7. Perforation of the gall-bladder may occur, causing localized or general peritonitis.

8. Through the perforation, a gall-stone may pass of sufficient size to cause intestinal obstruction.

9. Cancer of the gall-bladder may be a sequel of gall-stones.

10. As a result of infection hemorrhagic septicemia may occur, or because of the persistent jaundice, hemorrhages may arise or the character of the blood may become so altered as to interfere with its coagulation.

11. Gall-stones are not harmless tenants of the body.

12. With the definite evidence of their presence, surgical attention is required.

13. Early operations are attended with little danger, and the removal of gall-stones from a bladder followed by drainage promises permanent relief.

14. Neglected cases yield poor results, and fatal termination follows operations performed at the eleventh hour.

A CRITICAL STUDY OF LANGE'S COLLOIDAL GOLD REACTION IN CEREBROSPINAL FLUID.

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Lange,[1] in 1912, described the action of cerebrospinal fluid in various conditions upon a colloidal gold solution. He demonstrated that the reaction could be used as a delicate test, differentiating normal from pathological cerebrospinal fluids, and more particularly syphilitic from other affections of the central nervous system. Zaloziecki,[2] Jaeger and Goldstein,[3] Grulee and Moody,[4] and Eicke[5] have confirmed the value of the test.

The theory of the reaction is based upon the following observations made by Zsigmondy in the course of this study on metallic colloidal solutions.

1. Solutions of electrolytes precipitate colloidal gold.

2. Proteins in the absence of an electrolyte also precipitate a solution of colloidal gold.

[1] Berl. klin. Woch., 1912, No. 19, p. 897; Zeitsch. f. Chemotherapie, 1912, vol. 1, No. 1, p. 44.
[2] Deutsch. Zeitsch. f. Nervenheilk., 1913, vol. xlvii and xlviii, p. 783.
[3] Zeitsch. f. d. Ges. Neurol. u. Psychiat., 1913, vol. xvi, Nos. 1 and 2, p. 219.
[4] Jour. Amer. Med. Assoc., 1913, vol. lxi, No. 1, p. 13.
[5] Münch. med. Woch., 1913, No. 49, p. 2713.

3. Proteins in the presence of an electrolyte inhibit precipitation in colloidal gold solutions—the so-called "Gold-Schutz."

The relation existing between this opposed reaction of electrolyte and protein is definite for the same protein, but differed when a different protein is used, and is therefore a specific property of the individual protein.

Lange first applied these principles to the investigation of sera, but the results were without significance. In spinal fluids, however, he found differences between normal and pathological specimens, when he varied the Zsigmondy technique by decreasing the concentration of the NaCl solution to 0.4 per cent., a concentration which in itself would have no effect upon the colloidal gold, but sufficiently strong to prevent the precipitation of globulin and nucleoproteins, both of which substances often occur in pathological spinal fluids.. This latter technique was also used in the study of sera, but no consistent changes were observed in pathological or normal sera.

Briefly the Lange theory is (1) That substances in pathological spinal fluids will precipitate colloidal gold provided the globulin and nucleoprotein fractions are held in solution with a 0.4 per cent. sodium chloride solution, and (2) that there is a characteristic change for certain diseases involving the central nervous system.

The technique is comparatively simple and requires the following materials:

1. Double distilled water, free from protein substances and rubber extractives.
2. One per cent. solution of gold chloride (Merck) in double distilled water.
3. Two per cent. solution of potassium carbonate (Baker & Adams Chemical Company) in double distilled water.
4. One per cent. solution of formalin (commercial) in double distilled water.
5. Ten per cent. solution of sodium chloride in double distilled water.
6. Jena beakers of 1500 c.c. to 2000 c.c. capacity (preferably the tall form).
7. One 1 c.c. pipette. graduated in hundredths and four or five 10 c.c. pipettes.

At first we encountered considerable difficulty in preparing the "reagent." In spite of every precaution to duplicate the technique poor reagents occasionally resulted. Various factors which might influence the change to the colloidal state were separately studied. We found very rapid heating was apparently an important essential. We believe that the preparation of a good, translucent, "high red" reagent with a slight blue nuance which does not precipitate on standing is largely dependent upon freeing the distilled water from the gases in solution.

Our method is to heat 500 c.c. of doubly distilled water in a Jena beaker to 60° C., add 5 c.c. of the gold chloride solution, and follow with 5 c.c. of the 2 per cent. potassium carbonate solution. As the heating continues two types of bubbles are noticed: (1) those which come from the bottom of the beaker and are moderately large, and (2) those which arise generally throughout the liquid and are at first very small and gradually increase in size, and finally disappear after one or two minutes of boiling. As soon as these latter bubbles cease to arise the flame is withdrawn and 5 c.c. of the formalin solution are added. The beaker is given a rotary motion to aid in the rapid diffusion of the formalin. It is our experience that unless the color change is almost instantaneous the resulting reagent will be poor. By following this technique we have been able to secure reagents that are macroscopically identical. This reagent can be made up in considerable quantity, and apparently lasts indefinitely.

The technique of setting up the test is as follows: A suitable amount of 10 per cent. salt solution is diluted with double distilled water, so that the resulting strength is 0.4 per cent. For a single test a row of ten test-tubes, chemically clean, are placed in a rack and 1.8 c.c. of the 0.4 per cent. salt solution are added to the first tube and 1 c.c. to each of the succeeding tubes; 0.2 c.c. of spinal fluid, free from bacterial contamination, hemoglobin admixture, or red-blood corpuscles is added from a 1 c.c. pipette to the first tube. Thorough mixing is secured by pipetting in and out two or three times, and 1 c.c. is removed from this tube to the second, which is mixed in the same way. One c.c. is removed from the second tube and placed in the third tube, and so on until the ten tubes are treated in the above manner; the last tube will have 2 c.c. in it; 1 c.c. is withdrawn and rejected. In this way the dilutions are increased by geometrical progression, in the order 1 to 10, 1 to 20, 1 to 40, and so on up to 1 to 5160. After the specimens to be tested have been treated in the above manner, 5 c.c. of the reagent are added to each tube, which is shaken immediately after the addition. Although the change is very pronounced in many instances within a few minutes after the addition of the reagent, the readings are much more distinct when taken twelve to twenty-four hours after the test is set up.

In pathological fluids the change in color of the reagent is gradual in the series. A single tube showing marked change is always to be regarded with suspicion. Such tests are always repeated, and the usual result is uniformly graded reactions. Specimens from cases which have been receiving salvarsanized serum intradurally are excepted. Tests showing a change in only one tube upon repetition are usually found to be negative.

The success of the test depends upon (1) the use of scrupulously clean glassware; (2) accuracy in all measurements (for this reason

the same 1 c.c. pipette is used for every spinal fluid), (3) bacterial contamination in spinal fluids should be avoided.

We studied the effect of the introduction of bacteria into fluids giving a positive reaction. Bacterial contamination weakens the reaction and a considerable contamination may change a positive reaction to a negative. Spinal fluids kept "bacteria-free" have given the same reaction for weeks.

In Table I a group of typical reactions is indicated by expressing the color change with numbers, ± representing the slightest increase

TABLE 1.—TYPICAL REACTIONS.

Dilutions of cerebrospinal fluid	10	20	40	80	160	320	640	1280	2560	5120
Syphilis, weak		2	3	4	4	3	1	0	0	0
Syphilis, strong	1	4	5	5	5	5	5	5	3	0
Tubercular meningitis	±	±	±	±	2	4	2	0	0	0
Purulent meningitis	±	±	±	1	2	3	4	5	3	1
Negative	0	±	±	±	0	0	0	0	0	0

in blue tint, 1 a slightly greater change, and so on through 5, which represents an absolutely colorless solution. The maximum intensity of change and not the quantitative amount of change has diagnostic value. All readings were made in one hour and confirmed the next day.

In Table II the cases are grouped together with routine laboratory examinations of blood and spinal fluids and clinical diagnoses. We have taken 100 consecutive cases with 122 tests and have compared the results obtained by the gold reaction with the clinical diagnoses and other "laboratory tests."

In Group I, clinically diagnosed as Tabes, the gold reaction agreed with the clinical diagnosis in every case. In 9 of these cases the blood and spinal fluid were negative to the Wassermann reaction. In two cases all other laboratory data listed were negative; the patients had an acknowledged syphilitic history and the clinical evidences of tabes. In a second case the other data were negative except for the increased cell count.

In Group II, clinically general paresis, a positive gold reaction for syphilis was obtained in all cases with one exception, which was an early general paresis. In this case the other laboratory findings listed were also negative, clinical examination being the sole basis for diagnosis. The Wassermann reaction was particularly effective in this group.

Group III, cerebrospinal syphilis, is not noteworthy except in the relative intensity of the resulting gold reaction. Half of these cases show a strong reaction, being in this respect comparable with those of general paresis and greatly exceeding those of tabes, which only showed 25 per cent. of strong reactions.

TABLE II.

Disease.	Cases.	Tests.	Blood. Wassermann.				Spinal fluid. Wassermann.				Cells.			Globulin.				Gold reaction.		
			+	—	±	O	+	—	±	O	5 or more.	Less than 5.	O	+	—	O	±	Typical reaction for syphilis.	Positive reaction not typical of syphilis.	No reaction.
Tabes	24	28	4	12	2	6	11	12	1	..	10	11	3	7	7	10	..	28		
General paresis	12	17	8	3	1	..	10	1	1	..	10	1	1	9	1	1	1	16	..	1
Cerebrospinal syphilis	8	10	3	3	2	..	6	..	2	..	8	..	..	7	..	1	..	10		
Cerebral syphilis	3	3	1	2	..	..	..	3	..	..	1	1	1	1	..	2	..	3		
Spinal syphilis	4	5	3	..	1	..	3	1	..	..	3	..	1	3	..	1	..	4	..	1
Mental diseases	8	8	2	6	..	..	1	7	..	..	..	4	4	..	3	5	..	3	..	5
Tuberculous meningitis	4	5	1	1	2	..	..	..	1	3	4	..	..	4	..	..	..	..	5	
Purulent meningitis	1	4	..	..	1	..	..	..	..	1	1	..	..	1	..	..	..	..	4	
Epidemic cerebrospinal meningitis	1	2	..	..	1	..	..	..	..	1	1	..	..	1	..	..	..	..	2	
Influenzal meningitis	1	1	..	..	1	..	..	..	..	1	1	..	..	1	..	..	..	..	1	
Brain tumor	2	2	..	2	..	..	..	2	..	..	..	..	2	1	..	1	..	..	1	1
Poliomyelitis	1	2	..	1	..	..	..	1	..	..	..	1	..	..	..	1	..	..	..	2
Epilepsy	1	1	1	..	..	..	..	1	..	..	..	..	1	..	..	1	..	..	..	1
Miscellaneous diseases	15	15	..	15	..	..	..	1	..	..	2	10	3	1	7	7	..	..	..	15
Syphilis, but not of the central nervous system	8	9	4	1	3	..	..	8	..	..	2	5	1	..	4	4	..	4	..	5
Cases giving conflicting reaction	7	10	..	5	2	..	..	7	..	..	..	..	7	1	3	3	..	7	..	3

+ = positive. — = Negative. ± = Doubtful. O = Data not obtained.

Group IV, cerebral lues, presents one interesting case which was clinically diagnosed as polioencephalitis, and which later showed a typical gold reaction for syphilis. A syphilitic etiology was confirmed by a positive blood in spite of a negative spinal fluid to the Wassermann reaction. The patient died two weeks after the test, but there was no autopsy. A second case was negative to the Wassermann reaction in spinal fluid and blood, and the cell count was not increased, and there was no record of the globulin content. The gold test was positive.

Group V, spinal syphilis, contains a case of gumma of the cord in which all laboratory data except increased globulin content were negative. The gold reaction was also negative. This case improved under salvarsan. A second case was negative to the gold upon first examination, but later showed a positive result on another spinal fluid, the case being clinically syphilis, with a previous positive Wassermann reaction.

Group VI, which includes dementia precox, manic-depressive insanity, delirium tremens, alcoholic delusions, and a moral defective, shows the following analysis: One case of manic-depressive insanity with a positive Wassermann reaction on the blood had a gold test positive for syphilis. This latter result is not, however, absolutely trustworthy because of a slight blood tinge in the specimen of spinal fluid examined. Another case with a positive Wassermann blood and spinal fluid in a moral defective gave a positive gold test. A third case of questionable dementia precox in a woman, aged thirty-seven years, in which all the evidence was negative except that the spinal fluid was obtained under increased pressure, gave a positive reaction to the gold test. We have noted a number of cases clinically dementia precox which gave a positive Wassermann reaction in blood and spinal fluid or both.

Groups VII, VIII, IX, and X include the cases of meningitis. In the gold test all gave the changes of color in the high dilutions of the gold solution. (See Table I.) These reactions are easily differentiated from the reactions in the lower dilutions that are typical of syphilis.

Group XI. Two cases clinically brain tumor, one negative to the gold, but not typical of syphilis. The positive reaction in this case is similar to the reaction of tubercular meningitis.

Group XII. The one case of poliomyelitis on which two tests were done, gave negative gold reactions.

Group XIII. A case of epilepsy with other negative findings except a moderately positive Wassermann reaction on the blood, gave a negative gold reaction.

Group XIV consists of acute and chronic disease in which syphilis could be excluded with clinical certainty and gave a negative gold reaction in each case. This group includes one case of cerebral hemorrhage.

Group XV includes cases of syphilis, but with no evidence of any lesion in the central nervous system. The gold test was positive in four tests on three cases, all of which had positive Wassermann reactions in the blood.

The last group is summarized briefly as follows:

A case of cancer of the intestine which gave a positive and a negative gold reaction on the same fluid. The tests, however, were at intervals of over a week and the resulting bacterial contamination would easily account for this difference.

A case of gastric ulcer, with the same type of reaction as above, in which autopsy revealed gastric ulcer. The history was suspicious of syphilis, and the autopsy being a restricted one, gave no opportunity for examination of the spinal cord.

A case of acute pancreatitis, tested in our earlier experience with the reaction, gave a somewhat doubtful change.

A case of arteriosclerosis, with other negative findings for syphilis, gave a positive gold for this disease.

A case of pernicious anemia with nerve symptoms, which had been given salvarsan, showed a positive gold reaction for syphilis.

A doubtful case in a boy, aged four years, in whom either tubercular meningitis, poliomyelitis, or acute gastro-enteritis with cerebral symptoms was suspected, gave a positive reaction for syphilis on repetition.

A case with cancer of the stomach gave a positive and negative reaction under the same conditions as the second case. Autopsy revealed cancer of the stomach. The central nervous system was not examined.

In our experience the cases with syphilitic etiology do not give reactions typical for the resulting disease. For instance, it is not possible to differentiate between tabes, general paresis, and cerebrospinal syphilis, etc., except as above noted, that the reaction is more likely to be strong in general paresis and cerebrospinal syphilis.

Just how the reaction takes place and to what protein it is due is not known, and our study throws no light upon the question.

Discussion and Summary.—Scrutiny of the tables shows that the gold reaction is not parallel with the blood Wassermann reaction, the spinal fluid Wassermann reaction, the globulin or the cell count, but apparently more constant in syphilitic affections than any of the other tests.

The blood Wassermann reaction is present in only 43 per cent. of the cases diagnosed as syphilis of the central nervous system.

The Wassermann reaction on the cerebrospinal fluid was positive in 59 per cent. of the cases. Both were absent in 24 per cent. of the cases of presumable syphilis of the central nervous system. It is obvious then that it is not possible to exclude syphilis of the central nervous system on the basis of the Wassermann reaction on the blood or cerebrospinal fluid, or both.

Cell counts above 10 were found in 63 per cent. of the cases of syphilis of the central nervous system, and the counts were below 10 in 27 per cent. of the cases diagnosed as syphilis of the central nervous system. Cell counts under 5 are certainly within normal limits. Counts of 5 to 10 are doubtful. Counts above 5 were present in 75 per cent. of the cases. However, the cell counts are found in other conditions than syphilis beside purulent meningitis, notably tubercular and influenzal meningitis, anterior poliomyelitis, and brain tumor. One of us (Lee) has observed a cell count of 53 shortly after a uremic convulsion, in which case two days later the count was 0. The other tests were negative. The colloidal gold test was not done in this case. The cell counts are of distinct value, as an abnormal count is found in a high percentage of cases of syphilitic affection of the central nervous system. The value of cell counts is somewhat impaired by the fact that other conditions which may be confused clinically with syphilis often show a great increase in the number of cells.

The globulin test (Noguchi's[6] butyric acid test and Nonne's[7] ammonium sulphate test) has not been satisfactory in our hands. A standard of positive and negative reactions is difficult and ill-defined. There were many doubtful reactions.

The globulin test was positive in 77 per cent. of tested cases of syphilis of the central nervous system. This test is also positive in cases of tubercular meningitis, brain tumor, and other conditions.

The gold reaction typical of syphilis has occurred only twice in the absence of blood Wassermann reaction, spinal fluid Wassermann reaction, cell counts, and globulin. In both these cases the gold reactions were confirmed by the clincal diagnosis. The gold reaction usually occurs in combination with one of the other tests, but there is no constant association with any test. A gold reaction typical for syphilis has been obtained in the absence of each of the other tests. A negative gold reaction was obtained in only two cases in which the condition of the central nervous system was diagnosed as syphilitic.

The diagnosis of these cases is often difficult, and is occasionally determined by the laboratory findings. We have accepted the clinical diagnosis as final.

The disadvantages of the test are that the presence of blood or serum vitiates the findings, and that a certain amount of care must be used to prevent extraneous protein substances from contaminating the fluid or the reagent.

The advantages of the test are the small amount of cerebrospinal fluid required, 0.2 c.c., its technical simplicity, the sharpness of the reaction, and its delicacy.

[6] Serum Diagnosis of Syphilis (2d edition), p. 155.

[7] Syphilis and the Nervous System (translated by G. Ball), p. 341.

CONCLUSIONS. A gold reaction typical for syphilis is nearly constant in cases of syphilis of the central nervous system.

This test is more delicate than the blood Wassermann reaction, spinal fluid Wassermann reaction, cell count, and globulin content.

The test has the advantage that it gives a reaction with pathological spinal fluids due to other causes than syphilis, that is characteristic and easily differentiated from the reaction typical for syphilis.

Our experience confirms the findings of other observers that the gold test is delicate, and that the margin of error is exceedingly small.

THE EFFECT OF EXTRACTS OF SHEEPS' THYROID AND OF PATHOLOGICAL HUMAN THYROID UPON THE FATIGUE CURVE OF VOLUNTARY MUSCLE

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MUSCULAR weakness, independent of the emaciation which develops sooner or later as a feature of Graves' disease, is a symptom which has impressed many observers of this condition. Dock[1] in his article upon exophthalmic goitre in Osler and McCrae's *Modern Medicine* discusses this feature as follows: "Muscular weakness is another characteristic symptom. It is so rarely absent that it is strange that Askanazy's finding of muscular atrophy and degeneration has not been more widely confirmed. Fr. Müller gives some characteristic measurements showing the degree of weakness."

	Basedow's disease. Kilograms.		Normal woman. Kilograms.	
	R.	L.	R.	L.
Shoulder, adduction	3.8	3.6	13	12
Shoulder, abduction	1.9	1.5	15	12
Elbow, flexion	4.8	4.0	30	25
Elbow, extension	5.6	4.8	18	14
Finger, flexion	6.5	5.5	20	18
Hip-joint flexion	4.6	4.1	30	
Hip-joint extension	5.1	4.6	35	
Hip-joint adduction	4.5	4.5	15	
Hip-joint abduction	4.0	4.0	15	
Knee flexion	7.1	6.6	30	
Knee extension	13.4	12.1	40	

As a further development of the same line of observation, a definite muscular syndrome, that of myasthenia gravis, is not

[1] Exophthalmic Goitre, Osler and McCræ, 1909, vol. vi.