time, when he told me that an attack was coming on. His colour did not change, but he leant forward, resting his elbows on his knees, and was evidently considerably distressed. I again felt his pulse and found it distinctly smaller, and instead of beating 80 it was only beating 60. I asked him to take his coat off, and on taking his pressure found it had risen from 125 mm. to 145 mm.

This observation, to my mind, at once settled the question of diagnosis. This was a true angina pectoris minor, a condition I described years ago. My interpretation of the phenomena is that the state of the vessels, as revealed to the finger, and shown by the rise in the haemomanometer pressure from 125 to 145 mm., indicated that a hypertonic spasm had taken place; that this increased the pressure in the aorta, and thereby perturbed the heart, which, instead of being accelerated, was slowed down from 80 to 60 beats per minute. To speak of this as a neurosis almost always suggests that the symptoms are either fanciful or that the condition is mainly determined by a mental and central influence; and no men more warmly resent this view when applied to themselves than medical men do. Personally I interpret the phenomena as being determined by peripheral conditions and not by central ones. To me this is a vessel irritability, and its successful treatment lies in the removal of the cause keeping up that irritability. In this particular case the cause was probably tobacco.

Again I point out to you that the variation in haemomanometer reading was due to change in the vessel wall (the brachial artery); a mere increase of heart power represented by 20 mm. would not give rise to such symptoms. My patient could, I doubt not, stimulate his heart by cycling above that and without discomfort, but the moment a general angiospasm occurs the symptoms appear. It is always a question whether or no the coronary arteries participate in the spasm, but the practical fact is that if you counteract the general angiospasm the symptoms disappear. Your patient is cured when you have removed the tendency to this hypertonic spasm. The foundation fact is the vessel spasm, for the moment you relieve that the symptoms disappear; the spasm affects the brachial as well as the smaller arteries, and, I repeat, the haemomanometer gives you the record of it, when the vessels are normal as well as when they are sclerosed.

There are always the three factors to keep in mind—namely, blood pressure, structural change in the vessel, and hypertonus. There is no escape from the exercise of discretion and judgement when using this instrument, and those are the points; the significance and value of each have to be determined in every individual case. The instrument has opened no royal road to the determination of the all-important question of heart power, as we are called upon to judge of it clinically.

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UNDER the will of the late Mr. Alfred Bell of Newcastle, who died on November 25th last, the Royal Victoria Infirmary, Newcastle, and the Hull Royal Infirmary each receive a sum of £2,000, and Ingham Infirmary, South Shields, one of £1,000.

THE Yellow Fever Bureau *Bulletin* for January, 1912, contains a reprint of an interesting report on the yellow fever in Mérida by Dr. Mario G. Lebrede, Director of the Duque Laboratory of Investigations, Havana. After careful and prolonged study, Dr. Lebrede has come to the conclusion that there is an endemic focus of yellow fever in the Gulf of Mexico, that Mérida is to be considered as a seriously infected locality, and that because of the close contact, the lack of effective defences, and the short time since the last outbreak, Campeche is to be considered as suspicious. He believes also that persons coming from Quintana Roo should be watched by the Mexican sanitary authorities, who, by a careful study of the fevers affecting soldiers, might gain some insight into the histories of the past epidemics occurring at Mérida and Campeche. He recommends that Vera Cruz, and other ports in the Gulf where cases may arrive in the infective state, should establish a sanitary organization to observe and study all suspicious cases in order finally to determine the best methods for the complete and final eradication of the disease.

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

THE MIDDLEMORE PRIZE ESSAY, BRITISH MEDICAL ASSOCIATION, 1911.

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(Continued from page 592.)

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 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 affect 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 lacrymal sac.

The lacrymal 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 lacrymal 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 lacrymal sac is well supplied with blood, and infections react well to vaccine treatment.

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

W. T., aged 66. Right eye amblyopic. Attended first November, 1905, with left cataract and suppurating lacrymal 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 = 3.

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 lacrimal 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. Allen¹ 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 (+3 D.) 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.

Mayou³ 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 sties associated with phlyctenules and corneal ulcers, in one of which a complete cure was obtained; in the other three there was temporary relief, followed by recurrence. A case with boils and sties 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 sties and recurrent tarsal cysts cured by one inoculation.

Doync² 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. Allen¹ 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 15th, 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 20; tension full. Smears and cultures of gonococci obtained.

D

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 form.

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 of two days' duration, and the cornea was steamy. A large ulcer appeared at 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 new-born infants with doses of ½ to 1 million of vaccine; the disease became cured in each case without infection of the cornea.

Rubrecht⁴ 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 was no corneal ulceration, but when the conjunctivitis was well three attacks of peripheral keratitis occurred, extending over a period of one month. Weeks¹³ recommends doses of 2½ to 50 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.

Allen¹ 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. Mackay⁵ 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.

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 Edwards⁷ 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 bichloride was carried out.

Mayou⁸ 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 lacrimal 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. Lacrymal 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, on the 20th the ulcer had healed, and on the 22nd the eye was quiet. The discharge from the lacrymal sac became clear.

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*.—Stephenson⁹ 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:

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 Schweinitz¹⁴ 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 accessory 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—con-

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 (Adams¹²), 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,⁸ 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. Weeks¹³ 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 down 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.

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.

junctional 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) autoinoculation. 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.—Maddox¹⁰ 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.

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 $\frac{5}{60}$ was obtained.

I give the details of treatment and opsonic indices in the above chart.

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

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A CASE OF ADDISON'S DISEASE TREATED WITH TUBERCULIN.*

BY

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A WELL-EDUCATED and intelligent lady, aged 34, unmarried, consulted me in April, 1907, under the following circumstances.

Two years earlier, when in good health and having had no serious illness, she began to ail and has got gradually worse. She complained of lassitude and want of strength, whereas she was formerly fond of getting about and of occupation; said she had no appetite, but forced herself to eat. She had frequent headaches and suffered from constipation, varied during the last six months by a few attacks of diarrhoea; also had backaches (lumbar), which have been more frequent since last winter. She suffers from post-nasal catarrh, and the throat is sometimes sore, but she has no cough. Used to sing much, but has gradually discontinued it during the last two years; formerly could cycle 20 miles, but gave this up last summer. The hands and legs had been

* A paper read at Bath, April 28th, 1909, at the meeting of the Bath and Bristol Branch of the British Medical Association. Postscript added May 1st, 1911, and March 7th, 1912.