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**SUPERFICIAL PUNCTATE KERATITIS\***

A record of an epidemic of superficial punctate keratitis which appeared in Madras about May, 1928, and continued during the year that followed, embodying observations relating to the clinical appearances, biomicroscopy, epidemiology, aetiology and histopathology, of the disease, based on the investigation of over 900 cases

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SUPERFICIAL punctate keratitis was described independently by Adler, v. Carion, v. Reuss, and Fuchs, in 1889, and in its more usual aspects, it has been recognised clinically since that time.

It is represented in published accounts as an affection of the cornea and conjunctiva with an acute onset, attacking one, or less frequently both eyes, and characterised by the appearance of discrete opacities of the superficial layers of the cornea. These vary in size and number from a multitude of fine grey points only visible with a loupe to isolated spots easily seen with the naked eye. The epithelium at the affected points is commonly smooth, but may be raised; staining is variable, and actual vesiculation uncommon. The onset is like that of a mild conjunctivitis, and may be associated with catarrhal conditions of the respiratory tract, the

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corneal lesions appearing from a few days to a few weeks later. After a short time the eye becomes quiet and the opacities tend to disappear, but they may persist for upwards of a year or more, and exacerbations may occur. The vision is rarely interfered with to any great extent. The affection is not associated with iritis, but hypotonus may occur. It is most common amongst young adults, and recurrences are not observed.

A perusal of different records gives one the impression that the clinical features of the disease are liable to extensive variations and in its less characteristic manifestations it has sometimes, no doubt, found a place amongst the numerous descriptions of corneal affections of doubtful nature, in which isolated observations on morphological appearances are so confusing, in the absence of a knowledge of their cause. It is hardly to be expected that a composite picture of such an affection in all its manifestations should be available at present, as hitherto there has been no aetiological criterion to help in the diagnosis. That the disease might assume protean form was appreciated by many observers; Fuchs considered that superficial punctate keratitis and keratitis disciformis were probably of the same nature and were due to an unrecognisable organism. He also considered that there was a resemblance between herpes febrilis corneae and superficial punctate keratitis.

In 1911 Verhoeff made a detailed histopathological study of an eye affected by this disease (*Trans. Amer. Ophthal. Soc.*, Vol. XII, 1911). He regarded it as a neuropathic affection and considered keratitis disciformis to be of a similar nature. His paper constitutes a concise exposition of our knowledge of the condition up to that time, and forms a stage from which the present observations may well continue, as definite progress regarding the pathology or aetiology of the disease does not appear to have been made since. It was not very long, however, till Grüter identified herpes corneae febrilis with other forms of herpes simplex, and showed it to be due to a filter passing virus transmissible to animals. Since then Loewenstein, Lipschutz, Goodpasture, Levaditi, and numerous others have carried out investigations into the aetiology of these conditions, and their work constitutes a most important chapter in the progress of our knowledge of the so-called virus diseases. It is impossible for me to refer to the many authors who have contributed to these investigations nor, with few exceptions, will any attempt be made in this paper to quote references to the literature, since the necessary library facilities are not at my disposal. Those who are interested in the subject, and have facilities, may trace all the literature from the papers or authors quoted. It has now been established that herpes febrilis corneae (herpes simplex, dendritic ulcer), herpes labialis, herpes facialis

and herpes genitalis, are clinical manifestations of a condition due to a filter passing virus transmissible to animals, and capable of producing encephalitis in rabbits. Superficial punctate keratitis was, however, not generally looked upon as a member of the ultra-microscopic group, although, with the progress of knowledge in this field, the idea no doubt suggested itself to interested observers and actually may have been published without my knowledge. The herpetic affections of the cornea, which took on a new interest on account of this relation with the filter passing viruses, fell into two groups, herpes zoster ophthalmicus, and herpes corneae febrilis. They were clinically distinct, but had points in common. They showed relations with other conditions affecting the region of distribution of the fifth nerve. Paton, in his article in *THE BRITISH JOURNAL OF OPHTHALMOLOGY*, June, 1926, sums up the position as regards this group of affections up to that time. Whether these two conditions are different clinical manifestations of invasion by the same virus is a moot point, but until experimental evidence in support of this hypothesis is very much stronger, one must give due weight to the differences which exist in the clinical pictures. Up to the present the determination of the specificity of a filterable virus is a very difficult matter, and before different clinical syndromes can be regarded as having the same aetiology, the production of reliable experimental evidence is necessary, for example, the fixation of rabies virus in passage rabbits, or the establishment of protection in distemper.

In the present article, I attempt to give an account of an epidemic form of keratitis in which, with the help of my hospital staff and some members of the laboratory of the King Institute of Preventive Medicine, Guindy, a fairly extensive investigation was conducted. It will perhaps be acknowledged that clinically, the disease presented resembles the superficial punctate keratitis of ophthalmic literature rather than any other well-known corneal affection. The occurrence of large numbers of cases in a comparatively short time afforded an opportunity of observing wide variations in clinical appearances, which presumably, were due to the same causative agent. The composite picture thus afforded, embraced not only different types of superficial punctate keratitis as referred to in standard works, but also such forms as described by Herbert (*Ophthalm. Rev.*, Vol. XX, 1901) and Kirkpatrick (*Brit. J. of Ophthalm.*, Vol. IV, 1920), the keratitis epithelialis punctata of Koeppe and keratitis disciformis of Fuchs. There was no real resemblance to herpes zoster ophthalmicus or herpes febrilis corneae, and although there is sufficient evidence to place the various manifestations of superficial punctate keratitis along with these diseases amongst the neurotropic ectodermoses of Levaditi, the occurrence of a distinctive group of clinical and pathological

changes constituting a third herpetic syndrome, is strongly in favour of the hypothesis that the causative virus in such cases is different, even if it is of the same type.

### Clinical and Epidemiological Observations

Since Kirkpatrick described a variety of keratitis from this clinic in 1920, we have regularly, year by year, recognised and tabulated such cases. He regarded it as occurring in epidemic form in 1918-19 and recognised affinities, in some of its phases, with superficial punctate keratitis. He did not find an association with other diseases, although he remarked on the great influenza epidemic which prevailed about that time. There was not any increase in the incidence of herpetic affections.

The outstanding characters of this affection, which was locally called macular keratitis, were: the insidious appearance, without previous illness, of round grey spots in the superficial layers of a smooth, non-staining cornea, a tendency for these spots to thin out and become nebulous, showing a silk-like graining and to assume the appearance of complete or broken rings. The smaller spots were just visible to the naked eye, but large solitary forms might attain a diameter half that of the cornea. Kirkpatrick described three types of spots, small multiple, mixed large and small, the large spots being crenated or irregular, and solitary large spots. There was rarely any local discomfort or disability, unless the spots happened to be in the pupillary area. For the most part, one eye only was affected. We regarded this as an independent affection and saw a variable number of cases amongst about 20,000 out-patients annually.

1922	1923	1924	1925	1926	1927
28	18	33	109	67	14

Attempts made by Kirkpatrick and Cunningham, and subsequently by the latter worker and the author, to find an infective agent failed. Kirkpatrick considered the disease either parasitic or nutritional. The negative bacteriological findings were against the first hypothesis, the unilateral character against the second. He suggested a protozoal aetiology. He made the very important observation that there were numerous small granules in many of the epithelial cells, although, till now, the significance of this point was not appreciated. Since Kirkpatrick published his description,

I have had the opportunity of observing such types as he described with the corneal microscope. The smaller solid maculae appeared to be situated close below Bowman's membrane, and were not necessarily associated with any other change. The larger foci, on the other hand, approaching the disciform type, showed changes affecting the whole thickness of the cornea. The posterior surface of the cornea bulged into the anterior chamber. There were foldings of Descemet's membrane and deposits on the endothelium, for the most part pigmented in nature. I did not publish my observations on this condition, and it is unnecessary to go into further details here, because the changes which are hereafter described in superficial punctate keratitis, as seen by the corneal microscope, embrace those varieties which were formerly considered as an independent disease. In the year 1928, up to the end of May, there had been comparatively few cases of macular keratitis recorded in hospital; at the end of this month several private patients showed what appeared to be a similar condition, though it was atypical, inasmuch as there was a history of greater irritation. It was soon realised that we were dealing with a different type of affection, and as certain older cases subsequently gave a history of onset in May, the commencement of the epidemic may be placed about this month. During the next two months there was a great increase in the number of cases of keratitis in hospital: most of these were superficial punctate keratitis, but as we had not instituted a systematic verification by the corneal microscope, the figures for these months can only be taken as approximations and have not been included under the head of superficial punctate keratitis in the usual returns of the hospital for 1928. Only 801 cases are so included, but all of these were verified by the corneal microscope when necessary, as they occurred, from the month of August onwards. For 1929, the number of new cases up to the end of May was 122, giving a total of 923, to which figure reference will be made throughout this paper, unless otherwise stated.

*Simple clinical type.*—An early case, which may be taken as a typical clinical example of the simpler uncomplicated varieties of this affection, occurred in a member of our refraction room staff. Without any previous indisposition, a conjunctival hyperaemia made its appearance in the left eye. There was no lacrymation, or photophobia, except in strong light. The vision was not blurred, nor was there a conjunctival discharge. From the observer's point of view the chief feature was the unilateral hyperaemia. The patient had very little discomfort and went on with his work. The naked eye appearance of the cornea was apparently normal. At one place there was a little irregular elevation of the limbus; there was no staining. With the corneal microscope, the elevated portion

of the limbus showed oedema and engorgement of the vessels, and a few slightly more raised points. Close by, on the cornea, there were a few small rounded opacities. Gradually the number of opacities increased and in a couple of days they had invaded the pupillary area, where they were just visible to the naked eye. The vision, then, for the first time became blurred. The older spots tended to thin out as newer ones advanced on the cornea. The patient wore a shade over the eye at first, later a wet pad; dionine was given. In a month there was nothing abnormal to be seen with the corneal microscope.

This case was considered sufficiently like the superficial punctate keratitis of standard works to justify us in regarding it as such, although the absence of previous indisposition, the presence of limbal elevations, and uneventful progress to a speedy recovery, were noteworthy. The later stages, when the puncta became thinned out and nebulous, suggested macular keratitis, while the limbal elevations suggested the appearance described by Herbert in the Bombay epidemic.

With the observation of large numbers of cases it became clear that there were enormous variations in the clinical course of the disease, but certain features were frequent and prominent, and served as guides to the nature of the affection, even without recourse to the corneal microscope. The affection of the eye appeared without an antecedent febrile or catarrhal disturbance. The onset was suggestive of a mild catarrhal conjunctivitis in the great majority of cases. In practically every case, at least a history could be obtained of a slight change in colour of the affected eye. Sometimes this hyperaemia of the conjunctiva was only discernible when the patient was viewed at arm's length in a good light. The patient sometimes was unaware of this redness and was informed of it by friends or observed it in the looking glass. It may well be imagined that such a mild state might easily be missed, and should corneal opacities be detected later, it might readily be assumed that they developed in a purely non-inflammatory manner, as we had supposed to be the case in many of the attacks of Kirkpatrick's macular keratitis. There was every variation from this mild hyperaemia, to the rarer cases, where there was oedema of the lids with chemosis, and an appearance which suggested the onset of a very acute infective conjunctivitis. Discomfort was inconspicuous in the milder attacks, but definite irritation, lacrymation and photophobia were present in the cases which showed a more marked degree of hyperaemia. Blurring of the vision, if present, was usually associated with opacities of the cornea in the pupillary area. There was no conjunctival discharge in uncomplicated cases. In the majority of patients the disease was unilateral, in six only were both eyes affected. There was not a single instance of associated

skin affection of a herpetic type, or of neuralgic pain in the area of distribution of the fifth nerve. It frequently happened that the limbal region was definitely swollen and oedematous and that it showed small elevations. In a few cases there were similar little elevations on the bulbar conjunctiva at a distance from the limbus, but they were not identified on the palpebral conjunctiva. These elevations appeared as small translucent papules in the light reflex, not as grey infiltrated points. The cornea showed a range of appearance from perfect smoothness and apparent transparency, even with the loupe, to invasion with large solitary disciform opacities. Sometimes the corneal transparency was due to the fact that the puncta had not yet developed; at other times, the opacities were so fine, that they could only be detected with the microscope. The longest interval observed between the onset of conjunctival hyperaemia and the appearance of spots was six days but it is quite possible that longer periods may elapse. On the other hand in some cases corneal opacities were seen on the first day of occurrence of conjunctival hyperaemia. There is thus a considerable variation in this respect. The most common condition was that in which numerous small rounded grey spots were visible either to the naked eye or the loupe. They did not always stain, nor was the epithelium always elevated. Out of 224 cases tested with fluorescine, 88 did not stain. In the majority of cases, some of the puncta at least, showed slight epithelial elevation. The number of spots varied enormously. Their characters will be dealt with further when describing the corneal microscope appearances. A lowering of the tension was not a noticeable feature, although, in some of the severe attacks, there was a slight fall. Apparent recrudescences were occasionally observed, but relapses were not noted. The duration of the corneal opacities varied from a week to over a year. In the great majority of cases they disappeared completely in less than two months, in some cases, they remained as faint rounded macular spots, occasionally annular, which were possibly of a permanent nature. The cases could not be followed up for a sufficient length of time to be definite on this point. In rare instances there were dense, white, cicatricial remains which obviously were permanent. Corneal sensibility was nearly always within normal limits. Even in patients who showed severe lesions, the corneal sensibility was preserved. In the vast majority of cases the iris appeared to be normal, the pupils being symmetrical, and the reflexes unchanged.

In two of the bilateral cases, both eyes were attacked at the same time, but evidently a variable period might elapse before the second eye was affected, as an interval of fifteen days was noted in one case. As increasing numbers of cases were observed, it became evident that there were transitional forms of corneal involvement,

ranging from fine granular or curdy superficial opacities of an evanescent character, to large solitary foci of the disciform type affecting the whole thickness of the cornea, and associated with a greater or lesser degree of anterior uveitis. The condition which we had been accustomed to designate macular keratitis (Kirkpatrick), was apparently the same affection in which the onset had been unobserved, or perhaps had been atypical, and only the larger and more persistent types of opacification were seen, and, for the most part, in their later quiescent stages. The small, round macular forms, described by Kirkpatrick, are similar to the later stages of the larger, rounded spots of superficial punctate keratitis visible to the naked eye; whilst the larger irregular forms, and solitary foci described by him, merge imperceptibly into what is usually regarded as keratitis disciformis. The larger foci are usually few in number, but one cannot infer that the condition originated with a small number of spots, from the fact that there happen to be three or four foci of 1-2 mm. in diameter, or because there is a solitary opacity of double this size. Such large foci take time to develop, and usually represent the later stages of a corneal condition in which, at first, there were more numerous smaller opacities, one or two of which had outgrown and outlived the others.

I was interested to see quite recently that Prof. Salzmann, of Graz, had traced this transition from superficial punctate keratitis to keratitis disciformis. I gather that his experiences with regard to transitional forms are very similar to ours in Madras with macular keratitis (Kirkpatrick). Prof. Salzmann observed 50 of these transitional forms in 16 years at Graz, but not a single typical case of superficial punctate keratitis, although the latter was practically epidemic in that part of the world in 1889. He regards them as different manifestations of the same disease, and considers that local and temporary differences occur which explain his observations. The local variations of the disease, he had not observed elsewhere, and the typical superficial punctate keratitis, so common in 1889, was not seen during the period of his observations.

Typical dendritic ulceration of the cornea was only seen thrice during the period which our observations cover. In one case, that of a British soldier, there was a history of malaria immediately preceding the onset. The second, in an Indian patient, was associated with herpes labialis, the third was definitely diagnosed, but the case sheet was lost. Presumably, if one could observe herpes febrilis corneae in epidemic form, considerable variation would be found in the nature of the corneal lesions, from simple vesicles to complicated dendritic types, some of which might resemble superficial punctate keratitis. The association with a



febrile disturbance, herpes febrilis of the skin, and the greater severity of symptoms would perhaps be outstanding features.

Only one other case of herpes labialis was observed during the time under consideration, and in that there were no corneal manifestations; herpes zoster ophthalmicus was noted five times.

**Treatment**

The average patient improved rapidly when the eye was kept covered with a moist boric pad under an eye shade, or bandage, and treated with dionine drops twice daily and atropine ointment at night. Other simple remedies such as hot fomentations were employed from time to time. In more protracted types, additional measures were resorted to, as mentioned in connection with special cases. Treatment, on the whole, was along general lines, and there is little worth noting except that in those cases in which the eye was kept covered from the beginning the improvement was more rapid than in the others. To be more accurate, the most prolonged lesions were seen in patients who had not kept the eye occluded from the commencement.

The prognosis may be regarded as very good; only three patients showed a definite decrease in visual acuity. There may, of course, have been others who did not report.

Apparently one attack gives protection for a time, as recurrences were not observed.

The disease was most common in males between 20 and 30 years of age.

The relative frequency at various ages, and in the two sexes, as well as the influence of season and climate, are shown in the following tables:—

TABLE I.  
Influence of age and sex.

Sex.	Age periods.							Total.
	1-9	10-19	20-29	30-39	40-49	50-59	60-69	
Males ... ..	3	113	413	167	55	16	5	772
Females ... ..	4	43	55	27	9	11	2	151
	7	156	468	194	64	27	7	923
Percentage ... ..	0.76	16.9	50.7	21.02	6.93	2.93	0.76	

Ratio of males to females attending hospital 1.8 to 1.

TABLE II.  
Climatic conditions 1928-1929.

Year and Month.	No. of cases of superficial punctate keratitis.	Mean monthly temperature	Humidity.	Rainfall in inches.
1928				
May ... ..		89·6	61%	0·03
June ... ..	40 (Approx.)	89·0	54%	0·24
July ... ..	50 "	86·0	62%	3·27
August... ..	121	83·9	69%	4·70
September ... ..	242	83·7	74%	8·18
October ... ..	146	81·2	82%	20·81
November ... ..	133	79·4	77%	6·64
December ... ..	160	77·0	76%	4·24
1929				
January ... ..	58	75·8	78%	1·87
February ... ..	26	77·1	75%	6·41
March ... ..	16	80·5	73%	0·01
April ... ..	10	84·1	74%	0·55
May ... ..	11	88·3	65%	0·75

Race did not seem to influence the incidence; Europeans, Hindus, Muhammadans, appeared to be equally liable to attack.

The method of spread was not obvious. One individual working in an office with half a dozen others might be attacked, whilst the remainder escaped. In an orphan school in my medical charge, where 200 Anglo-Indian boys and girls, of ages ranging from four to eighteen, live under dormitory conditions, there were less than a dozen attacks in 1928. The cases recorded from this school are not included in the 923.

Trauma is noted in the history of a large number of cases and it is quite likely that it favours an attack.

### Distribution

As regards the distribution outside the city very little information was forthcoming. The disease was known to be occurring simultaneously on the west coast, in Bombay, and over the intervening Mysore plateau. It was not in evidence in parts of Hyderabad, the north of the Madras presidency, in Calcutta or Lahore. This information is derived from ophthalmologists who had seen the disease in Madras, and subsequently communicated with me. One may consider that the disease was making its appearance all over the south of the Peninsula with comparatively greater frequency than usual, but the data which are available are insufficient to allow of any definite opinion being expressed on this point.

### Superficial Punctate Keratitis as an Epidemic Disease

There seems to be very little doubt that we were dealing with superficial punctate keratitis in epidemic form, similar to the epidemic observed by Herbert in Bombay in 1900. Evidently when the disease appears in epidemic form, it shows the more typical characters set out above. These resemble the original description of the disease in 1889, when there were so many cases that it may be regarded as having been epidemic. Kuffler, of Berlin, has observed cases of superficial punctate keratitis occurring in such numbers as to give him the impression that it was in epidemic form. That the typical superficial punctate keratitis may appear sporadically is well-known, and supported by numerous observations. My notes include a few quite distinct cases occurring at long intervals during the years preceding the present epidemic. That the disease probably occurs in atypical forms, both sporadically and endemically, is suggested by the experience of Salzmann referred to above, and by our local observations in connection with the variety of keratitis described as a separate disease by Kirkpatrick. There seems to be much in favour of the view that the latter disease is but a variety of superficial punctate keratitis, which occurs as an endemic disease, and forms a transition stage between acute epidemic evanescent keratitis, and solitary sporadic cases of keratitis disciformis.

### Corneal Microscope Observations

The commonest change was the appearance to a greater or lesser degree, of small grey points of opacity in the superficial layers of the cornea. There did not seem to be any characteristic distribution, nor were the points of invasion necessarily confined to the cornea. It was frequently observed that the limbus was definitely raised, and showed vascular engorgement and oedema, with small elevations not only at the limbus itself, but at a little distance from it on the bulbar conjunctiva. Such cases often showed but one or two corneal spots close to the most affected portion of the limbus. Later, an increase in the corneal deposits sometimes occurred, involving the whole of the corneal surface within a day or two. Cases in which the involvement of the limbus was conspicuous we came to speak of as of a "limbal type." A patient might be under observation for several days before the full crop of superficial opacities developed. I did not concern myself much with the limbal or conjunctival spots, except to verify their existence side by side with the characteristic corneal lesions and their definite occurrence in cases in which the limbal type preceded a corneal invasion. This point is of interest in view of the fact that Verhoeff held Herbert's cases to be different from true superficial punctate keratitis, inasmuch as they showed limbal and conjunctival invasion. One had

only to watch a number of early cases to see that there was a regular march in the appearance of superficial points of invasion from the conjunctiva to the limbus and over the limbus to the cornea. The corneal lesions varied enormously in size and number, so that there did not seem to be anything typical in either of these features. The number of points varied from one to hundreds; they might be disposed altogether towards the periphery, or in one quadrant, while in some cases they were practically confined to the centre of the cornea.

The various types of opacification may be treated in more detail. A common variety gave the impression of a very fine curd when seen with the corneal microscope. These were referred to as fine curdy deposits. They were ill-defined in outline and were so small as to be invisible to the naked eye. The individual points which ran together to form the more obvious curdy masses were not well demarcated even with the high power. Sometimes the opacifications were more uniform, like a fine opaque precipitate, rather than a curd. These changes were situated in the epithelium, and possibly extended under Bowman's membrane, but this could not be determined with certainty without first removing the epithelial layers. The fine curdy deposits frequently raised the epithelium, so that eminences were visible in the zone of the specular reflection. Staining of the spots was sometimes noted, but more often not, although there might be a diffuse fluorescence of the epithelium. In certain cases, these fine curdy deposits disappeared altogether in the course of ten days or so. The shortest period in which they were observed to fade away was one week.

Another type of opacity was of a discrete angular type, sharply marked, and densely opaque, and sometimes visible to the naked eye. Most commonly the spots were round, all sizes and densities being seen, from minute circumscribed points, like tiny colonies on a culture medium, to large fuzzy, steamy-looking discs, of 2 mm. or more in diameter. The large discs were presumed to have developed from smaller discs; in a few cases this process was actually observed. An interesting feature of some of these rounded types (and indeed of some of the angular types too), was the transition to annular forms. Even where they were of small size, spots were observed with a clearer centre, and dense periphery. In fact, in the smaller varieties, sometimes the ring was very sharply marked off from the clear centre and the surrounding cornea. Evidently these forms arose from a desquamation of the heaped-up centre of the minute papule, which constituted the initial lesion, and apparently were disposed chiefly in the epithelial layers. For the larger rounded opacities of 1 to 2 mm. in diameter such an explanation of the formation of ring forms does not hold. In these, as the condition progressed, the superficial focus became larger and less

defined, spread deeper and definitely involved the superficial substantia propria. Later the epithelial centre became clearer, as also did the opacity of the anterior layers of the substantia propria, so that the more opaque periphery stood out in contrast to the clearer centre. Sometimes there was a central point of greater opacity, with perhaps two alternating zones of greater or lesser opacity outside this. It did not seem to be essential that an individual spot should form a ring by peripheral extension; the process might take place by a clarification of the centre, the original outline of the solid round spot remaining the same. The larger spots did, however, tend to spread, and fade off into the surrounding cornea in an oedematous haze. Large isolated infiltrations, of 3 mm. or more in diameter, of the disciform type, involved the whole thickness of the cornea. The epithelium might remain perfectly smooth and level in such cases, and stain in a faint diffuse manner, but more usually it was granular or rough. Swelling of the substantia propria manifested itself in the optical section by extensive humping of the internal limiting surface. In such cases the formation of zones, or rings, of greater or lesser density, depended on the altered refraction of the deeper layers, rather than on any absorption of the central epithelial layers. It is hard to say what the actual opacification of the epithelium is due to, as the histopathological investigation did not show leucocytes in the epithelium, whilst epithelial sheets stripped from the cornea showed definite spots corresponding to similar spots just below Bowman's membrane. Presumably, the degenerative changes taking place in the epithelial cells are sufficient to determine the opacity of the smaller lesions. Loss of surface epithelium was not a feature of the disease either in the smaller foci, or in the larger, as it presumably is in herpes febrilis. Invasion of the substantia propria was more marked the larger the individual opacities became, till it reached a maximum in the big solitary disciform types. In medium sized opacities, it was possible to trace the ring formation from the earliest foci right up to the complete rings, broken rings, and mutton chop forms which were previously recognised in macular keratitis (Kirkpatrick): so that one was led to the conclusion that this condition was a later stage of superficial punctate keratitis in which, for some reason, early acute manifestations had been absent or missed. Evidence in support of this view was the fact that patients used to appear during the epidemic with typical macular keratitis, who, when questioned, admitted to having had a slight redness some time before. With our present experience of superficial punctate keratitis it is difficult to understand how we can have observed up to 100 cases in a year of this macular keratitis, without having seen the initial stages, but it is likely that when the disease is occurring epidemically, the early

conjunctival hyperaemia is a more prominent feature. It should also be noted that even during the epidemic we saw cases in which the patient's first complaint was the dimness of vision due to opacities in the pupillary area, and these were of the small superficial punctate type. The freedom from irritation, the appearance of rounded opacities, and ring forms, which were usually unilateral and visible to the naked eye, were regarded as characteristics of the condition described by Kirkpatrick, but some of the cases which we considered typical of that affection, were observed both before, and during the epidemic, with considerable irritation and photophobia. At the same time, cases were presenting themselves with mild conjunctival irritation which, without observation by the corneal microscope, would have passed unnoticed.

*The deeper changes.*—Even in the mildest types of the disease, in which the initial conjunctival hyperaemia was not noticed by the patient, and the opacities were small and sparse, causing but a slight dimness of vision, there was nearly always some trace of a fine deposit on the endothelium. From this condition, there were numbers of variations up to the most extensive folding of Descemet's membrane and large pigmented deposits. In the less severe cases there was usually a fine white, or pigmented deposit, with or without a few foldings of Descemet's membrane. In all cases of the disciform type there were extensive foldings, and, outside the thickened zone, there were marked pigmentary deposits. There were, however, exceptional types and in a few cases, in which there was very little irritation, and the corneal opacities were small, round, and discrete, there were round translucent yellow keratic precipitates, the deposits being larger than the superficial opacities and easily visible to the naked eye. The aqueous too, in some mild cases, showed variations from an increase in relucency to obvious floating particles, pigmented and non-pigmented. In one typical case, the pupillary border showed a Koeppé's nodule which gradually disappeared while the patient was under observation. Except in this isolated case, the iris did not show evidences of disturbance. The retrolental space and vitreous sometimes showed fine pigmentary deposits similar to those seen on Descemet's membrane, but there was never any gross change observable in the vitreous with the microscope, or with the ophthalmoscope, such as extensive dust-like opacities, although of course, it was impossible to examine the posterior segment in the more severe types.

The corneal nerves did not show any constant changes. In certain cases a nerve would appear to be unduly prominent as it approached an opacification, but after numerous observations I was unable to say that there was a demonstrable lesion.

The endothelium was sharply defined in a good many cases, and

bedewing was certainly not a common feature, although sometimes it was present. Craters varied considerably in numbers in different cases. In some patients it was surprising how rapidly the superficial opacities, fine flocculent endothelial deposits, and folding of Descemet's membrane disappeared. In one case, this picture, seen by me on the fourth day, disappeared on the eleventh, and the eye was apparently normal to the corneal microscope on the sixteenth. In a certain number of cases the epithelial opacities cleared up, but grey spots remained in the superficial layers of the substantia propria; as far as one can see, these may be permanent. It is difficult to gauge the frequency of such a result as it was impossible to follow up hospital cases for long periods. Probably the vast majority of the smaller types of opacities cleared up absolutely, but at least six cases were known in which spots persisted at the end of a year. In one bilateral case the distribution was such as to give an appearance resembling a Groenouw's nodular dystrophy. The cornea was somewhat insensitive, but of course there was not a familial element. This case impressed me with the fact that not only Groenouw's dystrophy, but also other conditions might be simulated by the various late appearances following a superficial punctate keratitis. Even in cases where opacities, larger or smaller, persisted for months, loss of substance with dense leucomatous scarring was not noted during the period of observation, except in the case of one of our own nurses. She had a severe attack with marked irritation, and a group of five round spots, the largest being 2 mm. in diameter in the pupillary area. The largest spot was raised, became exfoliated at the centre and formed a definite ulcer involving Bowman's membrane and the superficial layers of the substantia propria, eventually leaving a depressed area in the anterior surface of the cornea. It is more than likely that the late opacities of the small rounded type are situated just below Bowman's membrane, and that Bowman's membrane and the epithelium are by this time intact, the original infection penetrating it, as suggested by Verhoeff, through the nerve apertures. Relationships with the more vesicular lesions of herpes febrilis might be traced in cases in which the opaque epithelium becomes heaped up to form a papule, then a vesicle, which bursts by desquamation at its centre, and forms the superficial variety of ring, which at this stage shows staining. There were also one or two cases of true vesicle formation. If one considers that the essential lesion of a herpes febrilis corneae is a simple vesicle, then there must occur isolated cases where the differentiation is practically impossible. The most representative lesion of herpes febrilis is said to be the dendritic ulcer, and the nearest approach to this condition which was observed was where a linear group of punctate opacities with one or two lateral offshoots

desquamated in parts and stained in a very suggestive way; but it did not stain throughout, and the symptoms were not so severe. In one of our experimental cases, where superficial punctate keratitis was transmitted to a man, a similar running together of small grey foci produced a dendritic appearance, which seen by retro-illumination, was exceedingly like a healing dendritic ulcer. The deep changes which were seen in two true dendritic ulcers which occurred during the epidemic were no more severe than in superficial punctate keratitis and could not have been used to differentiate the condition.

### Summary

Just as in the case of the naked eye appearances the changes seen with the corneal microscope are diverse; numerous features were seen which might have been regarded as isolated phenomena and so described had they not been observed in their proper setting, and recognised as different manifestations of the same aetiological entity. In publications on corneal microscopy, there is a tendency to describe isolated phenomena as such, not necessarily in their proper environment, and this feature often tends to obscure the aetiology. The study of a disease like superficial punctate keratitis in epidemic form, in all its phases, shows that there may be the greatest diversity in the lesions of the cornea as regards their biomicroscopical appearances, although the initial and essential change, which is a localised opacification immediately on either side of Bowman's membrane, is probably common to all. Similarly Descemet's membrane and the endothelium may show a great variety of changes, and the evidences of abnormal constituents in the aqueous fluid, may vary in character from an increase in relucency to gross pigmented and unpigmented keratic precipitates.

### Individual Cases showing exceptional or interesting features

#### 1. Long duration, marked keratic precipitates, untreated during early stages.

Mr. H. P. W., aged 30 years, European, male, first seen on January 10, 1929, noticed that the left eye was red about a month before. He played cricket daily during the Christmas holidays. The eye did not trouble him, and he thought the redness was kept up by glare. The sight became slightly blurred, the corneal microscope showed small round superficial punctate spots, with larger deposits of amber, translucent keratic precipitates. He had to play in another important match and would not have a bandage or atropine. About January 15, treatment was started with atropine, dionine, and bandage. The precipitates remained unchanged up to March. During the latter half of March, he was given milk injections and a sub-conjunctival cyanide injection. The precipitates cleared within a fortnight and eye was apparently normal at the end of April.

#### 2. Bilateral case with centrally disposed rounded spots.

Mr. L., Indian, male, aged 30 years, had a bilateral attack in July. The spots in each eye were small and round and disposed about the centre of the cornea in



considerable numbers. He would not have atropine or a bandage, but wore dark glasses and used dionine. The spots gradually became more nebulous, but interfered with vision. He was given irrigations of normal saline, or saturated magnesium sulphate, and dionine drops, regularly for weeks. He also had sub-conjunctival injections of normal saline. I saw him from time to time in consultation. He still showed a number of round nebulous spots, visible to the naked eye, about the centre of each cornea, a year after his original attack. The corneal sensitivity was normal. He complained that his vision was blurred, but he still retained 6/8 in each eye. If seen for the first time at this stage the condition might readily be mistaken for some other affection.

3. Long duration, dense scar, loss of corneal substance, interference with vision.

Miss de L., Anglo-Indian, aged 31, had an attack in the left eye July, 1928. There were three large rounded opacities at the centre of the cornea. These were raised, and stained with fluorescein. One increased in size to about 2 mm. in diameter. There was definite loss of epithelium and considerable irritation with marked folding of Descemet's membrane. In spite of atropine, dionine and bandage, the condition improved very slowly, and nine months later, three annular opacities remained. The central one was laminated, showing several concentric rings. The optical section showed a definite depression of the anterior corneal surface. The larger spot was near the pupillary area and the vision dropped from 6/6 to 6/18, but was improved with a cylinder to 6/9.

4. Deep changes, well marked, Koeppe's nodule.

Major H., European, aged 40 years. A crop of very fine curdy opacities developed on the cornea two days after onset. These disappeared in a week under atropine, dionine, and bandage treatment, but a most marked folding of Descemet's membrane (the most extensive observed in the whole series), was seen on the tenth day. This had largely subsided two days later, and instead, there were a number of large, rounded, pale greyish deposits of keratic precipitates. The corneal surface was clear by this time except for three small opacifications near the limbus. A rounded, amber-coloured, semi-translucent nodule (Koeppe's nodule), appeared near the pupil border on the iris face, and disappeared again some weeks later while the eye was under frequent observation. The eye was apparently normal in 8 weeks, all traces of the anterior uveal disturbance having disappeared.

5. True vesicle formation.

Capt. H., Indian doctor, aged 41 years, noticed slight hyperaemia of right eye when looking in his mirror. Four days afterwards, it got irritable. On the 12th day, when first examined at Hospital, the cornea showed a number of superficial opacities, with a definite vesicle in the inferior nasal quadrant. There were a number of very fine white deposits on Descemet's membrane, and a single large lardaceous keratic precipitate. The endothelium was sharp and distinct. The eye appeared normal within a month.

*Note.*—Only two cases were seen with true vesicle formation, *i.e.*, bullae. The papillary elevations of epithelium, no doubt, in certain cases, were raised above a small fluid accumulation, in or just beneath the epithelium, and when the summit exfoliated, there was a staining central abraded area which subsequently appeared under the microscope as a paler centre bounded by a more opaque ring.

6. Transition to the macular keratitis type.

B., Anglo-Indian, aged 22, was seen at the hospital with typical superficial punctate keratitis of the right eye on December 9, 1928. On February 15, 1929, he reappeared, and was regarded in the out-patient department as a typical case of macular keratitis (Kirkpatrick), with a smooth cornea showing moderately large opacities of the annular type.

This class of case was not very uncommon.

7. Transition stage between macular and disciform types.

R. M., Indian, male, aged 26 years, had irritation of the right eye for 10 days. He showed a number of fairly large rounded spots on the lower three quarters of the

cornea. One of these showed a central zone somewhat clearer like an early ring-form. Below, there was a large dense spot of disciform type paler above, denser below, giving a crescentic effect. The epithelium overlying this disciform opacity was steamy. There were folds of Descemet's membrane and deposits of pigment on the endothelium.

8. Marked conjunctival disturbance, chemosis, simulating an early gonorrhoeal ophthalmia.

M., European, male, aged 24 years, was seen in consultation because of oedematous swelling of lids and chemosis of the conjunctiva of 12 hours' duration. Gonorrhoeal conjunctivitis was suspected by his doctor. There was very scanty discharge; smear preparations from the conjunctival epithelium did not show any organisms. Next morning the corneal microscope revealed fine rounded opacities all over the cornea. With atropine and bandage he was well in three weeks.

9. Disciform type.

In X., European, male, aged 40 years, the cornea showed a few small superficial dots, one much larger about 3 mm.; the eye was irritable. The surface epithelium over the larger disciform opacity was sodden and looked granular, and was very slightly raised; it stained in a diffuse way. The cornea was thickened and its posterior surface showed bulging in the optical section. The centre of the bulge could not be observed, but there were folds of Descemet's membrane near its periphery and pigmented deposits on the endothelium.

Several cases of this type were observed, one with a 5 mm. central disciform opacity, over which the epithelium, although sodden and rough, showed no breach of continuity. The smaller disciform types pass imperceptibly into the larger macular types, and they both affect the whole thickness of the cornea. Of these the smaller varieties tend to develop into annular forms.

10. Limbal type.

B., Indian, male, aged 19 years, had slight irritation of right eye for six days. There were few small grey spots on the cornea near the limbus above and below. Just outside the limbus the dilated vessels formed prominent radiating lines. Between the vessels and the cornea the limbus was raised into an elevated rim, bounding the cornea, which carried several more prominent translucent points, best appreciated in specular reflection. There were also raised points of the same nature some distance from the cornea on the bulbar conjunctiva.

11. Transition to macular keratitis and apparent connection of nerves with opacities.

G., Indian, male, aged 21 years, developed superficial keratitis, left eye, on October 28, 1928, with fine spots on cornea. He remained away 15 days and when next seen, he had a series of round spots, diffuse and nebulous, with perfectly smooth epithelium, of the smaller solid macular type, as contrasted with the larger ring, or disciform types. The deep surface of the cornea showed nothing abnormal. The nerves were easily seen, more opaque than usual, and in the case of one spot, a nerve filament was definitely traceable to the deep aspect of the spot. Corneal sensation was normal.

12. Transitional stage between superficial punctate and macular types, with marked changes in the aqueous.

S. P., Indian, male, aged 30 years, was seen on October 12, 1928, with a typical attack. There were numerous superficial spots, but three larger ones in upper and outer quadrant, staining faintly. Seen again on October 27, 1928. The eye was in the quiescent stage; the three spots seen before were now larger and of macular type; two were superficial. Behind one the whole cornea was thickened; the posterior surface of the optical section projected backwards. There were very fine deposits on the endothelium, and fine floaters in the aqueous. Immediately behind the larger opacity there were folds in Descemet's membrane and some pigmented deposits. This type was not uncommon and showed similar deep appearances to those observed with the corneal microscope in the varieties of macular keratitis with larger opacifications which had been seen in previous years.

### Laboratory Investigations

Cultures were made on a variety of ordinary media, including Sabouraud's, from fresh material collected from 36 different recent cases, and incubated aerobically and anaerobically. The bulk of the tubes showed either no growth or infrequent organisms, known or unknown. No constant organism could be isolated. Slide preparations from scrapings of corneal epithelium, taken at the same time, were fixed, wet and dry, and examined microscopically : in these no predominant organism could be detected . An encapsulated organism, such as that described by Herbert, was not seen. Full details of all the cultivation work need not be given, as it proved negative. It will be sufficient to state the general procedure.

Cases of under a week's duration were selected in the out-patient department. They were verified with the corneal microscope. Only those with numerous definite opacities were chosen. The selected eye was cocaineised and thoroughly irrigated with sterile saline solution for about two to three minutes, then cocaineised and irrigated a second time. Thereafter with a speculum in position the epithelium was gently rubbed off with a Bowman's needle. Large numbers of planted tubes and slides were handed over to Dr. Theodore, of the King Institute of Preventive Medicine, Guindy. Dr. Theodore and Col. King verified the negative findings both cultural and microscopical in so far as organisms known or new were concerned.

### Dark Ground Observations

Preparations from recent cases proved negative.

### Histopathological Observations

*Method of obtaining material.*—It was found that the epithelial layers slid off Bowman's membrane more readily when obtained as above, in those areas where the punctate deposits were most numerous. It is, however, possible with such treatment, and a little care, to peel large areas of the epithelium right off Bowman's membrane even in normal eyes. This loosening and detachment of the whole thickness of the epithelial layer is not an uncommon event in the preparation of cataract cases for operation, by the irrigation method. This fact was made use of in obtaining large whole thickness sheets of corneal epithelium, both of affected and normal eyes, for subsequent histopathological examination.

After preliminary irrigation, the epithelium was first detached from Bowman's membrane over a short linear area, and then gradually peeled off with the flat or shaft of the needle, aided by the irrigator. It is thus possible to obtain pieces considerably over five sq. mm. Such sheets when floated out in normal saline, and examined with the binocular dissecting microscope, showed the

punctate mottling well. In patients from whom they were removed, opacifications corresponding to those on the epithelial sheets were still observable in or just beneath Bowman's membrane.

No harm ever appeared to result from denudation of the corneal epithelium by this method, nor from the scraping of the epithelium in order to obtain material for making cultures and slides.

Whole thickness sheets of corneal epithelium obtained as above were taken from recent cases of superficial punctate keratitis, and also from normal eyes. Twelve specimens of the former were prepared, and eight of the latter. The epithelial sheets were floated out in normal saline and examined under the binocular microscope so as to verify the presence of punctate spots in the one case, and uniformity in the other. They were then spread on slides, and while maintained flat with a superimposed slide, held lightly in position with thin rubber bands, were fixed in Zenker's fluid or methyl alcohol. The Zenker specimens were washed, and after graded dehydration in the usual way, stored in 80 per cent. alcohol; the others were transferred with one change. In the hope of finding evidence of cell inclusions it was determined to adopt methods such as were applicable to the staining of Negri bodies in sections of brain, a technique with which I had previous experience. For both diseased and normal epithelial preparations the following stains were used :

Haematoxylin and eosin	} For Zenker fixed tissue.
Haematoxylin and van Gieson	
Mann's stain	
Leishman's stain	} For alcohol fixed tissues.
Giemsa's	

The whole thickness epithelial sheets were much more difficult to stain satisfactorily than sections. After a number of failures to get satisfactory detail with the Mann's stain, Leishman, or Giemsa, successful staining was obtained with haematoxylin and eosin. The tissue was treated with ferric alum as a mordant, then overstained with haematoxylin, and differentiated under the microscope. In this way, the process could be controlled and a satisfactory haematoxylin staining obtained.

Looked at with the naked eye when stained thus, or for that matter by other staining methods, the diseased epithelium showed paler areas representing the opacities. These areas, when examined under the low power showed a thinning out of the epithelial layers with actual complete absence in some cases. The epithelial cells at these sites had evidently lost their normal staining characteristics and took up the stain feebly and atypically. There appeared to be a breaking up of the cell body and fragmentation of the nucleus

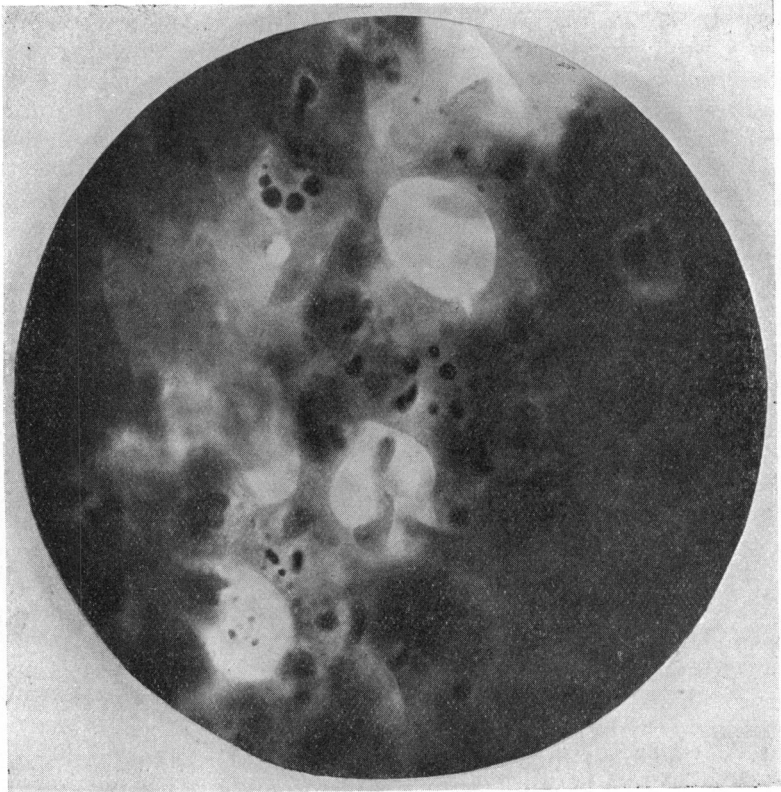
in many cases. There were obvious inclusion bodies rounded and sharply defined, large and small, both nuclear and cytoplasmic, more suggestive perhaps, morphologically, of Negri bodies, or the inclusions of variola, than of other varieties of cell inclusions. Some of these took up the red, others remained densely blue-black with the haematoxylin, still others showed a darker centre and pink periphery. I had previously observed similar staining effects when doing an experimental study of Negri bodies. The difference in staining reactions between the bodies in the same preparations could hardly be explained altogether by considering that the basic stain was removed from the periphery during differentiation, for, in the same field, one could see huge uniformly pink bodies and small blue-black bodies. In some cases, however, a grading off from the dense blue centre to a bright red periphery was very suggestive. As indicated, the bodies were of all sizes. Some were at least half the size of the cells, whilst others were minute, but definite. They were disposed in such numbers, and the cells had undergone such a considerable change at the points of invasion that it was difficult to trace the early stages. Outlying cells in some cases showed nuclear bodies, round and clear cut, without cytoplasmic bodies, and *vice versa*. It would serve no useful purpose here to go into the morphological variations, and there was insufficient material to attempt further methods of staining. It will be gathered that appearances differed very considerably from those seen in the rabbit's cornea in herpes febrilis, although perhaps too much stress should not be laid on differences in morphology, inasmuch as Negri bodies vary considerably in different animals. The distribution of the bodies may possibly be important as noted above. They are both nuclear and cytoplasmic, whereas in herpes febrilis they are said to be nuclear.

I was enabled through the kindness of Dr. Pandit and Mr. Hawley, of the King Institute of Preventive Medicine, to have microphotographs taken of some of the specimens, one of which is here reproduced.

There did not appear to be any leucocytes in the neighbourhood of the affected areas. Even had there been a slight leucocytic invasion superficial to Bowman's membrane, these cells might easily have been lost during the process of peeling off the epithelium, which also may be held responsible for excessive thinning out, or complete loss of the epithelial cells in some of the foci.

In addition to these inclusion bodies, another appearance was noted in five out of seven of the preparations of affected epithelium. In the superficial layers, both of the affected areas and elsewhere were larger or smaller patches of ill-defined, minute, ovoid or elongate particles. They were arranged, to a certain extent, in whorls. They lay on the superficial cells, and were traceable

between them. Near the thinned out areas, they were seen at a somewhat deeper level, but never in the cells. These may have been patches of invasion by small rod-shaped organisms. The concentric chain-like arrangement, which they sometimes formed,



Microphotograph of human corneal epithelium from a recent case of superficial punctate keratitis showing inclusion bodies (3rd day of disease).  
Haematoxylin and eosin.

suggested a growing colony. They were not sufficiently well-defined to photograph, nor were they seen at all in the Leishman or Giemsa preparations, but only in the haematoxylin preparations. I do not think they were artefacts, and Dr. Pandit concurred in this view. They may have been patches of some surface growth of an unfamiliar organism. They had not been seen in any of the slide preparations so that, if present, the ordinary staining methods did not reveal them. One naturally thought that they might be concerned with the earlier phases of the corneal invasion, which subsequently produced the cellular degeneration, represented by fragmentation and formation of inclusion bodies.

With nothing further to go on other than these appearances, one could only speculate as to the nature of the objects. They gave the impression of being more definite and larger than the extracellular particles which have been discussed in connection with virus diseases.

Cocci and bacilli were seen here and there throughout both the normal and diseased epithelial preparations in all of the specimens.

The histopathological investigation was curtailed by lack of time and material. Clinical observations, animal experiments, etc., took up so much of our available time that histopathological material was stored in order to be worked out later. This was limited in amount and the opportunity was not forthcoming to augment it later on. For this reason the further investigation of these extracellular particles was not possible.

#### **Experimental Production of the Disease in Man and Animals**

At first an attempt was made to transmit the disease by direct transfer of epithelial scrapings taken as described above from the corneae of recently affected patients to the healthy corneal and other tissues of man and animals. Later on suspensions of more finely divided scrapings were filtered before attempting to infect the experimental animals in the following manner.

The epithelial débris collected from recent cases was finely divided up in a watch glass with a drop of saline and used to implant on the cornea or other part of the experimental animal. When the cornea was utilised as a site for transplantation it was cocaineised and cleansed in the same way as the eye from which the material was taken. Corneae for implantation were usually traumatised, sometimes not. The trauma consisted in making one or more clean linear cuts with the sharp edge of a needle through the epithelium, impinging on, without actually cutting, Bowman's membrane. Epithelial pulp was transferred to the cornea thus prepared, and gently massaged in with the end of a smooth pipette, or rod. Sometimes this was repeated several times. When epithelial pulp was inoculated into the skin, the latter was prepared as for ordinary vaccination. Material from diseased corneae was usually obtained from several patients at the same sitting and mixed; sometimes, however, only one patient was available. We, fortunately, were able to secure a number of patients with suitable blind eyes, who allowed experimental inoculation and were agreeable to remain for a considerable time under observation. After the implantation, human eyes were covered with a wet pad and bandage till next day. Experimental eyes were subsequently subjected to routine examination with the corneal microscope. Cultures from the epithelial pulp were not made. Eyes from which

material was collected did not appear to be in any way adversely affected, and without exception they made an uneventful recovery with ordinary methods of treatment. When it was desired to filter the epithelial suspensions before transfer to the experimental animal, the technique was somewhat different. Several recently affected patients were chosen, three or more, and at one sitting material was collected as above, transferred to an agate mortar and broken up with sterile glass dust or sand, adding Locke's salt solution the while, to about 2-10 c.c. This suspension was then filtered through a Kitasato candle. A record of pressure was not kept in each case nor was a known organism mixed with the suspension to be filtered. The filters used allowed infective material to pass through under the conditions of the experiment, while under identical conditions, similar filters as tested at the King Institute, held back the pneumococcus and the B.influenzae. The filter candles used were Kitasato's porous tubes supplied by Messrs. Baird and Tatlock, London. This firm states that they are of German manufacture, the composition being about 80 per cent.  $Al_2O_3$ . The tubes are kilned at  $1,450^{\circ}C$ . and the porosity is about  $0.7 \mu$ . Three were new, *i.e.*, those used on November 28, 1928, December 11, 1928, and January 18, 1929. These small candles were selected on account of the scantiness of the volume of the suspension. The time and pressure, when available, is quoted for each experiment. In some cases cultures were made from the filtrate, and the filtrate examined for organisms under the microscope. The filtrate was used immediately for inoculation except in the last experiment.

Tables showing the details of the various animal experiments are appended. The positive findings may be referred to briefly here.

In experimental Group I, out of seven rabbits (five white, two black) inoculated on the cornea with unfiltered material, one developed superficial punctate keratitis. This was a black rabbit (No. 9). The eye showed no change for five days. On the sixth day, three discrete grey points appeared along the line of the needle scratch in the epithelium. They were slightly raised in the zone of specular reflection. Several other spots appeared after some days along the line, and an outlying point a short distance away. Some of these spots disappeared, but two of those along the line increased in size and became macular in type. The outlying spot became annular. The progress of the spots was very like that seen in the diseased human eye. At about the sixth week they resembled some of the types of macular keratitis very closely. There were, however, no pigmentary deposits or foldings of Descemet's membrane. Eventually on January 1, 1929, two months after inoculation, the three persistent spots had thinned out.



The left cornea of this animal was implanted with a large dose of unfiltered material with negative result.

In experimental group VI, out of seven cases in which unfiltered material was implanted on the human cornea three gave a positive result.

In the first case (woman No. 7) fine points appeared along the line of the scratch on the fourth day. By the ninth day the spots along the line were more numerous, and two outlying points some distance from the scratch were seen. These were rounded and slightly elevated and in one case a small dark centre developed (small ring form). About the twelfth day there was a very definite extension of the process and the upper part of the cornea became covered with spots. Some ring forms were observed. The opacities still continued and were diffuse till December 5, 1928, when the patient desired to leave the city.

In the second case, a man (No. 8), curdy superficial opacities, and a few discrete spots, appeared on the ninth day. Two days later there was a very definite crop all round the lower half of the vertical scratch in the cornea. Some of these spots ran together to form a larger opacity in a way which suggested the branching of a dendritic ulcer when seen by retro-illumination, but they did not stain. He was kept under observation for six weeks. Most of the smaller spots had gone by this time, but the larger group was still visible although thinning out. There were pigmented deposits on Descemet's membrane.

In the third case, that of a man (No. 10), a series of very definite spots appeared on the sixth day. Two linear scratches at right angles had been made in the epithelium. By the eleventh day there were numerous opacities all over the cornea, for the most part to the nasal side of the vertical scratch. Two larger spots developed in the superior and inferior nasal quadrants. They were of the solid macular type. The patient could only be kept under observation for a month.

Transmission from the second filtrate (Group VIII) gave two positive results. Only two cases were done, a man and a woman. In the case of the man (No. 14), the corneal changes started on the fourth day. Definite punctate spots were present on the sixth day. There were pigmented deposits on the endothelium. The crossed scratches on the cornea showed a number of grey foci and there were also discrete outlying spots. In the case of the woman (No. 15), the cornea was traumatised by two small cross cuts. She could not be examined with the corneal microscope till the thirty-first day on account of an attack of dysentery for which she was sent to another hospital. By that time there were a number of macular spots independent of the scratches.

The third filtrate was only used for implantation on a single eye,

that of a man (No. 16). Crossed scratches were made on the cornea. For some time, only points of opacity along the lines of the scratches were noted. On the thirteenth day there were outlying spots near the upper limb of the vertical line. After a month another isolated spot was seen. This was not considered to be a typical case.

The fourth filtrate (Group X) used for four human eyes and one black rabbit gave a definitely positive result on the cornea of a woman (No 9), and a doubtful result on a man (No. 17). In the case of the woman, her right cornea had previously failed to take with unfiltered material and after fourteen days her left cornea was traumatised with crossed scratches and filtered material was implanted. On the third day, several grey foci appeared on the scratch lines. On the eighth day there were outlying spots. Some of the opacities were vesicular. In the case of the man (No 17), a single macular spot developed on the third day, annular in type. It was more definite three days later, but no fresh spots had appeared. There were no foci along the scratch lines. The patient had to be transferred to another hospital and was lost sight of.

### Summary

The transfer of unfiltered epithelial suspension from a cornea affected by typical superficial punctate keratitis direct to the abraded cornea of a black rabbit reproduced the typical disease on the sixth day, as verified with the corneal microscope. It was only possible to obtain two black rabbits for this experiment. The second did not take the disease. In the case of seven white rabbits, the attempt was unsuccessful. Direct transfer of unfiltered material to the human cornea reproduced the disease in three out of seven. In one of these, the disease appeared on the third day. Under similar conditions the disease was not reproduced in the case of thirteen monkeys (*M. sinicus*). Attempts were made with unfiltered material to implant the disease on the skin of man, rabbits, calves, on the testicle of the rabbit, and on the brain by subdural inoculation in rabbits, but these were negative in so far as they went. Reproduction of the disease with filtered material implanted on the cornea was effected in the case of man in five cases out of eleven. Similar experiments failed in the case of seven white rabbits, three black rabbits and two monkeys. The earliest appearance of the corneal lesions was the third day. Apparently the disease is transmissible to man and black rabbits by corneal implantation. *M. sinicus* does not appear to be susceptible; possibly this is also the case with white rabbits. The animal experiments support the bacteriological and histopathological findings and the clinical features of the disease, and point to the aetiological agent being a specific filter-passing virus.

## EXPERIMENTAL TRANSMISSION WITH UNFILTERED EPITHELIAL PULP

Experiments are arranged in groups, according to the type of animal used and the site selected for implantation, not in the order in which epithelial scrapings were taken and used for individual transmissions.

### GROUP I.

#### *Corneal Implantation—Rabbits.*

Unfiltered material.

Animal.	No.	Date.	Site of Inoculation.	Nature of Inoculation.	Observation.	Result.
Rabbit, white	1	16/8/28	Cornea R	Trauma with needle	Corneal microscope for 3 wks.	Negative
			do. L.	Without trauma	do.	do.
Rabbit, white	2	do.	do. R.	Trauma with needle (single scratch)	do.	do.
			do. L.	Without trauma	do.	do.
Rabbit, black	9	30/10/28	do. R.	Trauma with needle (single scratch)	do. 2 months	Positive. Developed punctate keratitis on 6th day
Rabbit, white	10	do.	do. R	do.	do. 3 weeks	Negative
Rabbit, white	11	do.	do. R.	do.	do.	do.
Rabbit, white	12	do.	do. R.	do.	do.	do.
Rabbit, black	15	27/11/28	do. R.	Trauma with needle (crossed scratches)	do. 6 weeks	do.
Rabbit, black	9	18/1/29	do. L.	Linear trauma with needle	do. 1 month	do. R.E. of this rabbit had taken, see above

## GROUP II.

*Sub-dural Inoculation—Rabbits.*

Unfiltered material.

Animal.	No.	Date.	Site of Inoculation.	Nature of Inoculation.	Observation.	Result.
Rabbit, white	3	16/8/28	Sub-dural	About 0·25 c.c. inoculated subdurally through drill hole	Animal kept under observation for 3 weeks	Negative
Rabbit, white	4	do.	do.	do.	do.	do.

## GROUP III.

*Vaccination on skin—Man, calves, rabbits.*

Unfiltered material.

Animal.	No.	Date.	Site of Inoculation.	Nature of Inoculation.	Observation.	Result.
Rabbit, white	5	1/9/28	Skin, inner side of leg	Vaccination	Animal kept under observation for 3 weeks	Negative
Calf*	1	do.	Belly	do.	do.	do.
Calf*	2	do.	do.	do.	do.	do.
Man	1	do.	Forearm	do.	do. 2 weeks	do.
Man	2	20/10/28	do.	do.	do.	do.
Man	3	do.	do.	do.	do.	do.

\*Carried out by Mr. Theodore at the King Institute, Guindy, vaccine depot.

## GROUP IV.

*Intra-testicular injection—Rabbits.*

## Unfiltered material.

Animal.	No.	Date.	Site of Inoculation.	Nature of Inoculation.	Observation.	Result.
Rabbit, white	6	27/10/28	Testicle R.	Injected 0.25 c.c. epithelial suspension	Observed daily for 6 weeks	Negative
Rabbit, white	7	do.	do.	do.	do.	Testicle removed sixth day and testicular emulsion inoculated subdurally into rabbits Nos. 13 and 14
Rabbit, white	8	30/10/28	do.	do.	do.	Negative
Rabbit, white & brown	13	4/11/28	Sub-dural	Emulsion of testicle of rabbit No. 7 0.25 c.c. injected subdurally	Observed daily	On 17/11/28 developed vesicular eruption on back. Died 14/12/28. Brain removed and emulsified. Emulsion inoculated subdurally to rabbit No. 16
Rabbit, white	14	do.	do.	do.	do.	Negative
Rabbit, white	16	17/12/28	do.	Emulsion of No. 14 brain (kept in ice 3 days) 0.25 c.c. injected subdurally	Observed daily for 3 weeks	do.

## GROUP V.

*Corneal implantation—Monkeys (M. sinecus).*

## Unfiltered material.

Animal.	No.	Date.	Site of Inoculation.	Nature of Inoculation.	Observation.	Result.
Monkey (M. sinecus)	1	7/11/28	Cornea R.	Linear trauma with needle	Corneal microscope 1 month	Negative
Do.	2	do.	do.	do.	do.	do.
Do.	3	do.	do.	do.	Naked eye and loupe 1 month	do.
Do.	4	do.	do.	do.	do.	do.
Do.	5	do.	do.	do.	do.	do.
Do.	6	do.	do.	do.	do.	do.
Do.	7	do.	do.	do.	do.	do.
Do.	8	do.	do.	do.	do.	do.
Do.	9	do.	do.	do.	do.	do.
Do.	10	do.	do.	do.	do.	do.
Do.	11	do.	do.	do.	do.	do.
Do.	12	do.	do.	do.	do.	do.
Do.	13	do.	do.	do.	do.	do.

All the monkeys were supplied by the King Institute of Preventive Medicine, Guindy.

Nos. 1 and 2 were sufficiently tame to retain in hospital for daily corneal microscope observations.

The remainder were retained at the Institute.

**EXPERIMENTAL TRANSMISSION WITH FILTERED  
EPITHELIAL PULP.**

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Arranged in experimental groups in each of which the same filtered material was used.

GROUP VI.

*Corneal implantations—Human eye.*

Unfiltered material.

Animal.	No.	Date.	Site of Inoculation.	Nature of Inoculation.	Observation.	Result.
Man	4	8/11/28	Cornea	Linear trauma with needle (single scratch)	Corneal microscope daily, 1 month	Negative
Woman	5	do.	do.	do.	do.	do.
Woman	6	do.	do.	do.	do.	do.
Woman	7	15/11/28	do.	do.	do. 6 weeks	Positive 3rd day
Man	8	27/11/28	do.	do.	do.	Positive 9th day
Woman	9	28/11/28	do.	do.	do. 2 weeks	Negative*
Man	10	8/12/28	do.	do. (crossed scratches)	do. 4 weeks	Positive 6th day

\*Subsequently inoculated with filtered emulsion and gave a positive result.

## GROUP VII.

*First filtrate.*

Animal.	No.	Date.	Site of Inoculation.	Nature of Inoculation	Observation.	Result.
Rabbit, black	17	28/11/28	Cornea R.	Linear trauma	Corneal microscope 6 weeks	Negative
Rabbit, white	18	do.	do.	do.	do.	do.
Woman	11	do.	do.	do.	do.	do.
Rabbit	19	do.	Testicle	Injection	do. till 7th day	On the 7th day testicle removed and emulsified in sterile glycerine, kept on ice for 10 days and implanted on human corneae Nos. 12 and 13
Man	12	15/12/28	Cornea R.	Linear trauma	do. 4 weeks	Negative
Man	13	do.	do.	do.	do.	do.

New Kitasato filter candle used saturated with Locke's solution and autoclaved. The volume of the suspension made up from 3 cases was 10 c.c. Time of filtration 30 minutes. Pressure not recorded. Cultures from filtrate not made.

## GROUP VIII.

*Second filtrate.*

Animal.	No.	Date.	Site of Inoculation.	Nature of Inoculation.	Observation.	Result.
Man	14	1/12/28	Cornea R.	Linear trauma	Corneal microscope 1 month	Positive 4th day
Woman	15	do.	do.	do.	do.	Positive, day not noted, patient ill with dysentery. First seen on 31st day

Previously used filter employed. Saturated with saline and autoclaved. Volume of suspension from 4 cases 3 c.c. Time of filtration 45 minutes. Pressure not recorded. Cultures from filtrate not made.



## GROUP IX.

*Third filtrate.*

Animal.	No.	Date.	Site of Inoculation.	Nature of Inoculation.	Observation.	Result.
Man	16	4/12/48	Cornea R.	Linear trauma	Corneal microscope 1 month	Positive

Previously used filter employed.  
 Prepared as before.  
 Volume of suspension from 7 cases 4 c.c.  
 Time of filtration half-an-hour.  
 Cultures of filtrate not made.

## GROUP X.

*Fourth filtrate.*

Animal.	No.	Date.	Site of Inoculation.	Nature of Inoculation.	Observation	Result.
Woman	9	11-12-28	Cornea R.	Linear trauma	Corneal microscope 1 month	Positive 3rd day
Man	17	do.	do.	do.	do.	Positive (?) Only one annular spot observed 3rd day. Patient transferred to another hospital 6th day
Man	18	do.	do.	do.	do.	Negative
Man	19	do.	do.	do.	do.	do.
Rabbit, black	15	do.	Cornea L.	do.	do.	do. Had failed to infect this animal's R. E. with unfiltered material

New filter used.  
 Saturated with Locke's solution and autoclaved.  
 Volume of suspension from 5 cases 10 c.c.  
 Filtered in 20 minutes at a negative pressure of 25 cm.  
 Cultures from filtrate showed contamination as also did controls.

## GROUP XI.

*Fifth filtrate.*

Animal.	No.	Date.	Site of Inoculation.	Nature of Inoculation.	Observation.	Result.
Man	20	18/1/29	Cornea R	Linear trauma	Corneal microscope 1 month	Negative
Rabbit, white	20	do.	do.	do.	do.	do.
Rabbit	17	do.	do. L.	do.	do.	do.

New filter used.

Prepared as before.

Volume of suspension from 4 cases 10 c.c.

Filtered in 15 minutes at 20 cm.

Cultures from filtrate negative.

## GROUP XII.

*Sixth filtrate.*

Epithelial scrapings on different dates (March 16, 18, 20 22 and 25, 1929). Stored on ice at the King Institute and filtration carried out there.

Animal.	No.	Date.	Site of Inoculation.	Nature of Inoculation.	Observation.	Result.
Man	21	8/4/29	Cornea L.	Linear trauma	Corneal microscope 1 month	Negative
Woman	22	do.	do.	do.	do.	do.
Rabbit, black	21*	do.	do.	do.	do.	do.
Rabbit, black	22*	do.	do.	do.	do.	do.
Rabbit, black	23*	do.	do.	do.	do.	do.
Monkey	14	do.	do.	do.	do.	do.
Monkey	15	do.	do.	do.	do.	do.

\*Very young, bred by No. 15 of a white doe in the hospital laboratory, as it was found so difficult to obtain black rabbits.

New filter used.

Prepared as before.

Volume of suspension 1½ c.c.

Filtered in 10 minutes at 25 cm.

Cultures from filtrate negative.

The bulk of the work in connection with this investigation was carried out in the various departments of the hospital with the help and co-operation of the members of my staff. Dr. K. Koman Nayar (Assistant Superintendent), besides giving much other valuable assistance, took over the corneal microscope observations during my absences. Messrs. Venkatarangam Naidu, Narayanaswami Pillai, Narayanaswami Naidu, Narayana Iyer, and the late Dr. V. G. Muthayya, observed and made appropriate notes on the cases as they came under their departmental supervision. Mr. Narayanaswami Pillai, however, undertook the most laborious share in this combined effort, inasmuch as he was responsible for maintaining records of the individual cases, including the notes on biomicroscopical findings, selection of cases for experimental work, and all our hospital laboratory routine and animal work. Lt.-Col. H. H. King, I.M.S., Director of the King Institute of Preventive Medicine, Guindy, kindly gave his help and advice. He allowed Mr. Theodore of his staff to visit the hospital frequently and co-operate with us in connection with the laboratory investigations. In this way we were enabled to keep in touch with the King Institute, which is situated seven miles away. Col. King supplied some of the rabbits, all of the monkeys and also the culture media and apparatus in connection with the filtration experiments. Mr. Theodore carried out a large portion of the animal experiments in groups 3, 4, 5 and 12 and attended the hospital on numbers of occasions with all the necessary materials and apparatus to help in cultural and filtration work. Dr. Pandit, Assistant Director of the King Institute, Guindy, and Mr. Hawley of the Institute staff also lent their aid. To all these gentlemen my grateful acknowledgements are due.

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## TWO CASES OF SYMPATHETIC OPHTHALMITIS

BY

D. J. WOOD

CAPE TOWN

WITHIN the last year I have had two cases of sympathetic disease which, taken with the case described by me in this journal in May, 1927, form an interesting trio.

The 1927 case (R. W.), one of gross disease of the choroid and iris in the exciting eye, followed by a serious infection of the sympathising eye, was unusual in the complete recovery which the sympathising eye made, so that to-day it possesses  $\frac{6}{4}$  vision with scarcely a trace to tell the tale of what it had gone through.