The Occurrence of Organisms in the Blood and Cerebro-spinal Fluid in Mental Diseases. (1)

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IN the mass of conflicting evidence which has accumulated in recent years as to whether organisms are the exciting factor in the production of certain insanities, I have found it difficult to discriminate between cause and effect. Is the organism or group of organisms the specific pathogenesis of certain insanities or merely a bacteræmia secondary to the psychosis?

My own observations, which have extended over nearly three years, have, if anything, increased this difficulty, and yet have convinced me that there is a great field for further investigation.

Drs. Ford Robertson, McRae, and Jeffrey were the first in this country to state that a diphtheroid bacillus was the cause of general paralysis of the insane, and this bacillus was named *Bacillus paralyticans brevis* and *longus*, being of two types. In later publications Ford Robertson and McRae (1) demonstrated that the probable site of the infective focus was the genito-urinary and lower alimentary canal in tabes, and chiefly in the mucous membrane of the mouth and naso-pharynx in general paralysis. They state that they have also been successful in the treatment of these cases with a polyvalent serum.

Eyre and Flashman (2) have shown that diphtheroid organisms have been isolated in the mucous membrane of the throat of the sane as well as the insane, also in other insanities besides general paralysis.

Lewis Bruce (3), investigating other types of insanity, has shown that in acute insanities with excitement there is a hyper-leucocytosis with an increased polynuclear percentage, and that specific agglutinins are present in the blood-serum of cases of mania to certain types of streptococci rarely present in the healthy sane; at the same time there is an absence in 60 *per cent.* of maniacal patients of a normal protective agglutinin to certain streptococci. Bruce found that the *Bacillus coli* in the intestinal tract was largely replaced by streptococci, these also being excreted in the urine, and he suggests that the toxins formed in the bowel by this overgrowth, and possibly the organisms themselves, as he has succeeded in isolating streptococci from the

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blood of some of these insanities, are absorbed into the general circulation and act as a cerebral poison.

Bianchi (4) has isolated a bacillus, and members of his clinic cocci in the blood and meninges of acute delirious insanity, and yet maintains "that it remains to be shown whether such organisms are really pathogenic or aggravating concomitants."

It seemed to me, if an organism existed in connection with general paralysis, and was circulating or invaded the general circulation during a seizure, that although apparently more difficult, the isolation from the blood or cerebro-spinal fluid was of the greatest importance to obtain reliable evidence as to, firstly, whether there was an organism constantly associated with general paralysis, secondly, whether the organism was morphologically identical in each case.

I have not succeeded in achieving my object. I have isolated a bacillus in general paralysis, but also an identical bacillus in other acute insanities. To prevent confusion I shall call this bacillus "Organism A."

During life, from twenty-five cases of general paralysis I isolated an identical diphtheroid bacillus in pure culture in eight from the blood, and in three of these eight from the cerebro-spinal fluid. In four cases I reduplicated my results twice and in one case three times from the blood. Briefly, in 32 *per cent.* of general paralysis I isolated organism A from the blood, and in 7·5 *per cent.* from the cerebro-spinal fluid, as many lumbar punctures were performed.

TABLE I.—*Analysis of Positive Cases of General Paralysis of Insane during Life.*

No.	Stage of disease.	Blood.	Blood-film.	C.S.F.
1	3rd	R[1]	P[2]	R
2	,,	R	P	R
3	,,	R	–	R
4	,,	R	P	–
5	,,	R	–	–
6	,,	R	–	–
7	,,	R	–	–
8	2nd	R	–	–

R, recovery of organism A; P, bacillus present in blood-film; –, negative; [1], recovery of organism from spleen of mouse by inoculation; [2], see Fig. 1.

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The blood was withdrawn as early as possible after the commencement of a seizure, and it was especially in the early specimens that I succeeded in isolating A from the cerebro-spinal fluid. It is interesting to note that in only two of those three cases did I succeed in isolating A from the cerebro-spinal fluid *post mortem*. In the negative as well as positive cases I repeated the examination two or three times.

From twenty-seven *post-mortems* of general paralysis I succeeded in eight cases, or 29·6 *per cent.*, in isolating a pure culture of organism A. Fifteen of these were examined during life, five being positive, and in one of these cases (see Table II) *Bacillus paralyticans brevis* only was recovered from the cerebro-spinal fluid associated with another bacillus. In only one case did I isolate A from the heart blood.

The *Bacillus paralyticans brevis* was recovered three times or 11·1 *per cent.* from the cerebro-spinal fluid, and twice or 7·4 *per cent.* from the bronchi. On these two occasions organism A was recovered in pure culture from the cerebro-spinal fluid. I have not succeeded in isolating either the *Bacillus paralyticans brevis* or *longus* from the blood or cerebro-spinal fluid during life, and have been equally unsuccessful in isolating diphtheroid bacilli from the urine *ante-mortem*, and urine, intestinal mucous membrane and bronchial glands *post mortem*.

TABLE II.—*Analysis of* Post-Mortem *in General Paralysis.*

Positive.	Negative.	C.S.F.	H.B.	Lungs.	Bronchus.	Bronchial gland.	Intestines.	Urine.	Examination during life.
1	...	A	–	–	B.P.B.	o	o	–	o
1	...	–	A	–	–	o	o	–	o
1	...	A	–	–	–	o	–	–	o
1	...	A	o	–	B.P.B.	–	–	–	+ r
1	...	A	–	–	–	o	o	o	+
1	...	A	o	–	–	o	–	o	o
1	...	A	–	–	–	o	o	–	+ r
1	...	A	o	–	–	–	–	–	+ r
...	1	B.P.B.	–	–	–	o	–	–	+ r
...	1	–	–	–	–	o	o	–	+
...	1	–	–	–	–	o	o	–	+
...	1	–	–	–	–	o	–	o	+ r
...	1	–	–	–	–	–	–	o	+
...	1	–	–	–	–	o	–	o	+

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TABLE II—*continued.*

Positive.	Negative.	C.S.F.	H.B.	Lungs.	Bronchus.	Bronchial gland.	Intestines.	Urine.	Examination during life.
...	1	–	–	–	–	0	0	–	+
...	1	–	–	–	–	–	–	0	0
...	1	–	–	–	–	–	–	0	0
...	1	–	0	–	–	0	–	0	0
...	1	–	0	–	–	0	0	0	+
...	1	–	0	–	–	–	–	–	0
...	1	–	–	–	–	0	0	0	+
...	1	–	–	–	–	0	0	0	0
...	1	–	–	–	–	0	0	–	0
...	1	–	–	–	–	0	0	0	0
...	1	–	–	–	–	0	0	0	+
...	1	B.P.B.	–	–	–	0	0	0	+
...	1	B.P.B.	–	–	–	0	0	0	0
–	—								—
8	19								15

A, organism A; B.P.B., *Bacillus paralyticans brevis*; –, negative; 0, no examination; +, examination; r, recovery of organism A.

In conclusion, from an examination of fifty-two cases of general paralysis *ante-mortem* and *post mortem* I isolated an identical organism in sixteen of them, or 30·7 *per cent.*, and in five cases, or 9·7 *per cent.*, *post mortem* the *Bacillus paralyticans brevis* of Ford Robertson was recovered. Five of these general paralytics were females, and in only one *post mortem* I isolated A from the cerebro-spinal fluid. This woman was pregnant; the child was born alive at about eight months, with no signs of congenital syphilis, and lived a few hours. No diphtheroid organisms were isolated from the child, and the microscopical appearances of the brain were those of a normal fœtus. The only other living child presented some stigmata of congenital syphilis. Sections of the brain of all *post-mortems* were typical of general paralysis.

From twenty-nine cases of other insanities, I isolated organism A from the blood in seven out of twenty cases of delirious insanity, or 35 *per cent.* The twenty-first case of delirious insanity was suffering from enteric fever and the specific bacillus was isolated from the blood twice. All these

patients were acutely ill with rapid pulse, subnormal or raised temperature, and often a hyperleucocytosis. The temperature on admission usually was above normal; the extreme "ill look" of the patient was very obvious.

In many of the cases the cerebro-spinal fluid was examined bacteriologically with negative results, both for organisms and increase of lymphocytes.

I had no opportunity of making *post-mortems* in any of these seven cases.

The blood from four normal male controls proved sterile.

TABLE III.—*Analysis of Bacteriological Examination of Blood in other Insanities.*

Type.	No.	Positive.	Organism.	Negative.	P.M.
Senile insanity with seizures	4	—	—	4	Negative.
Delirious insanity[1] . .	20	7	Organism A	13	0
„ „ typhoid[x] .	1	1	*B. typhosus abdominalis*	—	0
Excited dementia[2] . .	1	1	Streptothrix*		C.S.F. streptothrix.
Dementia præcox . .	1	—	—	1	0
Delusional insanity . .	1	—	—	1	0
Acute cerebral softening .	1	—	—	1	Negative.
Normal controls . . .	4	—	—	4	0

0, No examination. [x], See Fig. 2. *, Associated with a delicate diplococcus. See Fig. 4. [1], Four of these delirious insanities were young women with symptoms of chorea. In one case in particular, a girl, æt. 16, the cause of her insanity being acute rheumatic fever, her condition was such as to give very little hope of her recovery. The blood was withdrawn a few hours after admission, and in the broth culture there were two organisms, A and a delicately growing diplococcus which might have been the *Micrococcus rheumaticus*; unfortunately I lost it at the second subculture. [2], The patient, a male, although over the usual age for general paralysis, clinically resembled a rapidly progressing one closely. He was so restless that an anæsthetic was necessary both for lumbar puncture and withdrawal of blood. The cerebro-spinal fluid was greatly increased in amount and pressure, the latter possibly due to the high blood-pressure, but no increase of lymphocytes was present and it proved sterile. In the broth culture from the blood there were two organisms, a very delicately growing streptothrix and a coccus. Both of these strains I was unable to cultivate artificially after the first subculture. Three months later I again isolated a delicately growing streptothrix from the fluid of a hæmatoma auris, this time associated with a diphtheroid bacillus of the Hoffmann variety. The former again lost at the second subculture. *Post-mortem* six months later; a streptothrix was isolated in pure culture from the cerebro-spinal fluid, this time a much coarser variety which grew vigorously for a few months and then quite suddenly died. This sequence points to more than a coincidence, and, if only such, is a very interesting one.

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Technique.—The arm at the elbow is sterilised as for operation; a compress of corrosive sublimate in spirit 1 in 1000 is applied, if in case of general paralysis, immediately on commencement of seizure, and, in case of acute insanities, soon after admission. This soak remains on half-an-hour to several hours according to the time at the disposal. A tourniquet is applied, the soak is removed, a little ether is rubbed over the exposed median basilic vein, and the needle of the syringe is immediately inserted into it; 10 c.c. of blood is withdrawn and at once emptied as equally as possible into three flasks containing 100 c.c. of Bouillon. Care must be taken to have no draught and the operation performed quickly.

For lumbar puncture the back is sterilised in the same way and all other precautions observed. With restless patients it seems to be easier to control them in bed, and if the patient is extremely restless it certainly is safer to give an anæsthetic, as even with a platinum needle there is danger of it being broken.

The syringe used for the blood is graduated to hold 10 c.c.; there are no joints, the point is ground to fit the needle accurately, and the other end drawn out and narrowed is plugged, not too tightly, with cotton-wool, and over this rubber tubing is slipped for suction if necessary. The whole syringe is enclosed in a glass tube plugged at the ends with wool. It is sterilised by hot air raising the temperature to 175 C°.

For lumbar puncture, platinum needles four inches long are conveniently sterilised by hot air in test-tubes, and again, if suction is necessary, Burroughs Wellcome & Co.'s all-glass hypodermic syringe, which has been sterilised in test-tubes by hot air, can be inserted into the needle and suction applied by the withdrawal of the piston. The fluid is collected into sterile centrifuge tubes.

Blood-films are made as soon as possible, the lobe of the ear is gently cleaned with water and ether, and films are made on clean slides or long cover-glasses 1½ by ½ in. with cigarette-paper, then stained with either Jenner or Leishman's stain. The broth flasks are incubated at 37° C. for forty-eight hours, hanging-drop preparations are then made, and also plate-cultures of agar or bynohæmoglobin agar 5 *per cent.* If there is a growth in the broth it is always very slight, and in the H. D. will perhaps show a very few small clumps of bacilli.

It is extremely difficult to subculture from the broth, and I have often made two or three plates from one flask, never using less than 1 c.c. of the broth for plating, which I collect in a sterile pipette, and possibly only one of these plates will have a single colony. Subcultured on agar the growth will be feeble for one or two subcultures at short intervals.

At *post-mortems* the brain is removed from the skull, the surface over the third ventricle is seared with a red-hot iron, a sterile pipette is inserted into the ventricle, and 5 c.c. of cerebro-spinal fluid is withdrawn; a certain portion is emptied into broth, while the remainder is emptied into a sterile centrifuge tube. If more fluid is withdrawn the surface is again seared and a fresh pipette is used. Cultures are made on agar and broth from the centrifuge deposit in each tube, and microscopic examination is also made.

Heart blood.—The heart is exposed, the surface seared, a sterile knife is plunged into this area, and the blood is withdrawn with a sterile pipette and emptied into an agar and broth.

Bladder.—The surface is seared, an opening is made with a sterile knife, the urine is withdrawn by means of a pipette and is emptied into broth. Microscopic examination is also made.

Lung.—Pneumonic or other patch is seared, a sterile knife is used to open inner surface, a platinum loop is drawn over the part, and the material is planted on agar and broth.

Bronchus.—The upper part of the tube is seared as far as possible with the pointed end of the iron, then a platinum loop is inserted into the tube and the material planted on agar and broth.

Intestinal mucous membrane.—The surface is seared, the peritoneal and outer coats are cut, the inner coat is gently scraped with a blunt director, and the material planted in broth.

Morphology.—Organism A is a bacillus which belongs to the group of Coryne-bacterium of the diphtheria type. Most commonly a short bacillus with a central segment and somewhat pointed ends, fairly pleomorphic, varying to a long cylindrical bacillus showing two or three segments, clubbed forms and "peg-top" forms, which have a tendency to being curved. Length varies from 1–6 μ, and in thickness from 0·4–1 μ at clubbed ends. On liquid media and stained smears the bacilli group in "Chinese letters," clumps, rosettes, or they may lie parallel; occasionally long unbranched threads. In

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blood-films I have found them as single bacilli, usually showing central segment, or small groups, and often with the bacilli parallel to each other. Metachromatic granules are also invariably present in twenty-four hours in agar and bynohæmoglobin agar cultures, bipolar, or irregularly distributed, and vary in size. Compared with two strains of typical diphtheria bacilli the granules persisted longer in old cultures and were more irregular in size and distribution. It stains well with all aniline dyes, Neisser positive, Gram positive, but very easily decolourised.

Pathogenicity.—Very slightly pathogenic to mice, possibly because of the large dose given relative to the weight of the animal. The first occasion in which I isolated the organism from the blood was by inoculating a broth culture from the blood into a mouse subcutaneously; this animal was killed in six days, and organism A recovered in pure culture from the spleen. A second control mouse was left, and in two weeks it was dying with symptoms of paresis of the left side of the body. No organisms isolated, and owing to an unfortunate accident brain and spinal cord were lost. Testing pathogenicity of thirteen strains of organism A, five of them were pathogenic to mice from one to three days with a dose of 2 c.c. twenty-four hours' broth culture subcutaneously. The mice used were all about the same age, and excepting for two strains those used were over two years old. It did not prove pathogenic to rabbits and guinea-pigs, although with intra-peritoneal inoculation a definite malaise was present lasting from twenty-four to forty-eight hours. The virulence for these animals was not raised by passage through a mouse.

Cultural reactions.

Agar	Very delicate, flat greyish growth confined to streak; discrete and confluent colonies, "frosted glass" appearance.
Bynohæmoglobin agar 5 *per cent.*	
Glycerine agar 6 *per cent.*	Semi-translucent, old cultures dryish.
Agar stab	Growth in course of stab small discrete colonies, somewhat beaded appearance, not spreading.
„ plate	Very small pin-point colonies, not spreading, flat, dryish, not symmetrically round, × 50; granular appearance; periphery wavy, yellowish colour and more dense in centre.

Cultural reactions.	
Blood serum (Loeffler) . .	Grows much more feebly than on agar and not a typical growth as with *B. diphtheriæ*.
Potato alkaline	No apparent growth; fair number of involution forms, short and swollen, not nearly so pleomorphic as with *B. diphtheriæ*.
Gelatine streak and stab 22° C. .	Grows very feebly.
Broth	Clear, fine powdery or slightly flocculent deposit, sticking to tube, acid, later slightly alkaline or neutral. Trace of indol.
Nitrate broth 0·5 *per cent.* . .	As in broth, most strains gave a trace of nitrites.
Lead broth 0·1 *per cent.* . .	No apparent growth; very few strains gave trace of H_2S.
Litmus milk	No coagulation, no change, or either slightly acid or alkaline.
Glucose peptone litmus water 1 *per cent.*	Clear, powdery deposit, acid no pellicle.
Dextrose peptone litmus water 1 *per cent.*	
Saccharose peptone litmus water 1 *per cent.*	Clear, powdery deposit, acid with majority of strains.
Lactose peptone litmus water 1 *per cent.*	
Maltose peptone litmus water 1 *per cent.*	
Inuline peptone litmus water 1 *per cent.*	Clear, powdery deposit, acid or alkaline equally.
Formate peptone litmus water 0·4 *per cent.*	Clear, powdery deposit, acid.
Anaërobic broth. . . .	Grows very feebly.
,, glucose formate broth .	

Temperature.—Grows best at 35–37° C., feebly at room temperature, and easily dies at temperature above 40° C. Subcultures made after ten days at 37° C., and six weeks at 22° C. grow very feebly. Subcultures after fourteen days at 22° C. grow well.

Hiss serum water media I have not found satisfactory. Variations were continually present in the cultural reactions with the same batch of media.

As regards vaccines in treatment, these failed to make any difference, and in only one case did I obtain any reaction, *viz.*, a general paralytic, third stage, who had been having small doses of his own vaccine without any result. The dose then

was enormously increased, jumping from 8,000,000 bacilli to 110,000,000; the temperature rose (no local reason), a leucocytosis was present, and mentally he became confused, excited, and dirty in his habits. He slowly returned to his normal condition. No control inoculation of a totally different vaccine, such as staphylococci, was performed.

The opsonic index I found too variable to be able to draw any reliable conclusions.

Conclusions.—What is the pathological significance of this organism in these two mental diseases? Is it a causal factor, or is it merely a concomitant? Can we attach any pathological importance to it? Where is the source of the infective focus?

In answer to the first of these questions, if this bacillus is a cause of general paralysis and delirious insanity it is absolutely impossible to ignore the incidence of syphilis in the former, which we therefore must reckon as a predisposing agent, and this predisposing agent must of necessity have the power to give general paralysis the characteristic symptoms which are present in no other type of insanity. Syphilis as a predisposing cause in delirious insanity is a negligible quantity. Now of those two different insanities where I have isolated this bacillus, in one, *viz.*, general paralysis, we assign to the almost invariable predisposing cause of syphilis a most important place, while in the other, *viz.*, delirious insanity, the predisposing causes are acknowledged to be many and varied, and "inherited instability" will possibly be the only condition almost invariably present.

Presuming that organism A is the cause of general paralysis and delirious insanity, it would appear that the predisposing factor of syphilis is a more important factor than the causal agent in the production of the former.

Again, the percentage of cases in which I have obtained this organism in both insanities is comparatively small.

The result of the few animal experiments has not as yet been confirmatory; there is a slight pathogenicity, but the toxicity of the organism appears to be low. Vaccine treatment also did not prove satisfactory.

Therefore I do not consider that I have brought forward sufficient evidence to justify a statement that organism A is the cause of general paralysis and delirious insanity.

In answer to the second and third points raised, it is quite possible that this organism is a concomitant and probably to a certain extent an aggravating one. I obtained it only once in a second stage general paralytic, and this man ultimately progressed rapidly, otherwise it was obtained in cases well advanced where the resistive powers were extremely low, and consequently the invasion of organisms would have been easy. Exactly the same condition holds in the seven cases of delirious insanity who were acutely ill, and I have only obtained this bacillus in such cases.

In the patient suffering from post-rheumatic delirious insanity there were two organisms, and it is quite possible that the diphtheroid bacillus was secondary to the coccus. In another rapidly progressing case, that of dementia with excitement, the organisms were also mixed in the blood and hæmatoma auris. That a mixed invasion should occur points still more to the lowered resistive power of these patients.

In negative cases during life, with one or two exceptions of contamination, the blood was sterile, and *post-mortem* the heart-blood most commonly, and the cerebro-spinal fluid on several occasions, were also sterile.

How can the incidence of the diphtheroid bacillus be explained? I do not know, unless it is possible that this type of bacillus has a certain selective affinity for the nervous system, with the production of a neuro-toxin of low toxicity. The fact that the vaccine treatment was not efficacious rather strengthens the deduction that whatever significance this bacillus has, it probably is of no great importance.

In answer to the fourth point, I have not yet obtained sufficient evidence to determine the source of the infection or to evolve any theories.

References.

(1) "Morison Lectures" and others, *Review of Neurology and Psychiatry*, 1906.
(2) *Archives of Neurology*, vol. iii.
(3) "Morison Lectures," *Journal of Mental Science*, April, 1908.
(4) Bianchi, *Text-book of Psychiatry*.

DESCRIPTION OF PLATES.

FIG. 1.—Blood-film from a case of general paralysis, made shortly after the commencement of a seizure. Stained with Jenner. × 1000.

FIG. 2.—Blood-film from a case of enteric fever, showing two *Bacilli typhosus abdominalis*. Stained with Jenner. × 1000.

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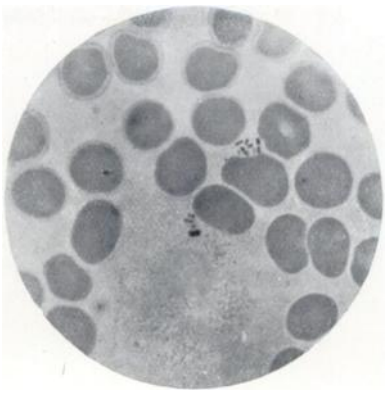

FIG. 1.

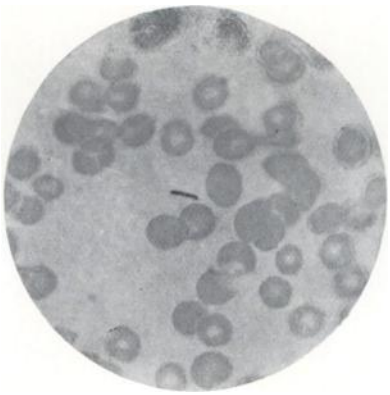

FIG. 2.

FIG. 3.

To illustrate Dr. Winifred Muirhead's paper.

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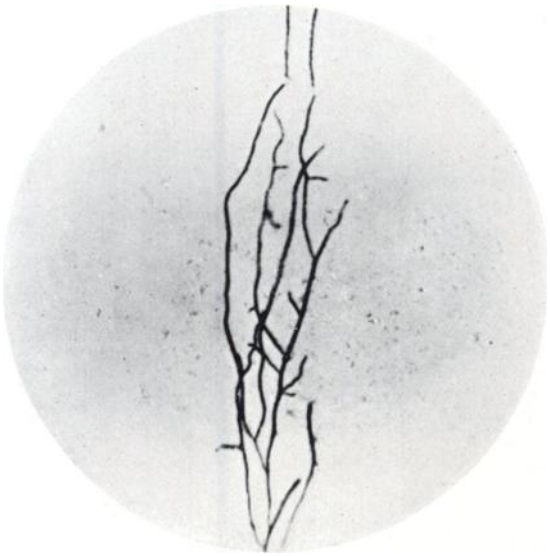

FIG. 4.

FIG. 5.

To illustrate Dr. Winifred Muirhead's paper.

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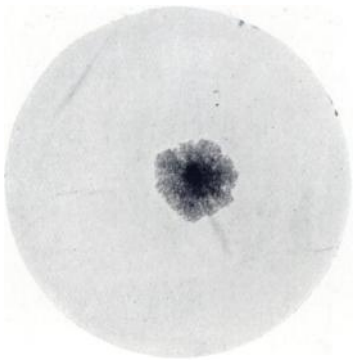

FIG. 6.

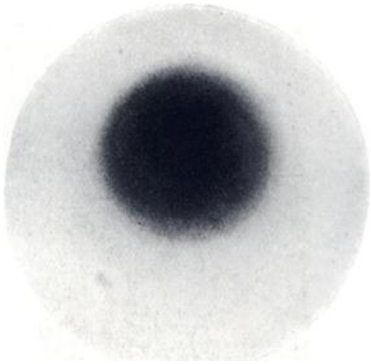

FIG. 7.

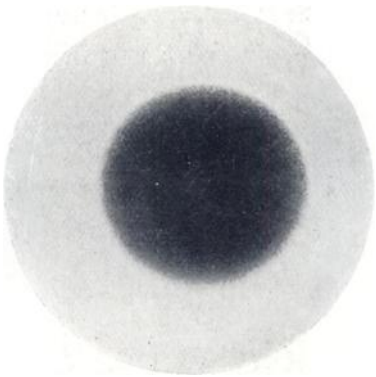

FIG. 8.

To illustrate Dr. Winifred Muirhead's paper.

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FIG. 3.—Film of organism A. Byno-hæmoglobin agar culture 24 hours. Stain carbol methylene blue. × 600.

FIG. 4.—Film of streptothrix. Plate culture from fluid of hæmatoma auris; byno-hæmoglobin agar 48 hours. Stained fuchsin. × 1000.

FIG. 5.—Culture of organism A on byno-hæmoglobin agar 48 hours. Photo from drawing.

FIG. 6.—Colony of organism A. Plate byno-hæmoglobin agar 24 hours. × 60.

FIG. 7.—Colony of *Bacillus paralyticans brevis*. Plate byno-hæmoglobin agar 24 hours. × 60.

FIG. 8.—Colony of *Bacillus paralyticans longus*. Plate byno-hæmoglobin agar 24 hours. × 60.

(1) The essay for which was awarded the second prize of the Medico-Psychological Association, 1909.

Occasional Notes.

The Superannuation Act.

After many years of effort the Superannuation Bill has passed into an Act of Parliament, and although not fulfilling the aspirations of the most sanguine, it is to the majority of prospective pensioners a most satisfactory solution of a previously unsatisfactory problem.

The gratitude of the Association is especially due to Sir William Job Collins, whose reputation and skill alone assured its passage through the House of Commons. It is perhaps not too much to say that in the hands of any other member of Parliament it would probably have failed.

To Lord Monk-Bretton an almost equal amount of thanks are due for his skilful pilotage in the troubled waters of the Upper House.

Dr. Shuttleworth's exertions have been beyond all praise, nor can there be any doubt that the weight of the Asylum Workers' Association greatly strengthened his indefatigable exertions.

The Association, too, must not forget the less conspicuous but by no means unimportant labours of the Parliamentary Committee. The steady work of this body for many years past contributed most importantly to the collection of facts and the formation of opinions, constituting the ground work on which the Bill was built.

Thus ends in a most satisfactory manner one of the most