reaction, quite as reliable, and probably of more value in the early diagnosis of neuro-syphilis.

(4) That the test is helpful in the recognition of acute poliomyelitis.

(5) That it may prove to be of much more value in the diagnosis of congenital syphilis than any other tests hitherto employed.

(6) That important points in its favour are: its simplicity minimising chances of error, its performance occupying only a few minutes, and its need of but two or three drops of spinal fluid.

(7) That its chief drawback is the uncertainty of being able to prepare a good goldsol at every attempt.

The present-day tendency to exalt laboratory diagnosis at the expense of clinical experience is liable to cause extravagant claims to be made for such a test as this. But it must be borne in mind that a diagnosis cannot be centrifuged nor extracted, nor even precipitated from a spinal fluid, and that any expectation of obtaining an infallible and characteristic laboratory test is unreasonable.

(The discussion which followed will be found on page 519, vol. lxvii, 1921.)

The Colloidal Gold Reaction in the Cerebro-spinal Fluid.[1] By W. WHITELAW, M.B., Ch.B.Glasg., Director of the Western Asylums Research Institute, Glasgow.

IN this paper I should like to emphasise the technique of the colloidal gold reaction rather than the results I have obtained, for the cerebro-spinal fluids I have been so far able to examine have been mostly from cases of dementia paralytica, and, though the results are interesting and suggestive, the number of cases is too limited to allow one to dogmatise on the findings.

The examination of the cerebro-spinal fluid is essential in the study of neurological conditions. From it we obtain information which is of diagnostic and prognostic value, and, also as shown in the work of Swift and Ellis (1), it is a valuable index of the efficacy of treatment. The three reactions in use at the present day, the Wassermann reaction, the cell count and the globulin estimation, suffice for most of the requirements of clinical diagnosis, but, in the syphilitic infections especially, they have their limitations. From such an examination we can say that a certain case is suffering from a syphilitic infection of the cerebro-spinal axis. We cannot go further. Any reaction that offers to yield fuller information has to be tested. This can only be done by the examination of a large number of cases of different conditions, so that one may establish a foundation from which to build.

An enormous amount of work has been done during the recent development of colloid chemistry towards the elucidation of some of

(1) A paper read at a meeting of the Scottish Division, March 18th, 1921.

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the perplexing and complicated reactions of biology. This has been done, to mention a few of these problems, in the blood oxygen content, enzyme reactions, Wassermann reaction, immunity, and the estimation and differentiation of protein substances.

Faraday in 1857 (2) found that goldsols (a sol is a liquid colloid system) were more stable when "jelly" (probably gelatine) was added to them—that is to say the goldsols were protected by adding another more stable colloid to them. Zsigmondy in 1901 (3) investigated this action quantitatively by means of his goldsol, which is itself very stable and is also very sensitive to the action of salts. He determined the protecting power of various proteins and other colloid substances to the goldsol. The degree of protection he expressed as the "gold number" of the particular substance under review. This reaction is used in the identification of proteins.

Lange (4) in 1912 applied the gold protection method of Zsigmondy to the cerebro-spinal fluid, and found that in certain fluids, instead of getting protection to the goldsol, quite the reverse occurred. This was noted in fluids that had an abnormal protein content and especially in cases of syphilitic disease of the central nervous system. There was an optimum dilution for this reaction and this was evidently specific, so rendering possible the differentiation between syphilitic and non-syphilitic conditions by the colloidal gold. There were two types of reaction recognised by Lange, the reaction in the "luetic zone" and the reaction in the "meningitic zone." The term "paretic zone reaction" was used by Miller and Levy in 1914 (5).

Technique of the Test.

All glassware used in the test requires to be chemically clean. The water used in the preparation of the goldsol and in the diluting fluid is double distilled through an all-glass still, using potassium permanganate. The preparation of the goldsol is as follows: 100 c.c. of the double distilled water are heated in a 500 c.c. Florence flask. During the heating process 1 c.c. of a 1 *per cent.* gold chloride and 1 c.c. of 2 *per cent.* potassium carbonate are simultaneously added and the flask well shaken. At the boiling-point the gas is removed, and 1 c.c. of a 1 *per cent.* solution of 40 *per cent.* formaldehyde is added rather slowly, the flask being vigorously shaken during this addition. The reaction commences in a few seconds, or at most a minute, when an intrinsic clear bright red colour is gradually developed. A good sol should be pure red in colour, with no suggestion of any blue by any light. It should be clear and transparent in both transmitted and reflected light. It should not dialyse or diffuse. Five c.c. of the sol should be completely precipitated by 1·7 c.c. of a 1 *per cent.* solution of sodium chloride in one hour. The solution should be neutral in reaction using alizarin red as indicator.

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The cerebro-spinal fluid is collected in two chemically clean tubes. The colloidal gold reaction is done with the fluid in the second tube, as a trace of blood interferes with the reading. Fluids can be kept several days provided they are uncontaminated, though I have examined all specimens as soon as possible.

The test is performed as follows: 11 chemically clean tubes are placed in a rack. Pipette into tube 1, 1·8 c.c. 0·4 *per cent.* saline, and into the other tubes 1·0 c.c. saline. Into tube 1 deliver 0·2 c.c. cerebro-spinal fluid, mix, withdraw 1 c.c. and place in tube 2, mix, and place 1 c.c. in tube 3, etc., to tube 10. Each tube will contain 1 c.c. of fluid in dilutions from 1–10 to 1–5120. Tube 11 contains 1 c.c. of saline only and serves as a control. To each tube add 5 c.c. of the colloidal gold reagent. This can be added with a burette. The reagent should be added and mixed as rapidly as possible. The reading is made after standing at room temperature for 12 hours. Half the above quantities may be used with no effect on the results.

The Reaction Observed.

The reaction observed in the tubes is a colour change due to an alteration in the dispersity of the gold colloid. A normal fluid at the end of 12 hours shows no change in any of the tubes. Such a tube may be represented by the figure 0. The colour changes consist of a series of shades passing from red through blue to a clear fluid with a deposit of blue granules. The shades usually selected to give a standard are red, reddish blue, lilac or purple, blue, grey-blue, and colourless. These shades are given the numbers from 0 to 5 respectively, and from the results one can plot a curve for each fluid examined.

Three types of curves are at present recognised: (1) The paretic curve. This zone comprises the first 3 to 6 tubes in which the reaction is characteristically of the 5 type. (2) The luetic curve. This zone also comprises the first 6 tubes, but the reaction is not nearly so complete. The maximum point occurs in the dilutions of 1 in 40, 1 in 80, or 1 in 160, and the reduction never exceeds a 4. (3) The meningitic curve. Here the reacting zone is in the higher dilutions, with no reduction in any of the tubes up to the dilutions of 1 in 40 or 1 in 80.

Results Observed with the Reaction.

The present results are based on the findings in 63 fluids from 62 patients. The following routine has been employed in the examination of the fluids: (1) A cell-count has been done with the Fuchs-Rosenthal counting chamber as soon as possible after obtaining the fluid. In the few cases in which the cell-count has not been recorded this was due to there being too little fluid, blood being present for too long after withdrawal. No attempt has been made at a differential count. (2) The increase in the protein content has been tested for by the Ross-Jones

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method. In a good number of cases this reaction has been confirmed by the butyric acid reaction of Noguchi. The results have been parallel in every case so tested. (3) The Wassermann reaction has been done by the Harrison method, and in the case of the blood, where that has been available, the Harrison method has also been employed. (4) The colloidal gold reaction has been performed as above.

The details of the results are presented in the four tables.

TABLE I.—*Dementia Paralytica.*

Case No.	W.R. blood.	Cerebro-spinal fluid.				Remarks.
		Cell count.	Globulin.	W.R.	Gold reaction.	
1		15 per c.mm.	+	+ + + +	5555542100	
3		1·5 ,,	+ +	+ + + +	5555553100	
4		40 ,,	+ +	+ + + +	4555553200	
5		54·6 ,,	+ +	+ + + +	5555551000	
6		19·1 ,,	+	anti-complementary	5555552000	
7		Not counted	± trace	+ + + +	5555530000	
12	+ +	153·8 per c.mm.	+ +	+ + + +	5555310000	
13	+ +	10·4 ,,	+ +	+ + + +	5555530000	
15	+ +	12·5 ,,	+ +	+ + + +	5542210000	
17		54·17 ,,	+ +	+ + + +	5554432000	
18	+ +	152·7 ,,	+ +	+ + + +	5555432000	
20	+ +	15·9 ,,	+ +	+ + + +	5555442000	
22		Not counted	+ +	+ + + +	5554422000	
23		7·6 per c.mm.	Negative	+	1111100000	Intra-spinous treatment one year ago, now stationary.
24	+ +	25·7 ,,	+ +	+ + + +	5555443210	
25		82·5 ,,	+ +	+ + + +	5555543000	
26		12·2 ,,	+ +	+ + ±	5554321000	
27		99·3 ,,	+	+ + + +	5554422100	
29	+ +	68 ,,	+ +	+ + + +	5555552100	
30	+ +	22·2 ,,	+ +	+ + + +	5555553100	
31	+ +	Not counted	+ +	+ + + +	5555544210	
32		,, ,,	No test	+ + + +	1243344420	Quantity of blood present in fluid.
33		,, ,,	,,	+ + + +	1234443422	Ditto.
34	+ +	116·6 per c.mm.	+ +	+ + + +	5555543200	
35	+ +	50·3 ,,	+ +	+ + + +	5555443200	
36		163·8 ,,	+ +	+ + + +	5554432000	
38		45 ,,	+	+ + + +	5555552200	
39		25·7 ,,	+	+ + + +	5555553200	
41		45·2 ,,	+	+ + +	4445321000	
42		41 ,,	+ +	+ + + +	5555553310	
43		61·7 ,,	+ +	+ + + +	5555554310	
44		Not counted	+ +	+ + + +	5555431100	
49		17·6 per c.mm.	+	+ + + +	5555543100	
51	+ +	37·1 ,,	+ +	+ + + +	5555542100	
52		98·6 ,,	+ +	+ + + +	5555543200	
53	±	40·6 ,,	+	+ + +	5555543300	
59		321·9 ,,	+ +	+ + + +	5555555210	
61	+ +	45 ,,	+ +	+ +	5555553210	
37		9·7 ,,	±	+ + ±	4433221000	

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The first table contains 39 fluids from 39 cases of dementia paralytica; of these 35 gave a typical reaction in the paretic zone. Two of the four fluids that did not give this curve contained a considerable quantity of blood. For the present these may be neglected, and I shall refer to them later. Another of these cases, No. 23, had a course of intra-spinous treatment over a year ago, and clinically he has remained stationary since that time. His cell-count was within normal limits (9 per c.c.), there was no reaction to the globulin test, the Wassermann reaction was slightly positive, giving a reaction only in the highest concentration of fluid, and the colloidal gold showed a slight reduction in the first 5 tubes, the reading being 1, 1, 1, 1, 1, 0, 0, 0, 0, 0. In one of Miller's and Levy's cases there was a marked diminution in the intensity of the gold reaction after intra-spinous treatment, though the usual result they obtained was to remain "gold fast" as well as "Wassermann fast" (5). The last case in Table I, No. 37, tended to the paretic curve. It read 4, 4, 3, 3, 2, 1, 1, 0, 0, 0. The percentage of positive cases so reads at 97 *per cent.* This is in general agreement with the findings of other writers. For instance, Miller and Levy (5) obtained 49 paretic curves from 49 cases of dementia paralytica; Miller, Brush, Hammes and Felton (7), 126 paretic curves from 130 cases of dementia paralytica; and Hammes, as quoted by Thompson (8), 42 paretic curves from 43 cases.

TABLE II.—*Dementia Paralytica which are Atypical Clinically.*

Case No.	W.R. blood.	Cerebro-spinal fluid.				Remarks.
		Cells.	Globulin.	W.R.	Gold reaction.	
2		3	+	+ +	1233221000	14/7/20.
2		20·4	+	+ +	1223221000	15/12/20.
11	+ +	30	+	+ +	1223310000	
16	+ +	93·7	+ +	+ + +	4442210000	
28		71·5	+	+ + +	1233321000	

The next group, as shown in Table II, includes 5 fluids from 4 patients who were atypical cases of dementia paralytica from the clinical point of view. The curves they gave were of the luetic type except in case No. 16, which was of the paretic type, and read 4, 4, 4, 2, 2, 1, 0, 0, 0, 0. Case No. 2, beyond the increase in the cell count, showed very little difference in the two examinations at an interval of 5 months.

TABLE III.—*Other Syphilitic Conditions.*

Case No.	W.R. blood.	Cerebro-spinal fluid.				Remarks.
		Cells.	Globulin.	W.R.	Gold reaction.	
14	+	5·5	±	+ +	3112210000	Syphilitic dementia.
57	+ +	7·6	—	—	1112100000	Syphilitic history.
62	+ +	15·6	+ +	+ + +	2223422000	Meningeal syphilis.

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Table III contains three fluids from syphilitic conditions. These all gave the reaction in the luetic zone. Case No. 62, a case of meningeal syphilis, is in agreement with those of Miller and Levy (5), who found that 13 out of 15 cases of cerebro-spinal syphilis gave a luetic curve; the other two cases gave no reaction. Thompson (8), on the other hand, out of 31 cases of this kind obtained 15 paretic curves, 6 of the luetic type, 6 atypical and 4 negative.

TABLE IV.—*Miscellaneous Group.*

Case No.	W.R. blood.	Cerebro-spinal fluid.				Remarks.
		Cells.	Globulin.	W.R.	Gold reaction.	
8	—	2·8	—	—	0000000000	Mania, simple.
9		2·2	—	—	0000000000	Dementia præcox.
10		3·9	—	—	0000000000	,,
48		8·6	—	—	0000000000	,,
55		2·1	—	—	0000000000	,,
19	—	1·3	—	—	0000000000	Dementia, alcoholic?
21		1·4	—	—	0000000000	,,
54	—	0·7	—	—	0000000000	Dementia, simple.
45		6	—	—	0000000000	Post-operative dementia; cerebral tumour.
63	—	Clot present	+ +	—	0000012210	Cerebral tumour, glioma.
60		4·5	±	—	1111122210	Traumatic dementia.
40	—	1·4	—	—	0000000000	Manic-depressive.
56		5·5	±	—	1111000000	,,
58		9·3	—	—	0112100000	Delusional insanity.
50		6·6	—	—	0000000000	Epilepsy.
47		4·5	—	—	0000000000	Melancholia.

Under W.R. blood: — = negative, ± = trace positive, + = positive, + + = strong positive.
Under cells: Number given per c.mm.
Under globulin: — = none present, ± = trace, + distinct, + + = marked ring.

Table IV shows the findings in 16 cases of various other conditions, such as dementia præcox, manic-depressive insanity, cerebral tumour, epilepsy, etc. Twelve of these were negative. Two cases, Nos. 63 and 60, one a case of cerebral tumour, the other a case of traumatic insanity, showed the reduction of the colloid in the higher dilutions—the meningeal or chronic curve. This change is obtained in acute meningeal infections and in the late stages of tuberculous meningitis (Miller and Levy). One also obtains such a reaction in fluids which contain a mixture of blood; Harrison (9), among others, mentions this. It is of interest in this connection to refer again to Cases 32 and 33—the two cases in the first table that had blood present. They showed as if they had two curves—a luetic curve and then a curve in the higher

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dilutions superimposed. One read 1, 2, 4, 3, 3, 4, 4, 4, 2, 0. One case of manic-depressive and one case of chronic delusional insanity showed a slight reduction in the luetic zone. Unfortunately the blood for the Wassermann test was not obtained from either case.

Nature of the Reaction.

The exact nature of the reaction is at present not known. This is natural when we consider that our knowledge of the chemistry of the proteins does not extend very far, and that the electrolytic changes which take place in the colloids are not fully understood. The generally accepted view regarding the reduction of the colloidal gold which takes place on the addition of a pathological spinal fluid is that it is due to the action of positively charged ions present in the fluid. Lange (4) was inclined to the opinion that the reduction was an indication of different qualitative mixtures of the protein substances rather than a quantitative change. This is supported by the fact that the reactions bear no relation to the amount of protein present as revealed by the ordinary tests.

Most colloid sols in water—hydrosols as they are termed—have a negative electric charge ; a few are positive, as the oxides of the metals, etc. Colloids are reduced or precipitated out by salts, and it has been shown that it is the ion of the opposite charge that is responsible for this, and the power of reduction is proportional to the valency of the ion (see Taylor, 6). Also it has been shown that, as well as one colloid protecting another, as I mentioned at the beginning of this paper, some colloids precipitate others. This also depends on the electric charge. Colloids with different electric charges precipitate each other (Lottermoser, 11, and Linder and Picton, 12). Colloids with the same electric charge do not precipitate out, but the mixed sol acquires the stability of the more stable component (Henri, 13). The precipitation of colloids with different electric charges takes place only at optimum dilutions, no reaction taking place at either side of this optimum.

McDonagh (10) has brought evidence suggestive of the fact that the reaction depends on the hydrogen ion concentration of the fluid. He added acetic acid or ammonia to normal and paretic fluids. No reaction took place on the addition of ammonia to a paretic fluid, but acetic acid with a normal fluid might give a paretic curve. Acetic acid is positive on account of its hydrogen group, while ammonia is negative from its OH group. Acetic acid should then precipitate colloidal gold, and also cause a precipitation when added to a normal fluid, since the colloidal gold is negative. On addition of ammonia to a paretic fluid the electric charge will be reversed and no precipitation will take place in the goldsol. This is what takes place according to McDonagh's facts.

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The nature of the particles in the cerebrospinal fluid which bear the positive charge is still not quite clear. Cruickshank (14) locates the substance giving this reaction in the globulin fraction.

A paretic curve has been obtained in conditions other than dementia paralytica. As noted above, out of 31 cases of cerebro-spinal syphilis, Thompson had 15 cases which gave a paretic curve. He states that of these 15, all but 3 showed marked mental symptoms; while in the 16 with the milder gold reaction the mental symptoms were in the background. In disseminated sclerosis Moore (15) showed that a paretic curve was the usual reaction, and in 20 cases obtained such a reaction in 18. Thompson had 5 cases of disseminated sclerosis which gave a paretic curve, and Adams (16), out of 41 cases of this condition, obtained a paretic curve in 5 and a luetic curve in 34. In addition to these a paretic curve has been occasionally found in a few other conditions, such as brain abscess, Warwick and Nixon (17), 1 case; cerebellar tumour, Thompson, 1 case; epilepsy, Larkin and Cornwall (18), 1 case; etc. These conditions would indicate a more or less destruction of nerve-cells, and, as Thompson suggests, a paretic curve points towards a parenchymatous involvement of the brain.

Conclusions.

(1) The colloidal gold reaction is a laboratory test, and can be performed rapidly with a minimal amount of cerebro-spinal fluid.

(2) Extreme care is necessary in the cleaning of glassware and the preparation of the reagents.

(3) The paretic reaction occurs in dementia paralytica with great constancy but is obtained in some other conditions, and so the results from a laboratory test such as this should only be considered in relation to the other evidence in the case, both clinical and pathological, as the tendency might be to depend too much on an unknown test of this kind at the expense of the other facts.

(4) Wider use should be made use of the test in order that numbers will eliminate discrepancies.

In conclusion I would like to thank the medical superintendents and medical officers of the various asylums for the facilities they granted me to obtain the material for this paper.

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Part II.—Reviews.

Sexualpathologie. Dritter Teil. Von Dr. MAGNUS HIRSCHFELD. Bonn: Marcus und Weber's Verlag. Pp. xi + 340, 8vo.

This is the third and last volume of Dr. Hirschfeld's handbook of *Sexual Pathology*. The earlier volumes have previously been noticed in the Journal, and this final volume confirms the impression that we here have a work of the first practical importance in this special field, and completely superseding Krafft-Ebing's *Psychopathia Sexualis*, once so well known but long since out of date, great as was its pioneering significance half a century ago. Dr. Hirschfeld is not concerned to discuss the literature of his subject, and seldom either criticises or approves the investigations of others. He relies on his own experience and the conclusions to which that experience has led him; frequently he devises his own technical terms (which are sometimes open to criticism). But his practice has been so extensive during the past twenty-five years, both privately and medico-legally, and his judgment is usually so sound, that no living expert could hope to put forth a treatise likely to rival this work in practical value. It is much to be hoped that it will soon be translated into English.

It is impossible here to deal in detail with the numerous subjects included in the present volume. It must suffice to mention a few of them. The author describes the general subject of this volume

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