FOCAL SEPSIS IN MENTAL DISORDER: THE "PATHOGEN-SELECTIVE" METHOD OF DIAGNOSIS.

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THE *rôle* of focal sepsis as a causative factor in mental disease has received increasing attention during the past few years since Cotton published his results in this field of inquiry (*Journal of Mental Science*, October, 1923). In England, prominent workers in this branch of medicine, while unable to report the striking therapeutic results of Cotton, have confirmed his main contention that many acute and subacute psychoses seem to be intimately related to some focus of sepsis. Thus confirmation of this main thesis has come from Graves (*Journ. Ment. Sci.*, October, 1923 and 1925), Chalmers Watson (*ibid.*, October, 1923), Hunter and Moynihan (*Brit. Med. Journ.*, November 5, 1927). On the other hand, equally prominent psychiatrists have called in question the results claimed, and the alleged "proven relationship" of sepsis and mental disorder, chief among whom are Henderson and Menzies (*Brit. Med. Journ.*, November 5, 1927, p. 818).

The fact that chronic sepsis is as common in the sane as the insane, and the difficulty of determining in any particular case whether a focus of sepsis is causative or incidental, constitute the core of the problem. Henderson says, "It is very dangerous to state that because something (a septic focus) existed in a given mental case, that something was the specific agent." And he goes on to say, "Many a healthy abdomen has been mutilated and many a serviceable tooth removed as the result of ill-grounded theories of the ætiology of mental illness." Is there any method whereby, before resort to wholesale dental extraction or other surgical intervention, we can confirm or eliminate a known focus of sepsis as the causative factor in any particular case? The present paper constitutes an attempt to answer the above query, but before proceeding we may profitably make a further quotation. Graves

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(*Brit. Med. Journ.*, November 5, 1927, p. 817) is reported as saying, "Dr. Bruce believed that the cause (of mental disorder) lay deeper than a toxæmia, *being the result of a failure to form antibodies.*" Or in other words, in any particular case where focal sepsis exists, if the defence mechanisms of the body (blood- and lymph-streams) were to "rise to the occasion" and produced antibodies of sufficient quality and quantity, these would prevent the occurrence in other parts of the body of remote effects consequent upon the local disease focus. If this hypothesis is correct—and it is certainly plausible enough—then we have a ready means whereby in any particular case we can incriminate or exonerate a focus of sepsis as the ætiological factor.

The method is that known as the "pathogen-selective" method, introduced by Solis Cohen in America, and utilized and elaborated in this country by Cronin Lowe, to whom I am indebted for introduction to the method and help in the early cases. Essentially it consists in the use of the patient's own blood as a factor in bacteriological culture. Where antibodies have been formed and are present in sufficient quantity they will effectively inhibit organismal growth, and such organisms can then be ruled out as causative. Originally we had intended to extend the method and employ the cerebro-spinal fluid in a similar inhibitory capacity to that of the blood, but repeated failure to demonstrate any inhibitory qualities in the cerebro-spinal fluid led us to abandon this procedure.

The actual technique employed is as follows: Under sterile conditions a platinum loopful (of constant size) of septic material is removed from the alleged focus—tooth-socket, tonsillar crypt, nasal cavity, accessory sinuses, etc.—and in a wide-mouthed sterile test-tube is mixed with three loopfuls of sterile normal saline. Two loopfuls of this mixed bacterial emulsion are then removed and "sown" on a plate of blood-agar. Then, employing aseptic technique, 5 c.c. of the patient's blood is removed from a vein and inoculated into the test-tube containing two loopfuls of the saline bacterial suspension. Both test-tube and agar plate are incubated (at 37° C.) for twelve hours, and then sub-cultures from the material in the test-tube are made on a fresh blood-agar plate and further incubation undertaken. Thus we now have two separate cultures on agar plates, viz.:

Plate A. Direct culture.

Plate B. Indirect culture through the patient's blood.

As a general rule in the direct culture (plate A) a very mixed growth of organisms occurs, but in plate B (indirect culture)

the inhibitory action of the blood is manifest, occasionally completely inhibiting all bacterial growth, but more usually limiting it to only one or few organisms. The explanation is obvious, and appears to be a practical vindication of the hypothesis attributed to Dr. Bruce by Graves and quoted above. Where the defence mechanism of the body has produced antibodies to the organisms of a septic focus, such antibodies will inhibit the growth of their complementary bacteria when culture thereof is attempted. Thus those organisms which grow on plate B (indirect culture) we assume to be pathogenic, as there are no antibodies in the blood capable of inhibiting their growth.

As we have stated above, we originally attempted to extend the method to the cerebro-spinal fluid. But we soon found that the latter has no power of inhibiting bacterial growth—an experimental confirmation of the clinical fact that bacterial invasion of the cerebro-spinal fluid is a most serious condition, the organisms multiplying rapidly and the condition generally ending fatally.

The clinical material which forms the basis of this paper is constituted by the following cases:

Post-encephalitis	26 cases.
Confusional insanity	1 case.
Delusional insanity	1 ,,
Dementia paralytica	1 ,,

The reason why we have investigated so many cases of encephalitis from this point of view is that clinical observation, together with subsequent investigation of *post-mortem* material, has led us to the conclusion that in many such cases the lesion is not the sequel to an acute process only, but a chronic progressive encephalitis (see paper by author on encephalitis in the *Journ. of Neur. and Psychopath.*, 1930). Most observers are agreed that the source of entry of the "virus" of this disease is through the nose and throat and associated sinuses, and in repeated examinations of this region in these cases we have been impressed with the marked degree of chronic inflammation (a granular naso-pharyngitis) present in practically all of them.

While this chronic naso-pharyngitis was present in all of these cases, in some of them there were in addition other possible sources of sepsis and infection in the teeth, tonsils, and in one case the middle ear. In such cases the pathogen-selective method of investigation has helped us to determine which of the foci was the causative factor and which were merely incidental.

The table which we have compiled shows not only the chief clinical features of the cases from the point of view of infective foci but in addition the results of the direct and indirect cultures of septic material obtained from the various foci.

Before proceeding to a detailed analysis of the table it will probably illustrate the value of the method better if we instance in some detail certain individual cases thus investigated.

CASE I.—Female, æt. 40. Post-encephalitic Parkinsonianism.

The onset of the illness occurred in 1924, since when the patient had been increasingly crippled by the disease, and in addition had become acutely depressed and melancholic, requiring certification. When admitted to hospital she was in a helpless, bedridden state, and she remained thus for about 18 months until treatment based on the present investigation was instituted.

The foci of sepsis present in this case were the teeth and naso-pharynx. The former were very bad indeed, the upper set consisting of numerous carious stumps in septic sockets and much associated gum absorption due to pyorrhœa.

The naso-pharynx was typically granular, and on mirror examination of the posterior nares numerous small lymphoid follicles crowned with beads of pus were visible. Transillumination revealed no infection of the accessory sinuses, and all other systems were free from ascertainable sepsis. Thus in this particular case there were two septic foci to be investigated, and, on the face of, it it looked as if dental caries and sepsis were the chief factor.

Septic material was obtained from the sockets of two of the worst teeth and also from the naso-pharynx, and subjected to the "pathogen-selective" method of culture. The following were the results thus obtained—

A. *Teeth* :—

Direct plate: Pneumococci and *Staphylococcus aureus*.
Indirect plate: Sterile, *i.e.*, complete inhibition.

B. *Naso-pharynx* :—

Direct plate: *Streptococcus hæmolyticus and B. proteus*.
Indirect plate: Pure growth of *B. proteus* only.

If the original hypothesis (attributed to Dr. Bruce and quoted by Graves) enunciated above is correct, then we must on the above findings adjudge the naso-pharynx and not the teeth to be the causative focus, the latter being merely incidental or companionate sepsis.

On the basis of the above findings the following treatment was instituted: Daily saline irrigation of the naso-pharynx together with antiseptic gargles to the throat and the bi-weekly administration hypodermically of a selective autogenous vaccine of *B. proteus*. The teeth were given no further attention at the time. On the above therapeutic *régime* the patient's general physical condition showed marked improvement, to the extent that she was able to get up from her bed and begin to help herself with regard to her toilet, etc. This physical improvement with corresponding brighter mental outlook has now been maintained for the past nine months, although the patient is still bowed down by the flexion attitude of her Parkinsonianism. Thus what improvement has been effected has been due to the treatment of the less obvious focus of sepsis, even while an apparently glaring focus is retained as part of the body economy. To complete the rationale of the above therapy the carious teeth and stumps were removed to see if any further improvement would ensue, but none has as yet occurred. Thus we have bacteriological and therapeutic confirmation that an apparently obvious focus of sepsis (the teeth) may in a given case be merely incidental and not causative.

Another case may be cited illustrative of the same truth enunciated by Henderson—"It is very dangerous to state that because something (septic focus) existed in a given case that something was the specific agent".

CASE 2.—Female, A. G—, æt. 48.

A case of delusional insanity. When admitted she was in very poor physical condition, the main features being advanced dental caries and pyorrhœa, flatulent abdominal distension with distressing eructations, and fibro-myositis of the hamstring group of muscles, resulting in contracture at the knees, the pain associated with which was interpreted by the patient as electricity being played upon her by imaginary persecutors. The teeth were so rotten that the visiting dentist said they were not worth saving and accordingly they were removed *in toto* under a general anæsthetic, the opportunity being utilized to obtain from the teeth-sockets septic material for culture. The following were the bacteriological results:

Plate A:
Direct culture—*Staphylococcus aureus*, *Micrococcus catarrhalis* and diphtheroids.

Plate B:
Indirect culture—Sterile.

Some time after the dental extraction the patient showed evidence of infection of the urinary tract (pyrexia, frequency of micturition, etc.), and on investigation of catheter specimens of urine the causative organism was found to be *B. Welchii* (*B. aërogenes capsulatus*). Pathogen-selective culture made from the urine revealed the same organism in pure culture, there being no inhibitory factor in the blood. In view of this bacteriological finding in the urine (a gas-producing organism), and the known clinical fact that flatulent eructation was a distinctive feature of the case, it was thought advisable to investigate the bowel content from the pathogen-selective point of view. In direct culture of material obtained by saline irrigation there was a luxuriant growth of *B. coli*, *Streptococcus fæcalis* and *B. Welchii*, whereas the pathogen-selective plate only grew *Streptococcus fæcalis* and *B. Welchii*. Therefore we concluded that the latter organism (*B. Welchii*) was the causative factor, and that the primary focus was located in the bowel. On this rationale, treatment was directed to the alimentary canal in the form of daily colonic lavage and the administration of an intestinal antiseptic orally, resulting in immediate clearing up of the physical symptoms, both alimentary and urinary, and allaying of the mental and physical restlessness. Up to the present time we cannot claim that the patient is in any sense cured mentally, but there has been undoubted improvement consequent upon the removal of the toxic restlessness.

At this juncture let us make an apparent digression, the reason for which, we trust, will become apparent as we pursue the theme. During the past three years the writer has treated some hundred cases of dementia paralytica, and has frequently been at a loss to account for the bizarre therapeutic responses of some of them. An apparently early case of the disease will run a fulminating and rapidly fatal course despite all treatment, while another case, seemingly more advanced and less hopeful, will make a fair recovery under similar treatment. In order to try and arrive at some assessment of prognosis in general paralysis the personal, clinical and serological details of 24 cases were carefully analysed, and as far as we could determine the chief factor common to these rapidly fatal cases was sepsis, generally in the oral cavity and genito-urinary tract. The latter especially is a serious factor with regard to prognosis. Now with the advent of malaria and tryparsamide as the important therapeutic measures in this dread disease, the possibility of factors other than the immediate syphilitic process has been overlooked and the investigation thereof neglected. It

will be remembered that before the essential syphilitic nature of general paralysis was established as a fact Ford Robertson and McRae described a diphtheroid bacillus as the cause of the disease. It is quite feasible that the presence of this organism was evidence of accessory sepsis, and if not actually causative, was probably contributive to the morbid destructive process in the brain. In this mental hospital laboratory we have on occasion found, in the brains of cases of general paralysis and in other conditions, diphtheroid organisms which have been looked upon as evidence of a terminal infection. The writer is of the opinion that the cumulative clinical and pathological evidence points to the importance of accessory sepsis in these cases as a factor which weights the scales against the response to the antisyphilitic measures.

The following case serves to illustrate the above line of argument, and also emphasizes in some measure the value of the pathogen-selective method of investigation.

CASE 3.—Female, A. P—, æt. 42.

Clinically a melancholic type of general paralysis. Treated with ten weekly injections of tryparsamide followed by a course of malaria. No definite improvement at the end of five months. Some weeks later the patient became pyrexial and showed signs of pyelitis. On investigation this yielded the ordinary coliform organism, but culture thereof by the pathogen-selective method demonstrated complete inhibition of growth by the blood. Treatment of the genito-urinary tract by the usual measures (alkalies and antiseptics) soon cleared up the local infection, but there was no corresponding improvement in the general clinical picture. While it had been noted on admission that the dental condition was unsatisfactory, no immediate investigation or treatment had been undertaken owing to the fact that the more pressing malarial-tryparsamide therapy occupied the field. Later, dental consultation recommended the removal of all the teeth, but as some appeared sound it was decided to remove in the first instance two only, one obviously diseased and the other looking fairly serviceable, although there was definite associated pyorrhœa. Cultures from the sockets of both teeth yielded identical bacteriological findings, the direct plate growing *B. Pfeiffer*, pneumococci and *Micrococcus catarrhalis*, while the pathogen-selective method yielded a growth of *B. Pfeiffer* and pneumococci. In view of this bacteriological confirmation of the teeth as the causative focus, complete removal was undertaken, with immediate improvement in the physical and mental health of the patient.

Twenty-Six Cases of Chronic Encephalitis.

No.	Name.	Sex.	Septic foci.	Bacteriological findings.						
				Streptococcus hæmolyticus.	*Streptococcus viridans.*	*Streptococcus non-hæmolyticus.*	*B. Pfeiffer.*	Pneumo-cocci.	*Catarrhalis* group.	Miscellaneous organisms.
1	M. S—	F.	Naso-pharynx	+	o	o	o	o	++	o
				**	—	—	**	—	*	—
2	M. O—	F.	,,	o	o	o	o	++	+	o
				—	—	—	—	**	*	—
3	E. J—	F.	,,	o	o	o	o	++	+	o
				—	—	—	—	**	—	—
			Teeth	+	o	o	o	+	+	+ (*Staph. aureus.*)
				—	—	—	—	**	—	—
4	S. F—	M.	Naso-pharynx	o	o	o	++	o	++	o
				—	—	—	**	—	*	—
5	G. H—	M.	,,	++	o	o	o	+	+	o
				*	—	—	—	**	—	—
6	A. R—	M.	,,	o	o	o	++	++	+	o
				*	—	—	—	**	—	—
7	J. D—	M.	,,	o	o	o	++	+	o	o
				—	—	—	—	*	—	—
8	R.P.T—	M.	,,	+	o	o	++	o	o	+ (*B. Friedländer.*)
				**	—	—	—	—	—	—
9	N. M—	F.	,,	o	o	o	o	+	++	o
				—	—	—	—	—	—	—
10	S. D—	F.	,,	++	o	o	o	o	o	+ (*B. proteus.*)
				—	—	—	—	—	—	**
			Teeth	o	o	o	o	++	o	+ (*Staph. aureus.*)
				—	—	—	—	—	—	—
11	W. L—	M.	Naso-pharynx	+	o	o	++	o	o	o
				—	—	—	—	—	—	—

12	E. G—	M.	Naso-pharynx	++ **	o —	o —	++ —	o —	+ —	o —
			Tonsils large and infected	+ *	o —	o —	o —	+ —	+ —	o —
13	J. H—	M.	Naso-pharynx	++ **	o —	o —	o —	++ —	++ * —	o —
			Teeth carious	+ —	o —	o —	o —	+ —	+ —	o —
			Tonsils large and infected	+ **	o —	o —	o —	++ —	o —	o —
14	K. C—	M.	Naso-pharynx	++ —	o —	o —	++ **	o *	o —	o —
15	W. H—	M.	,,	+ —	o —	o —	++ —	o —	+ —	o —
			Teeth good ; early pyorrhœa	o —	o —	o —	o —	+ —	+ —	+ (*Staph. aureus.*) —
16	J. H—	M.	Naso-pharynx	++ —	o —	o —	o **	o —	+ **	o —
			Tonsils infected	o —	o —	o —	+ *	o —	+ **	o —
17	T. G—	M.	Naso-pharynx	++ *	o —	o —	++ **	+ —	+ —	* (*B. Friedländer.*) o —
			Teeth	o —	o —	o —	o —	+ *	+ **	o —
18	T. M—	M.	Naso-pharynx	++ —	+ —	o —	++ **	o —	+ * —	o —
			Pyorrhœa	+ **	o —	o —	o —	o —	++ *	o —
19	J. B—	M.	Naso-pharynx	+ —	o —	o —	+ —	+ —	+ —	o —
20	T. R—	M.	,,	+ **	o —	o —	+ —	o —	+ —	o —
			Teeth	+ **	o —	o —	o —	+ —	+ —	o —

+ and o = Direct culture. * and — = Indirect or pathogen-selective culture.

Twenty-Six Cases of Chronic Encephalitis—continued.

No.	Name.	Sex.	Septic foci.	Bacteriological findings.						
				Streptococcus hæmolyticus.	*Streptococcus viridans.*	*Streptococcus non-hæmolyticus.*	*B. Pfeiffer.*	Pneumococci.	*Catarrhalis* group.	Miscellaneous organisms.
21	W. J—	M.	Naso-pharynx	+ **	o	o	+	o	+	o
				−	−	−	−	−	−	−
			Pyorrhœa	++	o	o	o	+	+	o
				−	−	−	−	−	−	−
22	J. C—	M.	Naso-pharynx	++	o	o	+	o	+	o
				−	−	−	**	*−	−	−
			Teeth	+	o	o	o	++	++	o
				−	−	−	−	−	−	−
23	E. G—	M.	Naso-pharynx	+ **	o	o	o	+	++	o
					−	−	−	−	−	* (*Staph. albus.*)
			Left tonsil large and infected	++ **	o	o	o	++ **	+	o
					−	−	−		−	−
24	H. S—	F.	Naso-pharynx	o	o	o	o	++	+	+ (Diphtheroids and *Staphylococcus aureus.*)
				−	−	−	−	**	**	*
25	W. B—	F.	,,	+	o	o	o	++	+	+ (*Staph. aureus.*)
				−	−	−	−	**	−	−
26	S. H—	F.	,,	+	o	o	o	++	o	o
				−	−	−	−	−	−	−
Totals . . .			Naso-pharynx .	19	1	0	14	13	20	4
				10	*0*	*0*	*7*	*9*	*7*	*4*
			Teeth . .	4	..	..	0	6	5	2
				1	..	..	*0*	*2*	*1*	*0*
			Tonsils . .	3	..	..	1	3	3	0
				3	..	..	*1*	*1*	*1*	*0*
			Pyorrhœa . .	2	..	..	0	2	3	1
				1	..	..	*0*	*0*	*1*	*0*

Three Other Representative Bases.

No.	Name.	Sex.	Septic foci.	Bacteriological findings.						
				Streptococcus hæmolyticus.	*Streptococcus viridans.*	*Streptococcus non-hæmolyticus.*	*B. Pfeiffer.*	Pneumococci.	*Catarrhalis* group.	Miscellaneous organisms.
27	A. P—	F.	Teeth	o	o	o	++	+	++	o
				—	—	—	**	**	—	—
			Urinary tract	o	o	o	o	o	o	+ (*B. coli.*)
				—	—	—	—	—	—	—
28	M. C—	F.	Cervix uteri, leucorrhœa	o	o	o	o	++	o	+(*Staphylococcus aureus.*)
				—	—	—	—	—	—	**(,, ,,)
29	A. G—	F.	Teeth	o	o	o	o	o	++	+ (Diphtheroids and *Staphylococcus aureus.*)
				—	—	—	—	—	—	—
			Colon	o	o	o	o	o	o	* (*B. coli, Streptococcus fæcalis, B. Welchii.*)
				—	—	—	—	—	—	* (*B. Welchii, Streptococcus fæcalis.*

+ and o = Direct culture. * and − = Indirect or pathogen-selective culture.
Ordinary figures = Direct culture.
Italic figures = Indirect or pathogen-selective culture.

Now to return to an analysis of the table indicating the cultural results, both direct and indirect, of material obtained from the various infective foci.

1. Twenty-six cases of chronic progressive encephalitis were investigated. All of these cases showed a typical granular naso-pharyngitis from which septic material for culture was obtained. In addition 6 of these cases had defective and carious teeth, and there were 3 cases in which, while the teeth appeared fairly healthy, there was widespread pyorrhœa. In addition 4 of these cases showed tonsillar infection. On analysis of the bacteriological findings the following results emerge:

(*a*) Five of the cases, while yielding bacterial growth in the direct culture, showed complete inhibition of all organisms in the " pathogen-selective " plate.

(*b*) The remaining 21 cases yielded a very mixed growth in direct culture, but the pathogen-selective culture usually reduced the growth to one or two organisms, hæmolytic streptococci and pneumococci being the preponderating bacteria.

(*c*) In the 14 cases in which the *B. Pfeiffer* was isolated in direct culture from the naso-pharynx, agglutination tests were undertaken, using the patient's own serum against the bacillus isolated. It will be noted from the table that only 7 of these 14 cases proved positive on the indirect plate and they gave the following agglutination results:

Name and Table number.	Agglutination.
M. S— . 1 .	Negative
S. F— . 4 .	,,
K. C— . 14 .	Positive 1/125 dil.
J. H— . 16 .	± 1/125 ,,
T. G— . 17 .	± 1/25 ,,
T. M— . 18 .	± 1/25 ,,
J. C— . 22 .	± 1/65 ,,

(*d*) Referring now to those cases in which other foci of sepsis existed besides the naso-pharynx, we find that in the case of the teeth those organisms which did grow on the indirect plate were also to be found in the cultures from the naso-pharynx. And the same statement is true also of those cases showing involvement of the tonsils and gums. This suggests that originally there was a primary infective focus in one of these sites, and that the infection spread thence to involve the

other areas. Further, it points the therapeutic maxim that where certain organisms shown on bacteriological investigation to be pathogenic in a particular case are found to be located in several different areas, treatment to be effective must be directed to eradicate each focus.

2. The other 3 cases representative of three different groups of psychoses—confusional insanity, delusional insanity and general paralysis—with added sepsis, 2 of which (27 and 29) have been dealt with in detail in the previous text, show the importance of fully investigating such cases from a bacteriological standpoint before incriminating as the specific causative factor a particular focus of sepsis.

3. *Therapy.*—In addition to eradicating the particular focus of sepsis (teeth, tonsils, etc.) and to local antiseptic applications, 20 of these cases were treated with autogenous vaccines prepared from the pathogen-selective cultures. Three of the 6 untreated cases were removed by their friends before any treatment could be undertaken, and the other 3 proved too obstreperous and antagonistic to warrant its continuation. Of the 20 who received a full course of vaccine therapy together with other local treatment the following is the end analysis :

Two have been discharged as recovered; that is, they have recovered sufficiently mentally and physically to be removed from certification, the physical signs of encephalitis still being present, although mitigated to some extent.

One male improved remarkably in his physical condition and was allowed out on trial, but had to return owing to getting into trouble with the police. His physical improvement is still maintained and he is capable of doing a good day's work.

Two others show definite physical improvement with accompanying brighter mental outlook.

Three advanced cases have died. Two are in a degenerative condition, and the other ten remain stationary.

With regard to the three non-encephalitic cases, all have registered distinct physical improvement and slight accompanying mental improvement, which as far as one can judge up to the present appears to be of a progressive nature.

Summary.

A series of cases of chronic encephalitis, confusional insanity, etc., have been investigated in order to assess the *rôle* of chronic sepsis as an ætiological factor.

The " pathogen-selective " technique has been employed throughout, and its utility in incriminating or exonerating particular foci of sepsis as causative has been illustrated in three cases.

Details of bacteriological results are set out in the table adjoined. They illustrate how by this simple method of using the patient's blood as a factor in culture the causative organisms can be detected, the method being based on the hypothesis enunciated by Dr. Bruce (" That the cause of mental disorder is deeper than a toxæmia, being a failure to form antibodies ").

This method adds bacteriological *finesse* to the preparation of autogenous vaccines, and makes such more selective in their action.

Where this method is employed, unnecessary surgical intervention (Henderson—" Many a healthy abdomen has been mutilated, etc.") will be avoided and what is undertaken will be based on a demonstration of causal pathology.

Finally, owing to the fact that in this particular series we have been dealing with chronic cases in which there has been much permanent damage to the brain, results have of necessity been meagre, but we believe that the method will be found distinctly useful in cases of recent origin. Perhaps in a mental hospital one of its most useful applications will be in the investigation of the accessory sepsis which complicates so many cases of general paralysis, and which we believe contributes materially to the high mortality.

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