjunctival sac. Yet the specificity of these phlycten-inducing reactions does not appear to be absolute, for staphylococci will induce phlyctenulae in the tubercle-sensitised rabbit (Rosenhauch's procedure), tuberculin will act likewise in animals sensitised to a variety of substances, and staphylococci act effectively in the rabbit sensitised to horse-serum (Riehm, 1928).

An elaborate series of experiments by Riehm (1928-32) suggests that the phlycten is a non-specific local anaphylactic reaction that can be induced by a variety of agents in various ways. Phlyctenulae can be induced in a specific manner by the use of horse-serum for sensitisation and as the local exciting agent; in a non-specific manner by sensitisation with horse-serum and staphylococci as the local agent; in an anaphylactic manner as when phlyctenulae are induced specifically by horse-serum and made to recur after subsidence by injecting the serum into the bloodstream; in the manner of selective sensitisation of the conjunctiva, as by inducing phlyctenulae in both eyes on the intravenous injection of horse-serum into a rabbit first sensitised locally by instillation of horse-serum in one eye. The mechanism underlying this anaphylactic reaction has been discussed by Mazzolo (1929), Iga (1930) and v. Szily (1930). A toxic effect on the capillaries is suggested.

The possibility of local desensitisation as a therapeutic measure has been indicated by Polev and Sawalsky-Fissan. These observers found that the development of phlyctenulae by the Rosenhauch procedure could be checked by prior treatment of the conjunctiva with a "staphylococcus antivirus," the preparation of which they described.

That carbohydrates may play a part in the production of phlyctenulae is suggested by the recent work of Katsnelson, Kachan and Yufa (1939), who obtained phlyctenulae in tuberculous-sensitised rabbits on the introduction of sodium lactate into the stomach. Furthermore they observed transient conjunctival reactions on the instillation of tuberculin into the conjunctival sacs of healthy, non-sensitised animals in whom a hyperlactaemia had been induced.

(To be concluded)