more or less severe, commences as soon as rotation occurs. The severity of the pain depends on the rapidity and extent of the rotation. In the case we have just recorded the rotation was very rapid and extensive and the pain correspondingly great. If rotation is very gradual the pain may be very slight and in some cases absent altogether. This explains those cases of adolescent coxa vara where one finds well-marked deformity with no history of pain. The extent of the rotation on the vertical diameter is estimated by the extent of the curve of the lower margin of the faint shadow of the separated surface of the epiphysis as shown in the diagram (Fig. 1, S.E.). The greater the rotation the nearer the arc of a circle this curve becomes, whilst in lesser degrees the curve is elliptical. The amount of antero-posterior curve, or rather deformity, in the neck of the femur depends on the amount of rotation of the separated epiphysis on its vertical axis.

The pathological change, which occurs at the epiphyseal line, is at present quite unknown. The skiagrams show no bony change. The disease apparently only occurs in the poorer classes, and does not appear to be due to any particular occupation. The reason why this condition is only demonstrable at the acetabular epiphysis of the femur is probably explained by the architecture of the joint. The weight of the body is transmitted through the pelvis, and the closely fitting bony cup of the acetabulum causes that pressure to act directly on the epiphysis. No other joint has this conformation and a corresponding pressure to bear.

In conclusion, we would urge the need of immediately skiagraphing all cases of slight limp or aching about the hip-joint in patients between about 12 and 18 years of age in order to detect the condition of separation in its earliest stage, and before the case passes into our second class.

Our best thanks are due to Dr. A. H. Greg of the x ray department of St. Thomas's Hospital for his assistance and for the use of his collection of skiagrams.

THE OPSONIC INDEX AND AGGLUTINATION IN CEREBRO-SPINAL MENINGITIS.

By ALICE TAYLOR, L.R.C.P. IREL.

THE value of the opsonic index in the diagnosis and treatment of various forms of infections having been demonstrated by Sir A. E. Wright, it was thought probable that it might also prove of service in cases of cerebro-spinal meningitis. The opportunity for such investigation presented itself at the Children's Hospital, Great Ormond-street, London, for in the early months of this year eight cases of cerebro-spinal meningitis were admitted to the hospital. The following table gives shortly the important features of these cases:—

Table of Eight Cases of Cerebro-spinal meningitis.

Case.	Age.	Rash.	Lumbar puncture.	Organism isolated in culture.	Result.
1	13 weeks.	3 crops: (1) petechial; (2) erythematous; (3) elevated spots and face scars.	*	Gram-negative diplococcus.	Death.
2	7 months.	Purpuric.	Turbid.	Ditto.	"
3	3 months.	Vesicular.	No fluid obtained*	No growth.	"
4	4 years.	Erythema.	Cloudy fluid.	? Few intracellular cocci.	Recovery.
5	2 years, 5 months.	—	Cloudy fluid under pressure.	No growth, very few intracellular diplococci.	"
6	2 years, 8 months.	—	Cloudy fluid.	Gram-negative diplococcus.	"
7	2 years, 5 months.	—	"	1 colony; no further growth.	—
8	1 year, 5 months.	Before admission.	Clear fluid.	Gram-negative diplococcus.	Convalescence.

* At the necropsy hydrocephalus, meningitis of vertex, little of base and sticky exudate on the posterior surface of the cord.

It will be seen that all these cases were proved, either by lumbar puncture or post mortem, to be cases of cerebro-spinal meningitis.

Method of investigation.—The method of investigating the opsonic index was that described by Sir A. E. Wright. The emulsion throughout was made from a culture on blood serum of meningococci isolated from the cerebro-spinal fluid of one or other of the patients. These meningococci were all Gram-negative. The emulsion was used alive. The stain was a strong solution of toluidin blue made up with sodium bicarbonate; this gave satisfactory results. The leucocytes were washed once in a solution of sodium citrate in sodium chloride and after that twice again in sodium chloride 0.9 per cent. The emulsion was also made up with 0.9 per cent. sodium chloride.¹ Considerable difficulty was, however, encountered in dealing with the organisms, for it was found that the older cultures underwent rapid degeneration during incubation. In the later cases in which a seven to ten hours' culture was used this degeneration did not occur and in these cases a very high index has been noted. Degeneration was shown by the swelling and irregular staining of the coccus and subsequently by its disintegration into a granular detritus.

The difficulty of working with an organism which so rapidly undergoes disintegration has also been noted by Davis in America and led to the (provisional) conclusion that the opsonic index was not delicate enough to be of any service in diagnosis or treatment.² In the earlier cases, where older cultures were used, the serum of the controls showed a high opsonic power; in the later cases, when a young culture was employed, the opsonic power shown by the controls was extremely small; whereas the serum from cases of meningitis showed enormously increased opsonic power, and the average number of organisms per leucocyte differed as much as 18 to 1.8, the incubation period being eight minutes in this case. The normal opsonic power appears unable to act until, according to Flexner,³ autolytic enzymes are being set free. The thickness of the emulsion is also an important factor to regulate, for if the emulsion be too thick the number of organisms in the leucocytes with the patient's serum may become uncountable.

Whilst observing the opsonic index it was noted in the later cases that agglutination was a marked feature. This has been observed after an incubation of ten minutes in a dilution of 1 in 3. The controls throughout the whole series never showed any agglutination, nor was it present in slides without serum, where the emulsion was incubated with 1 part each of washed leucocytes and saline solution. It was also tested against tuberculous meningitis and typhoid fever; in neither case was agglutination present. In testing for agglutination alone a thick emulsion is to be preferred. The clumps are then very much larger and are spread along the edges of the smear in the same manner as the leucocytes, and the contrast between the control slide, thickly strewn with pairs and some tetrads of meningococci, and the patient's slide, almost or quite free from loose cocci but with clumps along the edges, is a striking feature.

As a result of these observations the following questions suggest themselves: 1. Is this high index pathognomonic of the disease? 2. Is it present in all forms of meningococcal meningitis? 3. Will it be possible, by the difference in the opsonic index or agglutination associated with it, to distinguish between the various forms of meningococci which have been shown by observers to give slight cultural and staining differences? Some attempt will be made to answer these questions in part, but a complete answer can only be obtained by further and more extensive investigations than it has been possible at present to carry out.

The following charts show the results obtained. Charts 6 and 7, and Chart 4 above Index 2, are marked $\frac{1}{10}$ of the scale of the early charts. In Chart 4 the opsonic index against the tubercle bacillus is also recorded with dotted lines. The presence of agglutination in the opsonic index slide is designated by +.

CASE 1.—The patient was a female, aged 13 weeks, who was taken ill seven days previously. The opsonic index was in the early stages low, becoming higher towards the end of

¹ This strength of sodium chloride solution has been used throughout these experiments, for it was found on using emulsions made up with 0.9 per cent. sodium chloride and 1.5 per cent. sodium chloride concurrently, almost exactly the same opsonic index was obtained.

² David J. Davis: Studies in Meningococcal Infection, Journal of Infectious Diseases, vol. ii., 1935.

³ Contributions to the Biology of Diplococcus Intracellularis, by Dr. Simon Flexner, Journal of Experimental Medicine, March 14th, 1907.

the disease. In this case a vaccine was given which may have had some influence on the index.

CHART 1.

Case 1. Admitted on the seventh day of illness.

CASE 2.—The patient, a male, aged seven months, was taken ill five days previously and died on the eighth day of his illness. The index taken on the day of death was normal.

CASE 3.—The patient, a male, aged three months, was admitted in the third week of his illness. The opsonic index was only taken three times; on the second occasion it was high for the method then used. On examining a slide kept a tendency to form groups can be distinguished.

CHARTS 2 AND 3.

Cases 2 and 3. Admitted respectively on the fifth day and third week of illness.

CASE 4.—The patient, a female, aged four years, was admitted on the third day of her illness. The temperature remained continuously high for four weeks. The opsonic index to meningococcus was high on the eighth day of the illness. The opsonic index in this case having been taken by the two modifications used in these observations shows typically the difference in the index resulting from using a young culture. The index on this chart, after reaching 2, is marked $\frac{1}{10}$ of the size. It also shows the tubercle index remaining steady within normal variations.

CHART 4.

Case 4. Admitted on the third day of illness.

CASE 5.—The patient, a female, aged two years and five months, was taken ill five days previously. The temperature remained high for six weeks. The opsonic index was at first 1.2 and towards the end of the illness rose considerably.

CHART 5.

Case 5. Admitted on the fifth day of illness.

CASE 6.—The patient was a female, aged two years and

CHART 6.

Case 6. Admitted on the fourteenth day of illness.

eight months. The opsonic index was at first low; it rose rapidly and remained high during the whole course of the disease, showing considerable fluctuations. Agglutination was noted first in this case on the twenty-eighth day of the illness and has since been continuously present. Convalescence set in in the sixth week of the illness. This patient was treated with two injections of Ruppel's serum. A considerable rise in the index followed each injection and agglutination was first noted after the second injection; there was at the same time also marked improvement in the general symptoms. On April 9th, the fortieth day of illness, the patient sat up and a week later appeared perfectly well. There was still, three weeks later, marked agglutination and the opsonic index fluctuated somewhat above the normal.

CASE 7.—The patient, a female, aged two years and five months, was admitted in the sixth week of illness. The rash appeared five weeks before and there was head retraction three weeks before; she was very wasted. The opsonic index, taken after admission, was above normal and a marked tendency to agglutination was present. This case had also received one injection of Ruppel's serum; eight hours afterwards the index was two and a half times higher, the temperature became normal, and the general symptoms markedly improved.

CASE 8.—The patient, a female, aged one year and five months, was admitted in the fifth week of her illness. There were rash and head retraction three weeks before. The opsonic index was 12·2 and agglutination was present.

CHARTS 7 AND 8.

Cases 7 and 8. Admitted on the sixth and fifth weeks of illness respectively.

In Cases 1 to 5 inclusive the opsonic index was taken with cultures from 17 to 24 hours' old, and an incubation period from 15 to 20 minutes was used. It was necessary to count the degenerate forms and granules within the leucocytes, a matter of some difficulty, and one which could not be considered altogether satisfactory. In Cases 6, 7, and 8 an emulsion⁴ from a young culture from seven to 10 hours old was used. The resulting smears became as easy to count as those of other organisms. Chart 4 shows typically the difference obtained by working with a young culture, for whereas with old cultures an index of from 1·3 to 1·8 was obtained, with a young culture an index of 13 was obtained.

Agglutination associated with the opsonic index was first noted with Case 6, on the twenty-eighth day of the illness, and when the accompanying opsonic index was low. It has been similarly noted by Houston and Rankin in the Belfast epidemic.⁵ It was observed first after the second injection of Ruppel's antitoxin serum obtained from a horse immunised by cultures of meningococci rendered pathogenic to mice and guinea-pigs by culture on special media. Agglutination was also observed on taking the opsonic index after admission to hospital in Case 7 in the sixth week of the illness and in Case 8 in the fifth week of the illness.

In the paper already referred to by Davis he states that on testing the agglutination (by the ordinary Widal method) normal serum never showed any agglutination even undiluted. Gordon⁶ mentions two difficulties against employing agglutination diagnostically in cerebro-spinal meningitis by

Widal's method: (a) the impossibility with the meningococcus to make emulsions absolutely free from all aggregations; and (b) the delay that occurs before agglutination takes place. By the method in conjunction with the opsonic index these difficulties appear to be overcome: (a) aggregations of cocci have sometimes been noticed in the preparatory smear to test the thickness of the emulsion but this has ceased to be heeded, since in every case after incubation in the liquid medium of serum and washed leucocytes the aggregations spontaneously disintegrate and no aggregations are ever found in the slides of the controls or the patients unless agglutination is present; and (b) in these observations ten minutes have been the time limit. The dilution of 1 in 3 might be suggested as too low; it has, however, already stood the test of many observations. Dilutions of 1 in 12 and 1 in 36 have so far given no result in ten minutes.

A suggestion has been made that the clumps might be formed in drawing out the smear: (1) they would not in that case be invariably present with an altered opsonic index; (2) they can be observed if one part each of agglutinating serum, an emulsion of the strain of meningococcus causing it, and of saline solution are incubated ten minutes, dropped on to a slide and allowed to dry without being drawn out; and (3) on testing the result of using an obviously over-thick emulsion it was found the micrococci tended to be drawn out in lines round the cells and the edges of the smear. From the limited observations that follow it would appear probable that this agglutination is specific to the strain of meningococcus eliciting it and gains corroboration by the accompanying opsonic index.

Next the agglutination reaction of the serum of Cases 6 and 7 was tested—first, against the organisms isolated from the cerebro-spinal fluid of Cases 2, 6, and 8, and in every case they respectively gave a high opsonic index and interagglutination. Secondly, against two strains of organisms derived from Belfast—Belfast B. from cerebro-spinal fluid; and Belfast M. from blood. In these two striking differences appear: 1. The serum of Cases 6 and 7 against either Belfast organism gives a normal index and no agglutination. 2. With serum of normal blood against Belfast B. a high opsonic power against a young culture is shown, and the average number of organisms per leucocyte in two of the observations, instead of being limited to three, were 18 and 44 respectively, whereas the serum of normal blood against young cultures of Belfast M. showed a very low opsonic power, as noted against the London organisms. And in this case this low opsonic power has not been excited to action by the serum of Cases 6 and 7.⁷

Conclusions.—From the above observations it is now possible in part to answer the questions set forth at the beginning of this paper.

1. Is a high opsonic index pathognomonic of the disease? It appears possible from these eight cases to obtain a definite opsonic index in cerebro-spinal meningitis, either working with an old or a young culture. A high index has been shown to be present in all the cases examined. This index may under certain conditions attain a very high altitude. In Case 4 it is seen that the tubercle index at the same time runs its usual course. Two or three cases of tuberculous meningitis tested during these observations gave within two or three days a tuberculous opsonic index above the normal and did not give a high index to this meningococcus. This high index appears to be due in these cases to the characteristic feature that normal serum has scarcely any opsonic power against a young culture of this organism. It is therefore probable that a high opsonic index is pathognomonic of the disease.

2. Is a high opsonic index diagnostic in all forms of meningococcal meningitis? The results obtained on testing the serum of the present series of cases against the Belfast organisms⁸ show that a high index is not always obtained with different strains of growth and that a negative result may occur. So that although a high index indicates the presence of the disease a normal index does not negative its presence.

3. Will it be possible by the difference in the opsonic index or agglutination associated with it to distinguish

⁴ The emulsion must not be allowed to stand.

⁵ THE LANCET, May 4th, 1907, p. 1213.

⁶ Report to the Local Government Board on the Micrococcus of E.C.M., Dr. M. H. Gordon.

⁷ Sera since received from Belfast from three cases of chronic cerebro-spinal meningitis severally give a high index and agglutination against Belfast M. Against Belfast B. and the organism from Case 6 these sera give no agglutination and a normal index.

⁸ And the Belfast serum against the Belfast and London organisms.

between the various forms of meningococci which have been shown by observers to give slight cultural and staining differences? Among the organisms tested in these observations it appears possible to differentiate three strains or variations of organisms—Belfast B. from Belfast M. and the present London organisms by the high opsonic power against young cultures as constantly demonstrated with normal serum; Belfast M. from Belfast B. by its very low opsonic power against young cultures as constantly demonstrated with normal serum; and Belfast M. from the present strain of London organisms by the normal index and absence of agglutination with the serum of Cases 6 and 7, the same serum giving a high index and marked agglutination reaction against the London organisms. It appears probable in order to obtain the fullest effects from a vaccine or serum treatment that the strain of organism employed in its preparation is of great importance.

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AN INVESTIGATION OF SOME OF THE MORE UNUSUAL FORMS OF ACUTE CONJUNCTIVITIS.

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THE bacteriological identification of the Koch-Weeks bacillus in 1885 and of the Morax-Axenfeld diplo-bacillus in 1896 as specific causes of conjunctivitis form important landmarks in the history of the study of this disease. The resulting types of inflammation are in most cases associated with such characteristic clinical features as to present a more or less diagnostic picture. In cases of doubt the diagnosis may be confirmed by an examination of films prepared from the discharge, the organisms having distinct morphological appearances and their cultural characteristics being rarely called for in making a diagnosis. Recently accounts of these organisms have been published by Inglis Pollock¹ and by Usher and Fraser,² whose papers dealing with the bacteriology of conjunctivitis are largely concerned with Koch-Weeks and diplo-bacillary infections and afford strong evidence that these organisms, together with the gonococcus, are responsible for the causation of the great majority of the more acute cases of the disease met with in this country. In any large clinic, however, a considerable percentage of cases of acute conjunctivitis is met with in which the clinical features would appear to present no such generally recognised relation to their etiology. The aim of the present inquiry has been the investigation of cases of this nature met with by us during a period of 15 months, including several cases of gonorrhoeal conjunctivitis, while cases of Koch-Weeks and diplo-bacillus conjunctivitis have been entirely, or almost entirely, omitted from this account, the cases encountered having been diagnosed either from clinical features or from film preparations, and no special media for the demonstration of these organisms having been employed.

TECHNIQUE.

In every instance two or more film preparations were made from the discharge and a culture was taken on to some form of solid medium, in most instances blood serum. One of the film preparations was stained by Gram's method and a second film was treated by Leishman's stain, whenever a cytological examination of the exudate was considered necessary. With the exception of some cases of gonorrhoeal

infection, in which an attempt at cultivation failed, no diagnosis was made from film preparations alone. In all, 105 cases were thus examined, but a certain small proportion of these include cases in which either the Koch-Weeks or Morax-Axenfeld bacillus was, in all probability, the main factor at work and are considered here only to complete the account of the other organisms present in addition. In a few cases films and cultures were taken also from other lesions in the body when these were thought to have any bearing upon the condition of the eyes. The cases were derived mainly from the Royal London Ophthalmic Hospital; a considerably smaller number from the ophthalmic department of St. Thomas's Hospital are also included. The organisms met with were in order of frequency a diphtheroid bacillus (60 times), a white staphylococcus (28 times), the gonococcus (27 times), the staphylococcus aureus (24 times), a streptococcus (10 times), an intermediate staphylococcus (3 times), the diphtheria bacillus (twice), and an unclassified coccus (once).

The cases are grouped under the heading of the various organisms present, but since a mixed infection was frequent some overlapping is unavoidable.

GROUP 1.—STREPTOCOCCI.

There were altogether ten cases of streptococcal infection, and in each case an attempt was made to procure the full cultural characteristics of the organism; in two instances, however, owing to the additional presence of a diphtheroid bacillus the streptococcus could not be isolated. In one other case the diphtheria bacillus, and in another both albus and aureus were present in addition; the former case is considered under Group 7. In the two cases in which the streptococcus was not isolated one was a severe attack with membrane formation, the other of moderate severity only and unaccompanied by actual membrane. Five of the streptococci isolated were classed on the evidence of Gordon's tests as the streptococcus pyogenes according to the classification of Andrewes and Horder.³ In one of these five cases, a child, aged one week, a similar organism was present also in a sloughing hæmatoma of the face, and the fact that the mother died three days after delivery, presumably from some septic condition, points to the maternal passage as the probable source of infection. One of the pyogenes cases was accompanied by the diphtheria bacillus; there was well-marked membrane formation in this case and corneal infiltration. In the remaining three cases membrane formation was present in each instance and in two cases the eye was destroyed. A different variety of streptococcus was isolated in two instances and should probably be classed with the streptococcus faecalis group. The cultural characters were almost identical in the two cases. The coccus was Gram-positive and occurred in chains of from 10 to 20. On agar slant typical streptococcal colonies were found. On jelly slant, at 22° C., no liquefaction. Litmus milk: acid, no clot. Gordon's media affected were: maltose, salicin, lactose, xylose, raffinose, arabinose, mannite, dextrose, and glycerine. Unaffected: erythrite, sorbit, and cane sugar. These media were identical in the two cases with the exception that litmus glycerine was acidified by the one organism and not by the other. In neutral red broth, anaerobically, a green fluorescence was produced by one organism only.

The occurrence of this same organism, of unusual characters, is of the more interest since the patients were brothers who attended the hospital at about the same time, and there is little doubt that they infected each other. Of these brothers one lost his eye; the other had only a mild attack of conjunctivitis which was associated with the onset of measles and which cleared up rapidly, affording a good example of the difference of personal resistance to the same organism. In another case, occurring in a small child with severe conjunctivitis accompanied by membrane formation, a streptococcus of unusual cultural characteristics was obtained. The organism was Gram-positive and occurred in very long chains. It formed very delicate colonies on agar and grew on jelly without liquefying it. It was transferred into a large number of Gordon's media and, with the exception of sorbit, acidified all of them. It produced green fluorescence in neutral red broth anaerobically. The organism was inoculated into the peritoneal cavity of a

¹ Inglis Pollock: The Bacteriology of Conjunctivitis, Transactions of the Ophthalmological Society of the United Kingdom, vol. xxv., 1905.
² C. H. Usher and Henry Fraser: An Analysis of a Series of Conjunctivitis Cases seen in Aberdeen.

³ F. W. Andrewes and J. T. Horder: THE LANCET, Sept. 15th, 1906 p. 708.