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Serum and Vaccine Therapy in connection with Diseases of the Eye.

The Middlemore Prize Essay, British Medical Association, 1911.

BY

C. W. G. BRYAN, F.R.C.S.Eng.

Late Assistant in the Department for Therapeutic Inoculation, St. Mary's Hospital, and House Surgeon, Oxford Eye Hospital.

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SERUM AND VACCINE THERAPY IN CONNEXION WITH DISEASES OF THE EYE.

THE MIDDLEMORE PRIZE ESSAY, BRITISH MEDICAL ASSOCIATION, 1911.

BY C. W. G. BRYAN, F.R.C.S.ENG.,

LATE ASSISTANT IN THE DEPARTMENT FOR THERAPEUTIC INOCULATION, ST. MARY'S HOSPITAL; AND HOUSE-SURGEON, OXFORD EYE HOSPITAL.

I.

THE subject of serum and vaccine therapy in relation to diseases of the eye is one which has received a large amount of attention, and on which a great deal of work has been done during recent years.

The treatment of eye diseases by serums and vaccines differs from similar treatment of disease in any other part of the body owing to the anatomical peculiarities of the blood and lymph supply of this organ.

The cornea and vitreous have in the healthy condition no blood vessels, and are feebly nourished by lymph; the lymph circulation of the intrinsic parts of the eyeball is, however, not free, and this is exemplified by the rarity with which malignant growths of the interior of the eyeball give rise to secondary deposits in glands until the growth by direct spread has extended outside the sclerotic coat.

Again, in those parts of the eye where there is a supply of blood vessels, the distribution of the blood in these vessels is constantly varying owing to the unceasing movements of the eye as a whole, and of its various parts—the iris, ciliary body, etc. These movements are of importance when the eye is infected, as they cause the setting free of bacterial substances, toxins, etc., in the blood stream. This subject of auto-inoculation will be discussed later in connexion with vaccine therapy.

Immunity against disease due to infection may be acquired actively or passively. Vaccine therapy is concerned in the production of active immunity, serum therapy deals with the production of passive immunity.

VACCINE THERAPY.

Active immunity can be acquired in two ways—either by auto-inoculation by bacterial substances set free in the blood stream from some focus of disease, or by the methods of hetero-

inoculation—that is, by the absorption of vaccine, usually injected into the subcutaneous tissues. In disease of the eye auto-inoculation is an unsatisfactory method of producing immunity, owing to the limited blood and lymph flow in the eye, and to the fact that the size of the area of infection, as compared with the body as a whole, is small, and therefore great disturbance of this small area would be necessary to produce any marked auto-inoculation.

In using vaccines it is necessary as far as possible to prevent auto-inoculation by keeping the diseased part at rest, and this is a difficulty with which we have specially to contend in dealing with eye diseases. If auto-inoculation takes place at the time that treatment by hetero-inoculation is being carried out, substances of unknown amount may be set free in the blood stream at

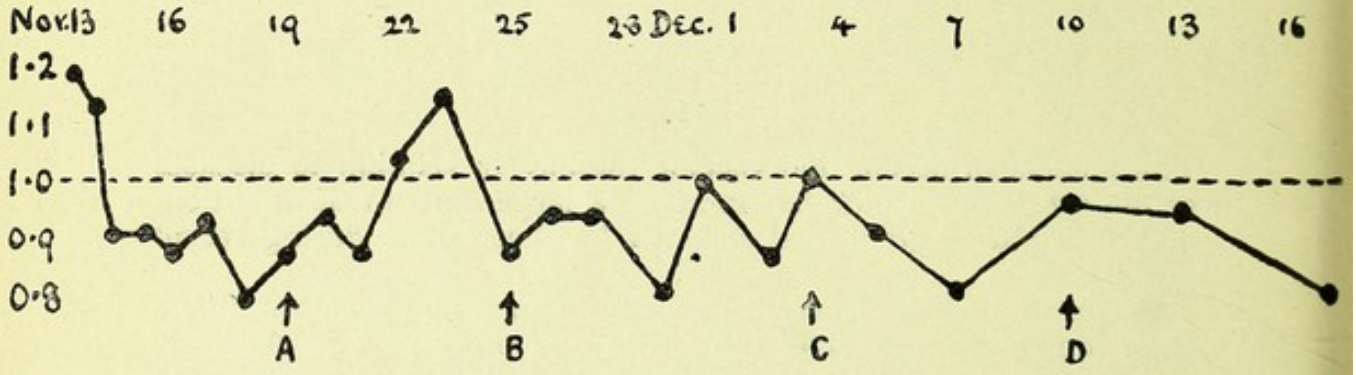

Chart 1.—A, 1/20000 mg. B, 1/10000 mg. C, 1/5000 mg. D, 1/4000 mg.

unfavourable times, interfering with the regulation of the dosage of vaccine.

Sir Almroth Wright and his disciples have shown by means of the opsonic index that the injection of vaccine into an infected subject causes changes in the blood, changes which vary with the amount of vaccine given. The opsonic index is a means of gauging the amount of opsonin in the blood serum, opsonin being some substance which so acts on bacteria that the phagocytes of the blood are able to ingest these bacteria. Injection of vaccine has as its aim the increase of the opsonins in the blood, but the effect of vaccine on the amount of opsonin, as shown by the opsonic index, varies with the amount of vaccine which is injected.

According to the amount of vaccine given, four effects may be obtained.

1. If a small dose be given to an infected person, no effect may be produced, as shown in Chart 1, of a patient suffering from undoubted tuberculosis. Here doses of tuberculin (bacillary emulsion) varying from 1/20000 to 1/4000 mg. were given, and twenty-four opsonic indices taken with no variation greater than would be within limits of normal.

2. A dose which has only a slight effect causes changes in the amount of opsonin in the blood—first, a rapid slight rise of the opsonic index, then a gradual fall to the level at which the index stood before the inoculation.

3. The usual effect of an efficient dose of vaccine is to cause first a fall (this being called the " negative phase ") followed by a rise (" positive phase ") the index gradually again falling to the level at which it was before the vaccination. A slight variation of this curve is occasionally seen in a small rise, lasting a few hours, occurring before the negative phase sets in.

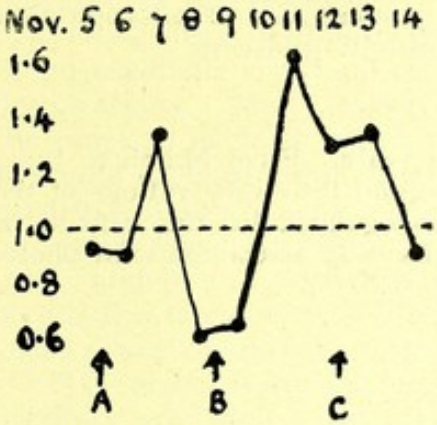

Chart 2.—A, Vaccine. B, Negative phase. C, Positive phase.

4. If an overdose be given, then the only effect is a negative phase lasting a long time, the index gradually rising to near its former level.

With regard to the doses necessary in diseases of the eye, the general statement may be made that larger doses of vaccine are necessary than in treating disease elsewhere, because the blood and lymph flow being limited, a less amount of opsonin will be brought in contact with the diseased area, and also the risk of toxic effect is less, as the area of infection is small.

It has been found that clinical symptoms vary directly with variations of the opsonic index. During the positive phase the patient's general condition improves, as shown by a drop in the temperature in febrile cases, and alleviation of symptoms generally; locally also symptoms are relieved. In eye disease pain becomes less, discharge decreases, ciliary injection diminishes, vision improves, etc. Conversely, during the negative phase symptoms are aggravated.

The aim of Wright's system of inoculation is to produce by repeated injections negative phases as short as possible, followed by positive phases as long as possible, the vaccine being re-injected as the positive phase decreases. In this way the disease gradually becomes cured. The dose to produce this effect, at first small, has to be gradually increased in amount. The interval between inoculations varies according to the nature of the disease.

It is possible without the opsonic index to regulate the amount of vaccine by observation of clinical manifestations. In febrile diseases the temperature varies in inverse ratio to the opsonic index, as is shown by Latham and Inman,[1] and, after a suitable dose of vaccine, the temperature falls, rising again when the effect of the vaccine wears off. The vaccine is then repeated.

In eye disease, by direct inspection, we have a ready means of regulating the treatment by vaccines. In disease of the iris, cornea, and sclerotic vascular injection of the conjunctiva decreases after an efficient dose of vaccine, though if a negative phase is produced the injection may, while the negative phase lasts, be

[1] Latham and Inman: *Lancet*, 1908.

temporarily increased. This is well shown by a case of tuberculous keratitis which was treated by myself, the course of treatment being regulated by the amount of vascular injection. Whenever the eye became inflamed tuberculin was given, and each dose was followed by a period of absence of injection and of photophobia, until finally the condition became absolutely quiescent.

CASE.

R. M. suffered from keratitis for five years. From March to June, 1908, was treated with tuberculin B.E., regulated by observations of the opsonic index; after this treatment was regulated by the amount of conjunctival injection, which, when present, was associated with photophobia.

June 5th. Eyes quiet.
June 10th. Right eye inflamed.
June 11th. 1/5000 mg. given.
June 14th. Both eyes quiet .
June 22nd. Slight conjunctival injection of left eye. 1/5000 mg. given.
June 23rd. Both eyes quiet.
June 30th. Much injection of right eye. Photophobia. 1/4000 mg. given.
July 1st. Slight injection of right eye.
July 2nd. Both eyes quiet.

After July 2nd the eyes showed no more sign of inflammation; corneae continued to clear and vision to improve. Tuberculin treatment was continued until August 26th.

Fromaget[2] mentions a case of tuberculous irido-choroiditis, treated by tuberculin, in which the first four doses were followed by ocular reaction, the fourth also by rise of temperature. Later doses led to marked improvement in local signs and in vision. Here, then, we have an example of negative phases shown by ocular reaction, and one by rise of temperature. The vision also improves during the positive phase as we should expect, and is diminished during the negative phase.

I now propose to deal seriatim with the various infective diseases of the eye which have been treated by vaccines.

TUBERCULOSIS.

Tuberculosis has been treated by vaccine since Koch first introduced his tuberculin in 1890. Disastrous results followed the use of this old tuberculin in the doses recommended by Koch. Treacher Collins[3] mentions the case of a child, aged 9, suffering from tuberculous nodules in the right iris, who was treated by ten injections of old tuberculin, beginning with 1 mg., the dose rising in a month to 7 mg. The original four nodules invaded the whole iris, and the eye was excised.

However, by using smaller doses at longer intervals, good

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[2] Fromaget: *L'Ophthal. Provinciale*, Juin, 1910.
[3] Treacher Collins: *Ophthalmoscope*, 1907.

results have been obtained with old tuberculin in eye diseases. De Schweinitz[4] describes two cases of scleritis and keratitis treated by old tuberculin—one case of eight years' standing cured by six weeks' treatment, the other case showing improvement, followed however by recurrence.

The general opinion is that the use of old tuberculin is attended by unjustifiable risk, and it has been superseded by less dangerous preparations. Many varieties of tuberculin have been placed on the market, each of which has had its supporters and opponents. It would be unprofitable here to mention more than a few of these products, many of which have been in use for but a short time.

Koch's new tuberculin (tuberculin T.R.) was very largely used, and it was with this preparation that Sir Almroth Wright placed the treatment of tuberculosis on a scientific footing, using small doses regulated by estimations of the opsonic index.

The next variety of tuberculin requiring special mention is the bacillary emulsion; this preparation has been, and is being, used extensively with good results. In a series of cases of ocular tuberculosis which I have treated I used this preparation of tuberculin, and I shall refer to some of my results later.

Mention must be made of the use by R. W. Allen[5] of bovine tuberculin in the treatment of tuberculosis of the eye in human beings. He holds that tuberculosis secondary to phthisis is due to human tubercle bacilli, but that, if secondary to cervical or mesenteric tuberculous glands, the disease may be due to bovine tubercle bacilli. He lays down the following rules:

1. If the disease is primary, commence treatment with human tuberculin, and if no improvement takes place in two or three months, the bovine tuberculin, or a mixture of the two varieties, should be used.

2. If the disease is secondary use the appropriate tuberculin.

Allen claims good results in eye disease from the use of this method.

In recent years the two most important methods of dosage which have been employed in using tuberculin in eye disease are:

1. Wright's method, commencing with a small dose, 1/80000 to 1/10000 mg., gradually increasing the dose over a long period of treatment with about ten days' interval between each inoculation, the dosage being regulated by estimations of the opsonic index.

2. Von Hippel's[6] method of treatment with tuberculin T.R., commencing with an initial dose of 1/500 mg., repeating the inoculation on alternate days, increasing each time by 1/500 mg. until 1/50 mg. is reached; after this the dose is increased each time by 1/50 mg. up to 1/5 mg.; then, by 1/10 mg. until a dose of 1 mg. is reached. During the treatment the temperature should not rise above 100° F.; if it does so, the previous dose, or a smaller

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[4] De Schweinitz: *Therapeutic Gazette*, October 15th, 1910.
[5] Allen: *Practitioner*, 1908, p. 737.
[6] Von Hippel: *Arch. f. Ophthal.*, B. 6, 59, p. 1.

one, is repeated until there is no rise of temperature after the inoculation.

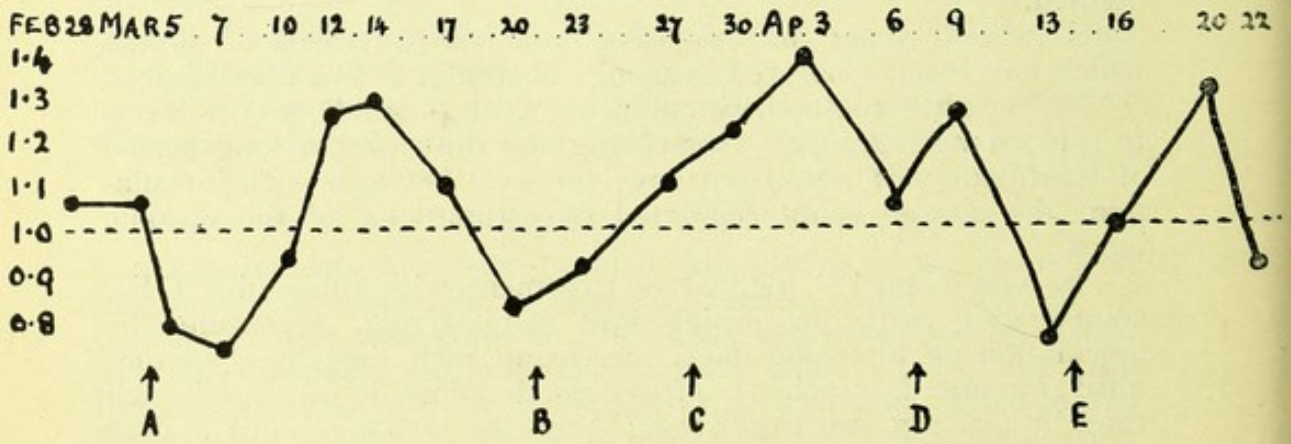
In treating a series of cases at the Oxford Eye Hospital I have used Wright's method, regulating the treatment partly by estimation of the opsonic index, partly by observation of clinical signs and symptoms, temperature, amount of pain and photophobia, effect on vision, and conjunctival injection.

I wish to take this opportunity of expressing my gratitude to Mr. Robert Doyne and the other members of the staff of the Oxford Eye Hospital for their help and encouragement; it was at Mr. Doyne's suggestion that I undertook vaccine therapy while house-surgeon at Oxford, and he not only fitted up a laboratory for me, but gave me permission to make use of all clinical material which was suitable.

Extrinsic Tuberculosis of the Eye.

1. *Tuberculous Conjunctivitis.*—I have treated one case of tuberculous conjunctivitis over a long period with good result.

J. R. aged 61, was first seen in March, 1907, for a lump in the right lower lid of three months' duration; this was removed, but was followed by the appearance in the upper lid of a mass which was treated by caustics and scraping, but continued to increase in size. At the beginning of 1908 the whole of the inner aspects of both lids was covered with fungating granulations, the upper lid projecting over the lower and being thickened to about the size of a hazel nut. Owing to the thickening of the lids the eyeball was hidden, but on raising the upper lid the cornea could be seen, rough and opaque. In January, 1908, a scraping from between the coarse granulations was taken and stained, and tubercle bacilli were found. Treatment by Tuberculin B.E. was commenced in March. The effect of the first five doses on the opsonic index is shown in the following chart.



A, 1/8000. B, 1/20000 mg. C, 1/15000 mg. D, 1/12500 mg. E, 1/12500 mg.

Until the end of 1908 the opsonic index was taken regularly and the injections were repeated every ten days, gradually increasing until at the end of the year 1/3000 mg. was being given. Since that time till the end of 1910 Dr. Coventon, of Oxford, kindly carried on the treatment,

and the patient had 1/2000 mg. every fourteen days. In December, 1910, the conjunctivitis was cured; the conjunctiva was smooth, no injection being present except one small area the size of a pin's head in the upper lid. The thickening had disappeared, the lids being of normal consistency. The eye could be fully opened, and the cornea was smooth and showed only slight opacity at the upper part.

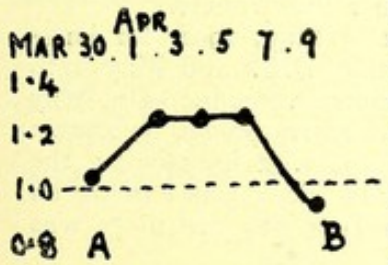
Saxl[6] reports a case of tuberculous conjunctivitis in a woman of 23, treated for two months with tuberculin, and showing improvement. Treatment then ceased, and the condition relapsed. On resuming treatment for a month the condition improved, but afterwards again relapsed, and the lids were scraped. Here treatment does not seem to have been persisted in with sufficient patience.

Ormond and Eyre[7] mention a case of tuberculous conjunctivitis in a child suffering from enlargement of cervical glands with sinus. The diagnosis was made certain by removing and microscoping a portion of the conjunctiva, where typical giant cell systems were found. Inoculation in a guinea-pig gave positive result. The patient was treated for eight months with tuberculin with good result, the vaccine being given every three weeks. Von Hippel[8] reports 3 cases of tuberculous conjunctivitis cured by tuberculin used according to his method. Torok[9] gives the result of tuberculin treatment in 16 cases of eye disease (including 5 cases of tuberculous conjunctivitis) eight of which were cured, and four showed marked improvement.

The results, then, of the treatment of tuberculous conjunctivitis are good, provided the treatment be persisted in over a long period.

2. *Interstitial Keratitis.*—I have treated one case of tuberculous interstitial keratitis with excellent result.

The patient, R. M., a boy of 11, had suffered from enlarged cervical glands and phlyctenular ophthalmia since 1901. In February, 1908, active interstitial keratitis was present in the left eye, the whole cornea was steamy, and there was intense ocular injection. The right cornea showed old nebulae and a recent ulcer. Treatment by tuberculin B.E. was commenced in March, regulated by the opsonic index. The effect of the first dose is shown.



A, 1/15000m mg. B, 1/10000 mg.

The patient was treated until August, when 1/4000 mg. was being given. For the first two months treatment was regulated by estimations of the opsonic index; after this, however, clinical signs, onset of redness and photophobia, were sufficient to indicate when a fresh dose of vaccine was required, the administration of vaccine on each occasion being rapidly followed by alleviation of conjunctival injection and pain. Meanwhile, the corneae were gradually clearing and vision improving,

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[6] Saxl: *Archiv f. Augenheilk.*, June, 1907, p. 328.
[7] Ormond and Eyre: *Trans. Ophthal. Soc. U.K.*, vol. xxviii.
[8] Torok: *Arch. of Ophthal.*, September, 1907.

and treatment was discontinued in August, both eyes being quiet and corneae clear but for old nebulae.

Derby[10] reports 9 cases of interstitial tuberculous keratitis treated with tuberculin with favourable results. Weeks[11] mentions 3 cases treated by von Hippel's method, all of whom recovered.

3. *Scleritis, Sclero-keratitis, Phlyctenular Ophthalmia.*—Nias and Paton[12] have shown the tuberculous nature of most cases of phlyctenular ophthalmia. They examined the opsonic index in a large number of cases, and believed that the condition was due to dead or attenuated tubercle bacilli escaped from a tuberculous focus elsewhere in the body. Allen[5], however, has found that patients with phlyctenules and episcleritis do not always give Calmette's reaction, and are therefore presumably sometimes not tuberculous. In the majority of cases the patients are children suffering from tuberculous cervical glands, and subject to repeated attacks of scleritis and sclero-keratitis over a long period. In almost every case the condition is associated with some error of refraction, usually hyperopic astigmatism, but the photophobia is such a marked symptom that it is impossible to measure the patient for glasses. These patients react well to tuberculin, and if by this means the eye condition is alleviated, and then suitable glasses are fitted, the treatment by tuberculin, provided there is no obvious focus of tuberculosis elsewhere, can be given up, and the eye trouble does not recur. But, in my experience, if, when the eyes are quiet, the error of refraction is not corrected, there is a great tendency for the keratitis, etc., to recur. The following cases illustrate the effect of tuberculin treatment :

1. N. F., aged 4½. Eyes had been inflamed, with corneal ulcers and phlyctenules, and intense photophobia, for six months. 1/15000 mg. tuberculin B.E. was injected, and four days later both eyes were well except for faint nebulae. Glasses to correct hypermetropia were fitted. Treatment by tuberculin was continued for nine months, as the patient had bad tuberculous cervical glands, which almost disappeared under the treatment ; during this time there was no further eye trouble.

2. V. D. S., aged 4, came under treatment in May, 1908, for large phlyctenule in left eye. On May 6th 1/15000 mg. B.E. and May 15th 1/10000 mg. were given, followed by gradual improvement. On May 22nd 1/8000 mg. was given, followed by a bad negative phase, as shown by the appearance of an ulcer of the right cornea, with hypopyon ; the patient also suffered from fever and malaise. The ulcer was healing on May 30th, and after 1/15000 mg. tuberculin on June 6th the ulcer was quite healed, and both eyes remained quiet.

3. F. B., aged 11, suffered from recurrent attacks of phlyctenular ophthalmia in November, 1907, on February 13th, February 18th, and February 25th, 1908. Corneal ulcer March, 1908. Cultures from the conjunctiva were taken in February, and *Staphylococcus aureus* was grown. The patient had three injections of staphylococcus vaccine

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[10] Derby : *Trans. Amer. Ophthal. Soc.*, vol. xii, Part II, 1910, p. 614.
[11] Weeks : *Trans. Amer. Ophthal. Soc.*, vol. xii, Part II, 1910, p. 598.
[12] Nias and Paton : *Lancet*, December 1st, 1906.

prepared from these cultures without any clinical effect. On July 2nd a fresh phlyctenule with conjunctivitis occurred, lasting thirteen days. The same condition set in on July 23rd, and on July 24th 1/10000 mg. of tuberculin was given, and next day the eye was quiet and the phlyctenule had disappeared. On September 19th conjunctivitis set in; 1/10000 mg. of tuberculin was given, and on September 21st the eye was perfectly quiet and well.

Here, then, we have a case in which tuberculin on the two occasions where it was used gave immediate relief to a condition which always before had proved very resistant to treatment. The patient showed no other signs of tuberculosis.

4. G. K., aged 1 year, came under treatment in November, 1906, and from then until April, 1908, suffered from phlyctenular ophthalmia and recurrent corneal ulcers; photophobia during all this time was intense. From April 17th to July 27th, 1908, tuberculin, in doses from 1/20000 to 1/10000 mg., was given, with gradual improvement. In August the eyes were quiet, and refractive error was measured; 3 D of hypermetropia was present. Glasses were worn, and the eyes remained well.

I have treated 17 other similar cases, all with good results, except one, a boy with enlarged cervical glands. In this case, in spite of tuberculin treatment in doses increasing from 1/20000 to 1/10000 mg., and very careful correction of hypermetropia, fresh attacks of phlyctenules continued to occur every few weeks. Derby[10] reports 15 cases of sclero-keratitis treated with favourable results by tuberculin.

Weeks,[11] using von Hippel's method, had 3 recoveries and 2 cases improved of 5 treated.

Hancock and Mayou[13] have treated 4 cases with tuberculin, guiding the treatment by estimation of the opsonic index; the results were good.

Mackay[14] describes a case of keratitis and scleritis of phlyctenular type, later becoming pustular. Treatment by a vaccine of *Staphylococcus aureus* was tried, with amelioration of symptoms, but later a relapse occurred. Tuberculosis was indicated, as the parents were phthisical. Tuberculin, therefore, was tried, and a positive phase, as shown by the opsonic index, was obtained. As I have mentioned, de Schweinitz[4] has obtained a cure in a case of scleritis and keratitis of long standing, using old tuberculin.

Internal Tuberculosis of the Eye.

In internal tuberculosis of the eye we have to deal sometimes with localized lesions of the iris or the choroid, but more often with a generalized tuberculosis of the inner parts of the eye, involving the iris, ciliary body, and the choroid. I have treated one such case over a long period.

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[13] Hancock and Mayou: *Ophthalmoscope*, July, 1907.
[14] Mackay: *Trans. Ophthal. Soc., U.K.*, vol. xxviii.

M. B., aged 10, first came under treatment in November, 1907, with iritis in the right eye. The vitreous was cloudy, with numerous dustlike opacities, and a few more gross ones. Fundus view poor, but with the appearance of a mass down and out. V. 6/12. Calmette's test gave a marked reaction in the diseased eye. This test seemed to have a very bad effect, and the eye, immediately after the test was carried out, became gradually worse. Patient was treated with tuberculin from March, 1908, beginning with 1/25000 mg., the dose being gradually increased, until in December, 1908, 1/2000 mg. was being given every ten days. The treatment was continued until October, 1909, and at that date the anterior chamber was occupied by a greyish exudate, there was exudation behind the lens, vision was only "hand reflex," and tension was soft. The dosage of tuberculin was regulated by the opsonic index, there being no clinical indications for guidance. The diagnosis was made certain by a positive von Pirquet's reaction, and a Wassermann test was also done and was negative.

In this case, then, the condition continued quietly to progress despite treatment. Better results than this have, however, been obtained in other hands.

Iritis.

Hancock and Mayou,[13] using Wright's method, report 5 cases of tuberculous iritis successfully treated. Weeks[11] reports a case of conglomerate tuberculosis of the iris cured by von Hippel's method. Shieck[15] commences with 0.002 mg., repeating the dose on alternate days, each time increasing it by 0.001 mg. He has treated 5 cases of tuberculous iritis, which have improved either immediately or after a temporary increase in intensity at the beginning of treatment. Treacher Collins and Lawford[16] mention good results obtained by tuberculin in the treatment of iritis. Clarke and Mayou obtained a cure in a case of tuberculous iritis in nine months, using 1/1000 mg. every two or three weeks. Von Hippel[8] obtained cures in 23 cases of tuberculous iritis.

Many other cases of tuberculous iritis cured by tuberculin have been reported by Haab,[20] Wolfrum,[23] and Zeigler.[24]

Kerato-iritis.

Derby[10] has treated 6 cases of kerato-iritis with favourable result.

Irido-choroiditis.

Fromaget[17] reports a successful and interesting case. A female, aged 28, with no signs of visceral tuberculosis, for three

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[15] Schieck : *Arch. f. Ophthal.*, 1900, II, p. 247.
[16] Treacher Collins and Lawford : *Trans. Ophthal. Soc. U.K.*, vol. xxx.
[17] Fromaget : *Ophthal. Provinciale*, Juin, 1910.
[20] At Ophthalmological Congress in Heidelberg, 1905.
[23] Wolfrum : *Arch. f. Augenheilk.*, B. I, p. 1.
[24] Zeigler : *Trans. Amer. Ophthal. Soc.*, 1906.

weeks had had painful irido-cyclitis of the eye; vision = $\frac{1}{6}$; fundus invisible. Two months of ordinary treatment did not improve the condition. In December, 1909, four injections of tuberculin were followed by ocular reaction, the last also by a rise of temperature. In January and February, 1910, nine injections were given, and later more injections. The irido-cyclitis became much better, the vitreous cleared, the vision improved to $\frac{1}{3}$. When the fundus was visible there was seen an atrophic patch in the choroid, evidently a cured tuberculous lesion.

Choroiditis.

Using von Hippel's method, Weeks[11] has obtained improvement in four cases of tuberculosis of the choroid. Ernest Clarke and Wright,[18] using the opsonic index as a control, cured a case of conglomerate tubercle of the choroid with tuberculin. The case was diagnosed by the varying tuberculo-opsonic index. Treatment by mercury and potassium iodide was carried on for the first nine months while tuberculin was being used. W. Kraus and A. Bruckner[26] report two cases of tubercle of the fundus treated successfully by tuberculin. Hay[25] mentions cases of tuberculous retinitis cured or treated with success by means of von Hippel's treatment.

In internal tuberculosis of the eye, then, we find that the results of treatment by vaccine are good, especially where the iris is the diseased tissue. The iris is favourable for treatment because it has a good blood supply. In tuberculosis of the fundus, where the blood and lymph supply are poor, treatment has to be prolonged, and is less certainly successful. It may be mentioned here that in disease of the iris it is necessary to use mydriatics to prevent the formation of synechiae, and, the blood supply in this way being diminished, treatment rather tends to be prolonged, owing to the difficulty of getting sufficient opsonins into the diseased tissues.

II.

Diseases of the Eye due to Pyogenic Organisms.

In treating tuberculosis by vaccine, it is necessary to use a "stock" vaccine, whereas, in dealing with other infections, in most cases it is possible to prepare a specific vaccine from cultures of the

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[18] Ernest Clarke and Wright: *Trans. Ophthal. Soc. U.K.*, vol. xxviii, p. 192.
[19] Clarke and Mayou: *Trans. Ophthal. Soc. U.K.*, vol. xxviii.
[21] Rennert: *Deut. med. Woch.*, 1905.
[22] Dorschleg, Inaug. Dissert., Griefs wald, 1905.
[25] Hay: *Ophthalmoscope*, 1908.
[26] Kraus and Bruckner: *Arch. f. Augenheilk.*, May, 1907.

infecting organism obtained from the patients to be treated. It is advisable to use a specific vaccine in most cases, but it seems to be unnecessary in cases of infection by staphylococcus. Here a mixed stock vaccine, prepared from cultures of *Staphylococcus aureus, citreus,* and *albus,* is usually efficient; if the use of such a vaccine is not attended by improvement in a reasonable time, a specific vaccine should be prepared. Again, in disease due to gonococcus, owing to the difficulty of preparing a vaccine, stock vaccine must usually be used, and gives quite satisfactory results.

Polyvalent stock vaccines have been used in infections due to pneumococci and streptococci, but the best results are obtained by the use of specific vaccines, as there are many different strains of these organisms.

In taking cultures from eye diseases for the purpose of preparing vaccines, it is advisable in most cases to use as culture-media serum or blood agar, as many of the bacteria which commonly infect the eye grow well only on these media.

The vaccine is prepared by making an emulsion, by shaking, of the bacteria in 0.85 per cent. sodium chloride solution, and standardizing by mixing a portion of the emulsion with a portion of blood (which normally contains 5,000 million of red cells to the cubic centimetre), and counting fields of bacteria and red cells on a microscopic slide. In this way the number of bacteria per cubic centimetre is estimated. The emulsion is then sterilized at a temperature of 58° C. for thirty minutes, and finally diluted to a convenient strength in 0.5 per cent. phenol.

I will now deal with the vaccine treatment of the various regions which come within the province of eye surgery.

External Infections.

1. The lachrymal sac.

The lachrymal sac is liable to acute and chronic inflammations. The acute inflammations are usually due to streptococci, and, as stock vaccines are unreliable, there is not time, as a rule, for vaccine treatment. I have treated acute lachrymal abscesses with stock streptococcus vaccine, combined with ordinary surgical treatment, but have not been satisfied that the vaccine influenced the course of the disease.

The most important variety of chronic inflammation is that due to infection by pneumococcus. The chief dangers of this disease are—first, that abrasions of the cornea may become infected and severe ulcers be produced; and secondly, that any operation carried out on an eye with such infection of the sac is attended with grave risk of sepsis. The region of the lachrymal sac is well supplied with blood, and infections react well to vaccine treatment.

Very Chronic Inflammation of the Lachrymal Sac Cured by a Specific Pneumococcus Vaccine.

W. T., aged 66. Right eye amblyopic. Attended first November, 1905, with left cataract and suppurating lachrymal sac. The sac was

washed through regularly without relief, so in August, 1907, the sac was extirpated, leaving, however, a sinus. Ordinary treatment by scrapings and antiseptics did not affect the condition, cultures of pneumococcus being obtained in February and April, 1908, making operation for the left cataract impossible. Treatment by a vaccine prepared from the pneumococcus cultures was carried out from May 2nd to August 3rd. The opsonic index was regularly taken and an inoculation given every ten days, commencing with 10 million and gradually increasing to 50 million. After the latter dose, however, a negative phase was produced, followed, however, by a rise of the index to 1.76 on June 9th. From June 12th until August 3rd 30 million were given every ten days. Cultivations on serum agar taken on July 6th and August 3rd gave no growth of pneumococcus, so on August 7th a left preliminary iridectomy was performed, followed by cataract extraction on October 6th, with no unfavourable symptoms after either operation. In December vision with glasses = 6/9.

In this case, then, pneumococcus infection of more than two years' duration was cured in two months by vaccine, enabling operation to be performed without risk.

Chronic inflammations of the lachrymal sac offer a hopeful field for treatment by vaccines. Next in frequency to pneumococcus comes staphylococcus as infecting organism, and such cases can be treated with success by doses of 100 to 500 million of stock vaccine repeated once a week. R. W. Allen[1] has treated successfully cases of dacryocystitis due to streptococcus by means of vaccines.

Diseases of the Lids.

Staphylococcus.—Staphylococcus aureus is the cause of many varieties of chronic or recurrent disease of the lids, and such disease can be cured by vaccine in doses of 100 to 1,000 million. Blepharitis is due to such infection, and is usually associated with an error of refraction. Cases may be cured by means of staphylococcus vaccine, and if the refractive error be corrected there is no tendency to relapse.

A. B. for twelve months suffered from blepharitis, which did not improve under ordinary treatment, though his hypermetropia (+3D.) had been carefully corrected. Cultures showed *Staphylococcus aureus* to be the causative organism. For two months the patient was treated with stock vaccine, an inoculation being given every ten days, commencing with 100 million, gradually increased to 250 million. A month later the lids were practically normal, only very slight thickening of the lid margins being present.

Chalazions and hordeola show great tendency to recur frequently in some patients; cure can be obtained by a three months' course of treatment by staphylococcus vaccine.

Mayou[3] has given the results of treatment by vaccine in infections due to staphylococci. He used doses varying from 500 to 2,000 million, regulated in most cases by the opsonic index. He reports four cases of acute styes associated with phlyctenules and corneal ulcers, in one of which a complete cure was obtained; in

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[1] Allen: *Practitioner*, 1908, p. 737.
[3] Mayou: *Ophthalmoscope*, 1908.

the other three there was temporary relief, followed by recurrence. A case with boils and styes on lids of one month's duration was given two doses, 500 million and 1,000 million, and was cured in a month. No recurrence six months later. He quotes also cases of styes and recurrent tarsal cysts cured by one inoculation.

Doyne[2] has described a variety of recurrent and obstinate conjunctivitis due to infection of the Meibomian glands with staphylococcus, and he reported a case cured by vaccine. The patient had for many months suffered from attacks of conjunctivitis every week or ten days. Staphylococcus was grown from secretion expressed from Meibomian glands, and a specific vaccine prepared. Treatment was carried on for three months, and no fresh attack occurred. Later there was a relapse, so treatment was resumed for a short time. Four months later he had had no further attacks.

Conjunctivitis.

Many varieties of acute conjunctivitis clear up so rapidly with antiseptics that there is no indication for further treatment. Allen,[1] however, recommends the use of vaccines in the treatment of conjunctivitis due to pneumococcus, streptococcus, *Bacillus coli,* and *Bacillus pyocyaneus.*

Acute gonococcal conjunctivitis is a disease of grave prognosis, and here vaccine is of great value. Of two severe cases which I have treated, in one a cure was obtained in ten days, in the other no apparent benefit resulted.

W. H., a middle-aged man; no history of infection; attended May 13th, 1908, the right eye having been bad four days. Much discharge and chemosis; cornea, ditch ulcer inner side, ring of disturbed epithelium all round rest of cornea at periphery, and greyish lines of infiltration at central parts. Vision less than 6/60; tension full. Smears and cultures of gonococci obtained.

May 14th: Right eye, cornea more infiltrated. Left eye infected, chemosis and discharge, yellow ulcer all round cornea, and three infiltrated spots more centrally placed. May 15th: Right eye better. Left eye, ulcer larger, cornea infiltrated. May 16th: Right eye, corneal ulcer healed. Left eye, less chemosis. May 22nd: Left corneal ulcer healed. May 23rd: No discharge from either eye—still slight conjunctival injection. May 31st: Both eyes perfectly quiet. June 9th: Vision in each eye normal. Depressed scars round both corneae.

The details of vaccine inoculations and opsonic indices are shown in Chart 5.

Here, then, very small doses of vaccine were followed by a most excellent clinical result. During the treatment frequent irrigation of the conjunctival sacs with antiseptics was carried out, and eserine was used with the object of increasing the blood supply of the cornea.

A boy, aged 12, on admission, had acute gonococcal conjunctivitis

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[2] Doyne: *Trans. Ophthal. Soc. U.K.*, vol. xxx, p. 86.

of two days' duration, and the cornea was steamy. A large ulcer appeared in the centre of the cornea, and perforated; the iris prolapsed and vision was lost. Three doses of 1 million each and three of 1½ million each of gonococcus vaccine were given. Vaccination appeared to have no good effect in this case.

I have treated three cases of gonococcal ophthalmia in newborn infants with doses of ½ to 1 million of vaccine; the disease became cured in each case without infection of the cornea.

Rubbrecht[4] reports a case of systemic gonorrhoea with conjunctivitis and keratitis in which three doses of gonococcus vaccine (5, 7½, and 10 million) were given with excellent results. There

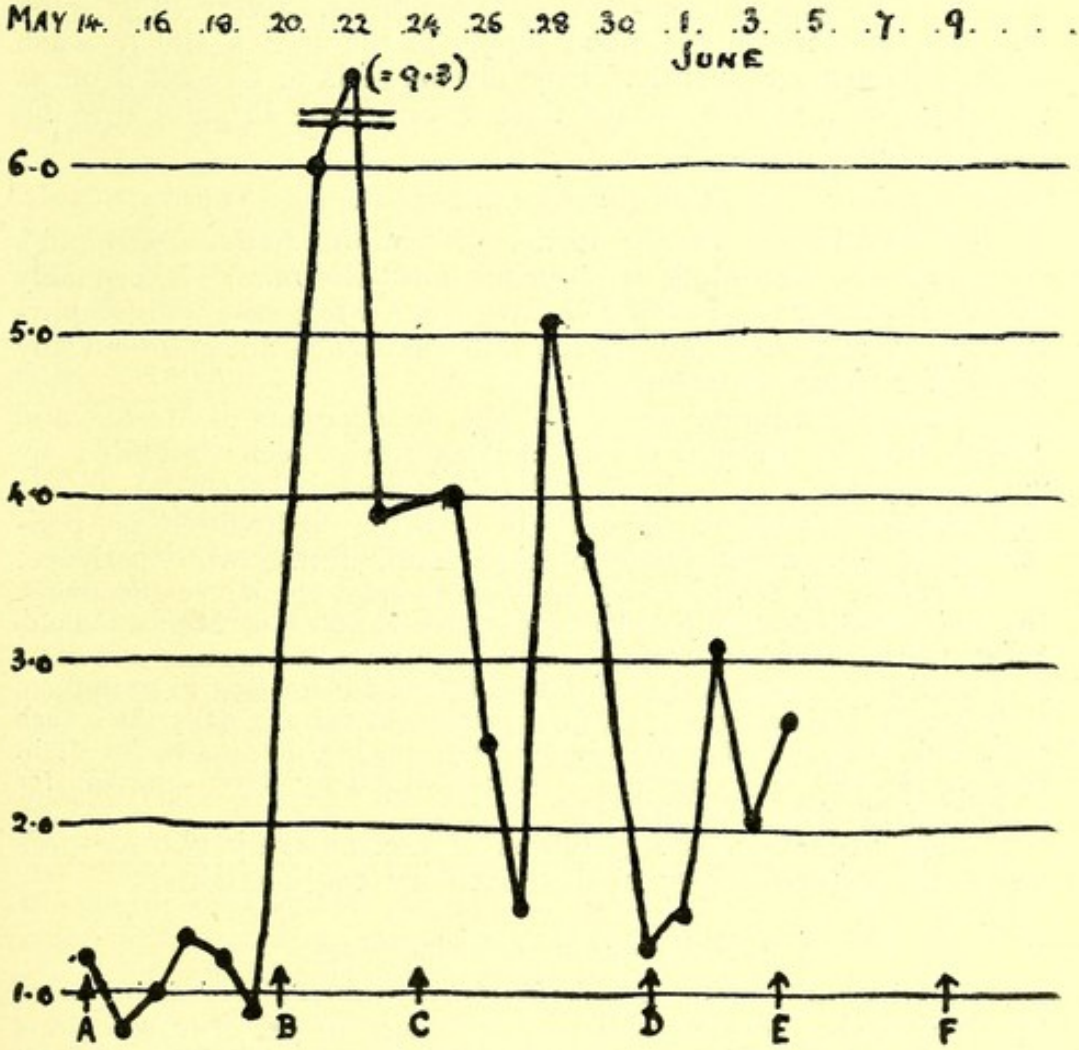

Chart 5.— A, 1.2 million; B, 1.2 million; C, 1.5 million; D, 1.5 million; E, 2 million; F, 1½ million.

was no corneal ulceration, but when the conjunctivitis was well three attacks of peripheral keratitis occurred, extending over a period of one month. Weeks[13] recommends doses of 2½ to 50

[4] Rubbrecht: *Bull. de la Société Belge d'Ophthal.*, 27, 1909, p. 82.
[13] Weeks: *Trans. Amer. Ophthal. Soc.*, vol. xii, Part II., 1910, p. 598.

million of polyvalent gonococcus vaccine, but has found it of little value in acute infections. I think he has used too large doses and has produced negative phases, from which there is not time for recovery in acute cases. McKee has treated with vaccine 3 cases of metastatic gonococcal inflammation of the conjunctiva with success.

We see, then, that in acute gonococcal conjunctivitis, if the treatment be commenced before the internal parts of the eye are affected, good results may be obtained with vaccine, but it is necessary to use very small doses repeated at short intervals, the object being to avoid as far as possible negative phases, and to obtain only rapid and repeated positive phases. Every effort must be made to increase the blood supply of the cornea and to wash away discharge frequently. Free discharge is to be looked on as useful, as it is by this means that opsonins are brought through the diseased tissues.

Chronic Conjunctivitis.

Of the more chronic forms of conjunctivitis, Parinaud's conjunctivitis, according to Sinclair and Sherman,[6] is probably due to *Staphylococcus albus*. I have treated one case with staphylococcus vaccine for some weeks, but was unable to make out any good effect from the treatment.

Cases of conjunctivitis due to the diplobacillus of Morax, and others due to Friedländer's bacillus, have been benefited by vaccine treatment. It is difficult to prepare a vaccine from the diplobacillus owing to its delicate growth; cultivation on peritonitic serum agar has given the best results in my own experience.

Case.—A. C., for ten years had suffered from chronic conjunctivitis. In June, 1908, the conjunctiva gave pure cultures of Morax's diplobacillus, from which a vaccine was made. For five months treatment was carried on, commencing with 10 million and increasing to 50 million, with benefit. There was marked improvement for ten days after each dose, and at the end of treatment the eyes were healthy, except for slight crusting at the outer canthi. Clinical symptoms were sufficient for regulating the dosage in this case.

Allen[1] recommends 100 million of vaccine every two or three weeks in obstinate cases of diplobacillary conjunctivitis.

Phlyctenular Ophthalmia.

As I have mentioned, in dealing with tuberculosis, most cases of phlyctenular conjunctivitis would seem to be of tuberculous origin, although frequently *Staphylococcus albus* can be cultivated from the conjunctival discharge, but should be regarded as a secondary infection. Mackay[5] has used staphylococcus vaccine for phlyctenular conjunctivitis. Reporting a case of phlyctenular keratitis and pustular episcleritis of long standing and many recurrences, he claims a good result.

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[5] Mackay: *Trans. Ophthal. Soc. U. K.*, vol. xxviii, p. 201.

[6] Sinclair and Sherman: *Trans. Ophthal. Soc. U. K.*, vol. xxvii, p. 40.

Ulceration of the Cornea.

I have dealt with the treatment of gonococcal keratitis associated with conjunctivitis. I will now mention other corneal infections which have been treated by vaccines.

1. *Staphylococcus.*—Staphylococcal ulceration of the cornea is a severe disease, but by no means so severe as the ulceration due to some other organisms mentioned later. Vaccine treatment has given good results. The bacteriological diagnosis must first be made by taking scrapings from the growing margin of the ulcer and planting on serum or blood agar; if staphylococcus only grows we know that it is the primary infection, and not merely an added infection secondary to some more virulent organism.

Grey Edwards[7] reports three cases of hypopyon ulcer treated by staphylococcus vaccine. The first, an acute case, rapidly recovered after one dose of 250 million; the second, a chronic ulcer recovered after one injection of 100 million; the third case, also a chronic hypopyon ulcer, after three injections, likewise recovered. In all three cases treatment by subconjunctival injection of mercury bicyanide was carried out.

Mayou[3] mentions a case of neuroparalytic keratitis with a hypopyon staphylococcus ulcer, which was cured three months after receiving an injection of 500 million of staphylococcus vaccine.

The most severe forms of ulceration of the cornea are those due to pneumococcus and streptococcus.

2. *Pneumococcus.*—Acute ulcer of the cornea due to pneumococcus is the commonest form of "hypopyon ulcer," and is usually associated with similar infection of the lacrymal sac. Treatment by vaccines has been followed by a fair measure of success, but it is necessary to begin the treatment early, as the disease usually progresses rapidly. Immediately the diagnosis is made, 25 millions of polyvalent stock pneumococcus vaccine should be given; cultures of the patient's own organisms should be planted, and a specific vaccine made as rapidly as possible. Twenty million of this is a suitable dose to commence with, but may be increased in four or five days, the treatment being regulated by estimations of the opsonic index and clinical appearances. The following case, an example of so-called "ulcus serpens," shows the good effect that may be obtained by the use of vaccine.

S. I., aged 64, attended May 11th, 1908, with pain in the right eye of four days' duration following a slight injury. Eyes "watery" for years. Right eye showed deep and superficial conjunctival injection, chemosis, and a small hypopyon. Tension full. Lachrymal regurgitation of muco-pus. Near the margin of cornea was a grey infiltrated ulcer, and the whole cornea was steamy. Scrapings from the ulcer showed pneumococci. The case was treated with a stock pneumococcus vaccine, as shown in the chart, the opsonic index being frequently taken. The condition rapidly improved; on May 12th the hypopyon had disappeared,

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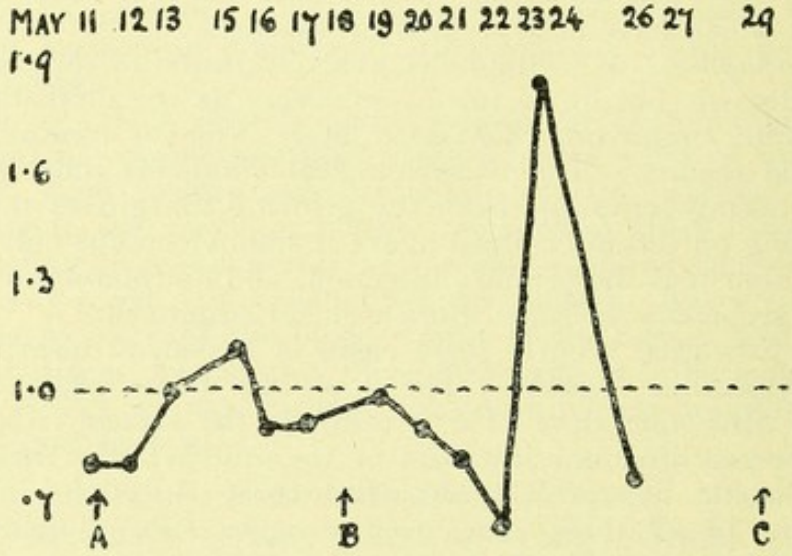
[7] Grey Edwards: *Ophthalmoscope*, 1908, p. 79.

on the 20th the ulcer had healed, and on the 22nd the eye was quiet. The discharge from the lachrymal sac became clear.



A, 15 million. B, 30 million. C, 50 million.

It will be seen that the first dose slightly raised the opsonic index, and that the increased dose of May 18th gave a negative phase, followed by a high positive phase. During the negative phase for one day the eye was more inflamed.

Another case treated with the same stock vaccine gave no good result, but it was from the beginning much more unfavourable.

T. I., aged 77; eye had been bad for four days following an injury. On admission one-third of the cornea was occupied by a sloughing ulcer. Large hypopyon. Cultivations of pneumococci obtained. The whole cornea sloughed and perforated six days after admission, and the iris prolapsed. On the day after admission 25 million of stock pneumococcus vaccine were given.

Two other varieties of pneumococcus infection of the cornea are described:

A. *The Hypopyon Keratitis of Children.*—Stephenson[8] has found pneumococci in four out of seven cases as a mild infection commencing in an ulcerated phlyctenule. In these cases my own results would show that tuberculosis is nearly always the primary cause, though staphylococci and pneumococci are sometimes present as an added infection. In such cases treatment by tuberculin gives good results.

B. *Keratomalacia,* a form of gangrene affecting the cornea in children enfeebled by wasting disease. The outlook for vaccine treatment in such cases is unfavourable.

3. *Streptococcus* is the cause of a very virulent form of hypopyon ulcer. The following case illustrates the rapid course of the disease:

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[8] Stephenson; *Ophthalmoscope,* 1908, p.79.

S. S., aged 63, having had chronic conjunctivitis for six months, came to hospital with history of acute pain in the left eye for three days; no injury. Condition on July 27th, 1908: Muco-purulent discharge, much chemosis, superficial and deep injection. Deep ulcer 3 mm. in diameter at centre of cornea, with sloughing base. Large hypopyon. Streptococcus was grown. Condition rapidly became worse, the whole cornea sloughed and perforated, and the eye was excised on August 10th. In this case, on admission 5 million stock pneumococcus vaccine was given; next day 5 million polyvalent streptococcus vaccine; four days later 10 million of a specific vaccine prepared from the culture obtained on admission; five days later 20 million of the same specific vaccine.

A variety of acute streptococcal infection is the pseudo-membranous ophthalmia of infants. Toxaemia is intense, and death is the usual result. Vaccine in small doses should be tried in such cases, but I know of no recorded results.

De Schweinitz[14] reports the recovery of a hypopyon ulcer. A vaccine was prepared from cultures of streptococcus obtained from the anterior chamber, and three doses (50 million, 100 million, and 100 million) were given. We see, then, that few cases are on record of acute pneumococcus and streptococcus ulcers cured by vaccine. I believe these cases are so acute that they offer a more hopeful field for the use of serums than vaccines. With serum treatment many good results have been recorded.

Ulcers of the cornea may be due to other organisms—*Bacillus coli*, diplobacillus, etc.—but I can find no records of such cases treated by means of vaccines.

As an accessary to vaccine treatment, the local light treatment by cadmium-zinc lamp, described by Hertel,[9] is valuable. He claims that the treatment causes (i) direct bactericidal action; (ii) indirect effects—conjunctival and ciliary injection, oedema, and cellular infiltration of the cornea.

Here, then, we have a means for producing (1) increased passage of serum to the diseased part, (2) increased local leucocytosis, (3) auto-inoculation. If we raise the opsonic index by vaccines, such treatment should give even better results than in the hands of Hertel using the light alone (25 cures out of 47 cases of serpent ulcer of the cornea).

Post-operative Infection.

In post-operative infection excellent results have been obtained with vaccines. Cultures must be taken from the wound, and a vaccine used as early as possible. Staphylococci, streptococci, and pneumococci are the commonest infecting organisms.

Staphylococcus.—Maddox[10] reports an infected case of cataract extraction, with pus along line of incision; vitreous grey and turbid, and iris "rotten-looking." Injection of staphylococcus vaccine gave rapid improvement, followed by cure.

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[9] Hertel: *Klin. Monats. f. Augenheilk.*, August and September, 1907.
[10] Maddox: *Ophthalmoscope*, June, 1908.
[14] De Schweinitz: *Therapeutic Gazette*, October 15th, 1910.

Streptococcus.—I have obtained a very striking result by vaccine in a case of late post-operative infection by streptococcus.

E. P., July 13th, 1908: Lids healthy. Right preliminary iridectomy performed. July 19th: Much ciliary injection. The inflammation became rapidly worse, with intense chemosis, the edges of the incision oedematous, iris discoloured, and a hypopyon developed. Cultures from wound showed pure growth of streptococcus. July 22nd: Increased ciliary injection and hypopyon. July 23rd: Less chemosis. July 24th: Hypopyon disappeared, injection and chemosis less. July 29th: Aqueous clear.

August 8th. A small hypopyon reappeared, lasting until August 14th. The inflammation gradually subsided, and the eye became quiet by August 23rd. Extraction and needling were performed later, without complication, and vision 6/9 was obtained.

I give the details of treatment and opsonic indices in Chart 7.

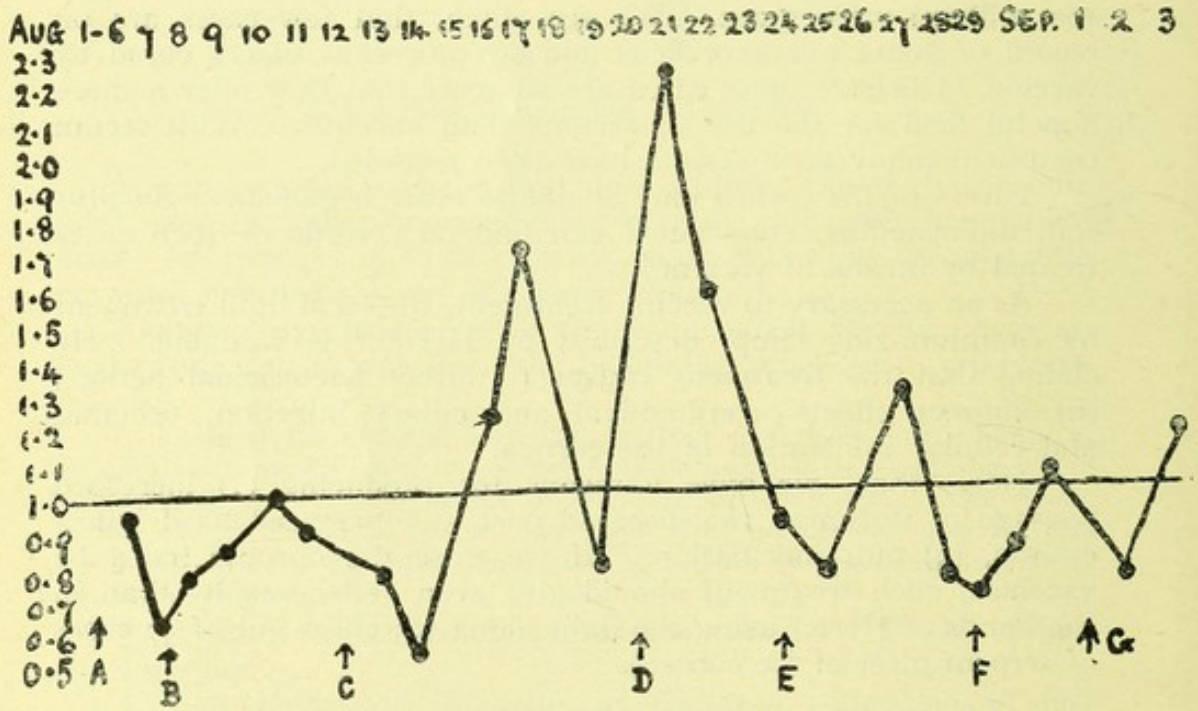

Chart 7.—Case E. P.—A, 10 million of "stock" streptococcus vaccine. B, 5 million of specific vaccine. C, 15 million ditto. D, 10 million ditto. E, 12 million ditto. F, 15 million ditto. G, 20 million ditto.

We see, then, that vaccine treatment is of great value in post-operative infections, the prognosis of which has been so bad in the past.

Internal Infections.

In internal disease of the eye due to pyogenic organisms the obtaining of a bacteriological diagnosis is difficult. The disease may be primary or secondary to a focus elsewhere in the body. Lesions of the eye secondary to disease of other parts have been

described by Holmes Spicer,[11] and may take the form of irido-cyclitis, retinal abscess, or retinal phlebitis. Such cases may be secondary to skin abscesses, puerperal infections, pleuropneumonia, etc., and the causative organisms are usually staphylococci or streptococci. Another variety of metastatic infection is irido-cyclitis secondary to pyorrhoea alveolaris (Adams[12]), where staphylococcus or pneumococcus is the infecting agent. In all such cases vaccines can be used with good hope of success, cultures being obtained from the primary focus of disease.

On the other hand, in internal infections of the eye without obvious lesions elsewhere, the difficulty arises of obtaining cultures of the causative organism and making a bacteriological diagnosis.

However, in cases of irido-cyclitis cultures have been made from the aqueous after paracentesis by Mayou,[3] and he reports a case in which *Staphylococcus albus* was grown, and the irido-cyclitis cured by vaccine, using doses of 1,000 million. Two other similar cases of irido-cyclitis treated by staphylococcus vaccine are recorded by the same author, one being cured, the other relieved. Weeks[13] records two cases of gonococcal iritis treated by stock vaccine with success, and he mentions two similar cases treated by C. A. Oliver, and one, recorded by Posey, of severe gonococcal uveitis which improved. Streptococcus has been cultivated by other workers from the anterior chamber in cases of irido-cyclitis.

The general rule must be laid dwn that larger doses of vaccine are necessary in internal diseases of the eye owing to the peculiarities of its blood supply.

Lastly, mention may be made of a result obtained by Trantes,[15] who used cow-pox vaccine in a case of trachoma, with resulting cure; the experiment was suggested by the observation of a case of trachoma which became well after an attack of small-pox.

III.

The Serum Treatment of Diseases of the Eye.

Serums, antitoxic and antibacterial, have been used very extensively in treating cases of eye disease, and may be divided into two classes—those which have a specific action and those which are non-specific (the so-called "paraspecific serum").

Serum has usually been injected either into the subcutaneous tissues, the most frequently used and safest method; into muscular tissues; or into the blood stream, the method by which the most rapid effect is obtained. It has also been given by mouth

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[11] Holmes Spicer: *Trans. Ophthal. Soc. U. K.*, vol. xxvii, p. 230.
[12] Adams: *Trans. Ophthal. Soc. U. K.*, vol. xxx, p. 148.
[15] Trantes: *Soc. Française d'Ophthal.*, 1907.

and by rectum. Darier[8] concludes that serums given by mouth immunize but exert no bactericidal effect.

Specific Serums.

1. *Diphtheria Antitoxic Serum.*—As in diphtheria elsewhere, so in diphtheria of the eye extremely good results have been obtained by the use of this method of treatment. Sydney Stephenson[1] has reported cases successfully treated in this way. The dose should be 2,000 to 10,000 units, and at least two doses are usually necessary. In membranous conjunctivitis due to the Klebs-Loeffler bacillus the Roux serum is valuable; Axenfeld[2] has analysed the results obtained and reports favourably. In corneal diphtheria the serum is less effectual, and this is due to the fact that, though the serum does overcome the toxic effects of the *Bacillus diphtheriae,* the severity of the corneal complications depends on the mixed nature of the infection from the presence of the ordinary organisms of suppuration, staphylococci, streptococci, pneumococci, etc.; the serum has only a non-specific effect on these organisms. In such mixed infections Römer's antipneumococcus serum and polyvalent anti-streptococcus serum are of use. Post-diphtherial paralysis of eye muscles: Aubineau[24] reports a case of paralysis of accommodation cured by injection of anti-diphtheria serum. Three relapses subsequently occurred, each of which yielded to the treatment. Four doses (10 c.cm., 20 c.cm., 30 c.cm., 60 c.cm.) were given in this case.

2. *Tetanus Antitoxic Serum.*—This serum, of the same nature scientifically as antidiphtheria serum, is of value in treating tetanus having its primary point of infection in the eye. Such cases are rare, but Ellis has had two recoveries of three cases treated. Lewis also has reported the recovery of a case. Diphtheria and tetanus are the two diseases due to organisms possessing an extracellular toxin, and for this reason are especially suitable for the use of specific antitoxic serums. Specific serums have been prepared and used in infections by many other organisms with varying results. Possibly the benefit obtained in some cases does not depend on the specific nature of the serum as it does in diphtheria and tetanus. As I shall mention later, in infections due to the ordinary pyogenic cocci excellent results have been obtained with non-specific serums.

3. *Specific Antipneumococcus Serum.*—Many methods of preparing antipneumococcus serum have been employed. Kornel Scholtz[3] finds that the serum produced by infecting an animal with one culture of pneumococcus usually has no effect in agglutinating other cultures of that organism; these experiments

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[1] Sydney Stephenson: *Trans. Ophthalmol. Soc. U.K.,* vol. xxl, p. 12.
[2] Axenfeld: *Lancet,* ii, 1908.
[3] Kornel Scholtz: *Arch. f. Augenheilk.,* September, 1906.
[8] Darier: *La Clin. Ophtalmologique,* December 10th, 1910.
[24] Aubineau: *Ann. d'oculistique,* September, 1906.

demonstrate the existence of different strains of pneumococci. It is impracticable in clinical medicine to prepare a serum by immunizing animals to cultures obtained from individual patients, and therefore the employment of a polyvalent serum, prepared from many strains, becomes necessary. The best known polyvalent antipneumococcus serum was that of Römer. Römer[4] has lately modified the method of preparation of his serum, and has introduced a new serum on the lines of Bail's antiaggressin containing serum; using this new serum, he reports success in the treatment of pneumococcal ulcers of the cornea.

4. *Antirheumatic Serum.*—Rosenthal claims good results in rheumatic iritis by the use of a specific antibacterial serum prepared by immunizing animals against the *Streptococcus rheumaticus*. The results have not been corroborated, and Darier[8] says better results are obtained in such cases by using Roux's serum.

5. *Antistreptococcus Serum.*—Polyvalent antistreptococcus serum has given occasional good results in streptococcal infections of the eye, but the results are not constant owing to the enormous number of strains of streptococcus which have been demonstrated. Recent methods of analysing the strain infecting any particular case by means of the sugar reactions may make possible the use of antistreptococcus serum prepared with a corresponding strain. Snell[5] reports a case greatly benefited by antistreptococcus serum. The patient had suffered from suppuration of the lids of the right eye for seven days, the temperature was 103°, delirium was marked, and the general condition grave. Streptococci were found in pure culture. Three injections, each of 10 c.cm. of polyvalent antistreptococcus serum, were given over a period of forty-eight hours. On the following days the temperature was subnormal, delirium abated, and eventually a cure resulted. On the other hand, Lawson[6] found antistreptococcus serum of no use in a case of acute streptococcus infection of the cornea.

Antigonococcus Serum.—An antigonococcus serum has been prepared by Rogers and Torry by injecting living gonococci into the peritoneum of sheep. Knapp[7] reports results of the use of this serum. He has found it of no value in conjunctivitis, but in treating four cases of gonococcal iritis he has had three cures, the result in the fourth case being indefinite.

Antistaphylococcus Serum.—At various times serums obtained from animals by immunizing them against staphylococci have been employed, with no results of value. As we have seen, staphylococcal infections are most favourable for the employment of vaccine.

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[4] Romer : 24 Versammlung d. Ophthalmol. Gesellschaft, Heidelberg, 1907.
[5] Snell : British Medical Journal, July 4th, 1908.
[6] Lawson : *Trans. Ophthalmol. Soc. U.K.*, vol. xxvii, p. 33.
[7] Knapp : *Trans. Ophthalmol. Sect. New York Acad. of Med.*, Nov. 18th, 1907.

Eye affections due to the diplococcus of epidemic cerebro-spinal meningitis are not unknown, and in these cases Flexner's serum has been found to be of value.

The results, then, of the treatment of eye diseases by specific antitoxic and antibacterial serums are promising but uncertain, and a method of treatment giving more constant results has been looked for. Great attention has been given to the use of non-specific (so-called " paraspecific ") serums.

Non-specific Serums.—Darier[8] carried out an extensive search through the columns of *La Clinique Ophthalmologique,* and reported his results and conclusions in a long paper; his paper largely is an exposition of the value of paraspecific as opposed to specific serum-therapy, and he shows particularly the value of the Roux serum in treating disease other than diphtheria. The following infections were inquired into: **Pseudo-membranous conjunctivitis,** infective corneal ulcers, parenchymatous and scrofulous keratitis, iritis and irido-cyclitis, traumatic and post-operative infections. Except in the case of diphtheria and tetanus, paraspecific serum treatment has given better results than specific serums, that is, the antistreptococcal serums, the antipneumococcal serums of Römer, and the antirheumatic serum of Rosenthal.

In the majority of ocular infections the result is the same whether one employs the serum of Roux, antitetanic serum, anti-rheumatic serum, or Deutschmann's yeast serum. It is found that every antitoxic serum acts in two ways: in addition to its specific action on the disease against which it has been prepared, it also possesses the property of bringing to every organism invaded by any infective agents some elements of general defence, capable of neutralizing or of attenuating to a greater or lesser degree the majority of the morbid symptoms caused by the said infection.

Roux's serum has been, perhaps, most extensively used as a paraspecific serum, and very many infections of the eye have been treated thus. Alexandroff[9] advises its use in 10 c.cm. doses, and as many as four doses may be necessary.

Conjunctivitis.

Excellent and permanent results have been obtained in infective conjunctivitis by Alexandroff,[9] and by Darier,[11] who has treated simple purulent conjunctivitis, gonococcal conjunctivitis, and pseudo-membranous conjunctivitis. Fromaget[10] reports two cases of purulent ophthalmia with false membrane due to pneumococcus cured within forty-eight hours by injections of anti-diphtherial serum.

Ulceration of the Cornea.

Here also good results have been obtained. Darier, in 1903, was the first to use Roux's serum paraspecifically in a case of staphylo-

[9] Alexandroff: *La Clin. Ophtalmol.*, October 10th, 1910.
[10] Fromaget: *Ann. d'oculistique*, t. cxxxviii, p. 182.
[11] Darier: *Die ophthal. Klinik*, 5, June 20th, 1907.

coccus conjunctivitis with ulceration of both corneae; the ulcers disappeared with scarcely a trace of scar. Since that date the same author has reported good results with pneumococcal[13] and other varieties of hypopyon ulcer.[11] Monbouyran[12] reports six successive cases of hypopyon ulcer cured by Roux's serum, using 10 c.cm. about every three days. Alexandroff[9] treated a case of serpent ulcer in a woman aged 42. There was no lacrymal disease. Under ordinary treatment the condition became worse, so 10 c.cm. of Roux's serum were given, and the case improved. Two further injections were followed by recovery, and two years later vision was normal.

Post-operative and Traumatic Infections.

Teulières[15] reports good results from the use of Roux's serum in infected wounds and perforations leading to irido-choroiditis and traumatic cataract. Alexandroff,[14] Darier,[11] and other authors have used it with success in post-operative infections.

Darier[11] describes a modification of the use of antidiphtheritic serum. He follows its use by that of collargol injections in gonococcal cyclitis, septic corneal ulcers, panophthalmitis and septic wounds, and claims that the results are better than those obtained by the use of Roux's serum alone. He believes the effect obtained resembles that of a specific serum, but I think we ought rather to consider it as a treatment by auto-inoculation, the collargol by its toxicity producing reaction, which causes auto-inoculation, by which means the patient may produce in his serum a great variety of protective substances.

Exophthalmic Goître.

Mention must be made of Burkard's[16] experiments. Using antidiphtheritic serum in four cases of exophthalmic goître, he reports three cases relieved. The results resemble those obtained by many methods of treatment, where rest of the patient commences only at the same time as the special method of treatment, and it is rather to the rest that the relief of symptoms is due.

Deutschmann's Yeast Serum.

Deutschmann[17] introduced a paraspecific serum for which excellent results have been claimed in many forms of eye disease. The serum originally was prepared by feeding rabbits on yeast in ascending doses, the serum of these rabbits being then injected into patients suffering from staphylococcus, pneumococcus, streptococcus, or other infections. Later, the method of preparation underwent modification, and Deutschmann,[18] in August, 1908,

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[12] Monbouyran : *La Clin. Ophtalmol.*, January 29th, 1908.
[13] Darier : *La Clin. Ophtalmol.*, February 10th, 1907.
[15] Teulières : *Die ophthal. Klinik*, March 20th, 1908.
[16] Burkard : *Journ. Amer. Med. Assoc.*, November 5th, 1906.
[17] Deutschmann : *Münch. med. Woch.*, May 7th, 1907.
[18] Deutschmann : British Medical Journal, 1908, p. 737.

described before the British Medical Association two modifications of his serum, prepared from horses, for human use :

1. Deutschmann's serum, consisting of the serum of horses fed on yeast and trikresol; this serum is obtainable in 2 c.cm. bottles.

2. Deutschmann's Serum E, which is the active serum precipitated and redissolved. It is of double the concentration of (1), and possesses the merit of never producing serum sickness.

Dosage : In children 1 to 2 c.cm. is given as a dose. In adults 2, 4, 6, or 8 c.cm. should be given two or three times weekly (occasionally more often), regulating the dose by the effect on temperature (which rises after an overdose) and clinical symptoms of the local disease.

It is given as an intramuscular injection; but, if this is for any reason impracticable, has good effect when administered per rectum.

As a curative measure Deutschmann has used his serum with good results in perforating wounds, hypopyon keratitis, post-operative infections, recurrent iritis, acute purulent irido-cyclitis, gonococcal infections, and in a case of sympathetic ophthalmia, in which, in spite of the fact that the exciting eye was not removed, a cure was obtained. Deutschmann and Neunhardt report the cure of a case of severe metastatic panophthalmitis due to endocarditis probably of gonococcal origin.

Deutschmann's results have been corroborated by many workers. Caravaria of New York has had success in septic wounds, rheumatic iritis, acute purulent irido-cyclitis, ulceration of the cornea following a burn, phlyctenular pannus, and post-operative irido-cyclitis in a patient suffering from diabetes. Cases of hypopyon keratitis healed rapidly with very slight opacity remaining. Darier[8] reports favourably, as does Schwalbach[20] in recording a severe case of inflammatory exophthalmos cured rapidly by the use of Deutschmann's serum; two relapses occurred, but each disappeared after a further dose of serum.

Von Hippel[21] has treated forty cases and gives his results. He obtained success in ulcus serpens, iritis plastica, and non-tuberculous iritis serosa. On the other hand, he found it useless in severe affections of the vitreous body. In the hands of certain other workers, however, no good has resulted from the use of Deutschmann's serum. Schmidt Rempler has been able to see no curative effect in severe hypopyon keratitis, and Napp[22] of Berlin has likewise obtained no success with this treatment. W. Zimmermann[23] lays great stress on the importance of using Deutschmann's serum early, and demonstrates its use in pneumococcal ulcers, iritis, and post-operative infections. He also

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[20] Schwalbach : *Freien Vereinigung de Chirurgen,* Berlin, March, 1908.

[21] Von Hippel : *Deut. med. Woch.,* November 27th, 1908.

[22] Napp : *Ophthalmoscope,* 1908, p. 1,000.

[23] W. Zimmermann : *Die ophthal. Klinik,* 1908, No. 13.

advocates its use as a prophylactic against infection in perforating wounds and in operations on decrepit individuals, etc.

We see, then, that for a great variety of infections the use of Deutschmann's serum is upheld by many authors, but the nature of its action is unknown. The more likely explanation is that of Neisser and Guerrin, who consider it a leuco-stimulant.

Non-specific antitoxic serums are, then, of great value in eye infections, and their action corresponds probably with the action of normal horse serum, the use of which was advocated by Horder.

Römer's Jequiritol Serum.

Römer employs a serum to counteract the excessive reaction which follows the use of jequiritol for pannus. The serum may be given subcutaneously or locally into the conjunctiva; the former method is preferable. Also, to avoid the occurrence of dacryocystitis from jequiritol, the serum may be instilled into the lacrymal sac before using the drug.

Coley's Fluid.

Cases of sarcoma of the antrum and orbit can be benefited by Coley's fluid containing the toxins of streptococcus and *Bacillus prodigiosus,* and cases treated thus have been recorded by Jack, de Schweinitz, Bandoux, Coley, and Weeks.

Syphilis.

The relation of serum treatment to syphilis of the eye must be mentioned. No antisyphilitic serums of any clinical value have been obtained up to the present time. The Wassermann serum test and its modifications have a close relation to the general treatment of syphilis by mercury, etc., in regulating the duration of such treatment.

Sympathetic Ophthalmia.

There is some promise of success in the treatment of this condition by means of serum. Santucci[25] has reported some experiments on animals, as the result of which he believes that there is a cytotoxin for the organ of vision which by its appearance may cause the attack of sympathetic ophthalmia. Three series of experiments were carried out :—

1. One eye of an animal was enucleated and an emulsion prepared from it, which was injected under the skin and conjunctiva of another animal, A.
2. The serum of the animal A was inoculated into another individual of the same species.
3. One eye of an animal was badly damaged and allowed to shrink, then enucleated, and emulsion injected under the skin and conjunctiva.

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[25] Santucci : *Rivista Ital. de Ottalmologia,* September, 1906.

Results.—1. After three injections, keratitis, iritis, and three nodules of exudate in the anterior chamber were set up. These gradually disappeared and the eye returned to its normal condition. Another injection was made and the other eye was attacked by similar inflammation. No result followed the subconjunctival injection.

2. Experiment negative.

3. Intense iritis set in after the subconjunctival injection, pointing to the development of an autocytotoxin.

These experiments would show that there is formed in a damaged eye a toxin which is absorbed into the blood stream and gives rise to the formation of antitoxin. If the amount of toxin is small the antitoxin formed can deal with it, but if it is large and the amount of antitoxin formed small, an attack of inflammation in the uninjured eye may be caused. If, therefore, an animal be immunized by injecting into it eye emulsion, the serum of this animal may be used as a curative agent in cases of sympathetic ophthalmia.