ABDERHALDEN'S TEST OF PREGNANCY.

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INGESTED albumin is acted upon by the digestive juices and split into its component molecules before it is suitable for entrance into the blood stream. If a foreign albumin be injected hypodermatically, protective ferments are elaborated in the blood plasma of the organism, which have the power of digesting this albumin. Schmorl, Weichard and Veit found syncytial elements in the blood during pregnancy, and Abderhalden felt that in case this were true these cell elements could only be removed from the blood stream by the action of the protective ferments which this foreign albumin had caused to be elaborated. Feeling that these ferments were more or less specific, he tested the proteolytic activity of the blood of pregnant individuals to the placental albumin of the same species.

To demonstrate this activity he used the polarimeter and the dialysis method. For the polarization method he prepared a placenta peptone. If serum is added to a clear solution of this peptone and the mixture incubated at body temperature, the presence of digestive ferments will be shown by the occurrence of a change in rotation to light. Observations are taken at intervals during the course of twenty-four hours. By comparing the rotation using nonpregnant and pregnant sera, he established a standard of rotation for each. In the first communications Abderhalden called attention to the difficulties surrounding the optical method, because of the uncertainty of securing a usable peptone even when his directions were carefully followed. He also placed emphasis upon the necessity of a very precise polarization apparatus and experience in its use. Consequently only a few have attempted to put the optical test into use.

The dialysis method is simpler. Albumin cannot pass through the pores of an animal membrane since the individual molecules are too large. If, however, the albumin is broken up by ferment action then the molecules become small enough to pass. If, when albumin and a digestive are dialyzed to water, the split products pass through the membrane and may be demonstrated in the dialysate by suitable reagents.

For dialyzing Abderhalden originally used fish skin condoms, but since these were of varying thickness the results were uncertain and now especial dialysis tubes have been prepared for the purpose. In the original technic the cleavage products were to be tested for by the Biuret reaction, but since the dilution was so great, the reaction was frequently in question. Abderhalden then used triketo-hydrindenhydrat or "ninhydrin" which gives a distinctly blue color upon boiling with albumin, peptones, polypeptides and amino-acids in extremely dilute solution.

Though Abderhalden has himself continued since the first to get perfect results, he has modified the technic in many of the steps from time to time, probably because of the failures reported by others. He insists upon the importance of every step in the technic, described below, and especially upon the maintenance of asepsis.

Preparation of the Placenta.—A fresh normal placenta is stripped of its cord and membranes and is washed free of all blood. It is then cut into pieces the size of a dime, placed in gauze and washed in running tap water until it is free of pink stain. This may be facilitated by squeezing the placenta in the gauze. Usually this requires from thirty minutes to an hour. Schlimpert and Hendry believe that the best results are obtained when the tap water is not too soft. They relate their ability to secure usable placental substance at Abderhalden's laboratory, but their inability to do so when they returned to Freiburg. They ascribe their difficulty to the fact that the Freiburg tap-water was too soft. They advise in such instances to work and squeeze the placental chunks in 0.9 per cent. sodium chloride solution until there is no question as to the absence of blood.

The blood-free placental fragments are then placed in two liters of boiling water to which has been added two drops of glacial acetic acid. If the placental fragments become brown, or the foam on the water is brown, the placenta has not been sufficiently freed of blood in the preliminary steps. After cooking briskly for one minute the water is poured off, the placental tissue drained and added to another two liters of fresh boiling water and cooked for five minutes.

Some of the water is then filtered through a hard filter paper. To

5 c.c. of the filtrate in a test-tube containing some glass beads is added 1 c.c. of a 1 per cent. solution of ninhydrin. If, upon boiling the mixture for one minute, it becomes blue, or a blue color appears within thirty minutes after boiling, the placenta is not yet free of the reacting substances and should be cooked repeatedly in fresh water until upon performing this test the fluid remains colorless or yellowish. The prepared placenta may be conserved for future use by placing it and some of its water in a sterile, wide-necked bottle, adding a few drops of chloroform and covering with a layer of toluene. We have found empty celloidin bottles very useful for this purpose, since they have wide necks and glass stoppers and are of suitable size. This material is to be kept in an icebox or other cool place and when care to prevent contamination is exercised may be kept usable for months.

When using this preserved placenta a quantity large enough to allow a bit the size of a pea for each test to be performed is removed by sterile tissue forceps and is rinsed under the tap in the grasp of the forceps. It is then placed in five times its volume of water and cooked for five minutes and the water then filtered through a hard filter. To 5 c.c. of the filtrate is added 1 c.c. of 1 per cent. ninhydrin. After a vigorous boiling for one minute and allowing to cool for one-half hour, no blue color should appear; in case the mixture remains clear or is slightly yellowish that placenta can be used for the tests. In case, however, the filtrate gives the blue color, then the boiling and testing is to be repeated until the placenta is freed of the test-giving substances. In order to do away with the possibility of contamination of the placenta conserved in this way, Hendry, after getting the placenta free of substances reacting to ninhydrin, dries and powders the placenta to a fine consistency and uses the powder in the tests. Abderhalden objects to the suggestion and claims that Hendry's contrary results are directly due to this departure in technic.

Dialysis Tubes.—The diffusion shells No. 579A of Schleicher and Schüll, of Düren, Rheinland, are used for the purpose. They may be secured of the chemical supply houses in boxes of twenty-five. These shells should be thin enough to allow cleavage products to pass, yet thick enough to retain albumin. The tubes are placed in sterile water until thoroughly soaked, then sterilized in boiling water.

To determine that the tubes are not too thin, 2 c.c. of serum is added to each tube and according to the further rules to be elaborated the tubes are incubated for twenty-four hours. The surrounding water should not give the test to ninhydrin; only such tubes as do

not are usable. To see that the tubes are not too thick 2 c.c. of a 0.1 per cent. Seiden peptone solution is used in the same way. The surrounding fluid in this instance should give the test; such tubes as do not should be discarded.

Reagent.—"Ninhydrin" (Farbwerke vorm. Meister Lucius and Brüning, Hoechst a. M.) may be secured from the chemical houses in this country in phials containing each 0.1 gm. The contents of this bottle added to 10 c.c. of sterile water gives the 1 per cent. solution necessary for the test. This compound is unstable in solution and should be kept in a colored bottle in the ice chest.

Since the quantities of ninhydrin used are 2 c.c. and 1 c.c. the tests may be facilitated by employing a pipette with markings to show these necessary quantities.

Securing the Serum.—Ten or more cubic centimeters are drawn from the median basilic vein either with a Luer syringe or by a specially arranged blood pipette. Since at the height of digestion the blood may contain sufficient dialyzable substances to confuse the test, it has been advised that the blood should be secured before the patient has breakfasted.

Care must be taken that all receptacles which will hold the blood are free of all moisture or substances which might produce hemolysis. Immediately after withdrawal the blood is gently ejected into a sterile centrifuge tube and put away on the ice to clot. If it is not possible to wait until enough serum is extruded, the tubes may be centrifuged at a low rate of speed until the serum floats in sufficient quantity for the test. Spinning at a high rate produces hemolysis. It is difficult always to secure clear serum, but only such serum may be used; if the slightest trace of hemolysis occurs the serum is unfit for the test.

Performance of the Test.—Everything which touches the serum or placenta or the inside of the tubes is to be strictly sterile and the hands of the tester are to be kept clean. A piece of the placental substance, which has been retested, the size of a pea, is placed in the bottom of each dialysis tube. To each tube is then added 1.5 c.c. of the suspected serum. This is transferred from the centrifuge tube to the dialysis shell by means of a long bent pipette such as is used in the Wasserman test or other serum work. Care is exercised that none of the serum touches the outside of the shell. The tube is then rinsed thoroughly under the tap while holding the thumb over the open tube end. The hands should be freely washed that no substances may be left on the outside of the tube to confuse the results. The tube is then placed in its sterile container. (For this

purpose we used a nitrogen funnel of about 30 c.c. capacity from which the lead tube had been cut short. Over the cut end we placed a bit of rubber tubing, the lumen of which was kept closed by a simple pinch-cock. This makes a receptacle of suitable size and allows the withdrawal of the liquid later without admixture of toluene. For the purpose of incubating these funnels were placed in ether cans containing a layer of fresh cotton in the bottom.)

Twenty cubic centimeters of sterile water is placed around the tube and a layer of toluene is introduced into both vessels, care being taken not to contaminate either the water or the serum.

The tubes are then placed in a reliable incubator for eighteen to twenty-four hours at 37.5° C. For each test to be made one tube should hold serum alone, another serum plus placenta, another placenta plus 1.5 c.c. of sterile water. The sterile water outside the tubes in every case should stand higher than the level of the fluid in the dialysis shells.

At the end of the incubation period 10 c.c. of the surrounding water is removed to a large test-tube containing some glass beads. Care must be used not to include the toluene. When the funnels are used all the water is to be drawn off first and mixed before the 10 c.c. is taken for the test, since the diffusion does not seem to occur equally throughout the water, the upper part being more thoroughly saturated usually than is the lower part. To the 10 c.c. of water is added 0.2 c.c. of a 1 per cent. solution of ninhydrin and the mixture boiled briskly for one minute and allowed to stand for thirty minutes. If a blue color is obtained the reaction is positive, when negative the solution is colorless or slightly yellowish. In case of doubt, looking through the liquid from above allows one to come to a decision; even faint traces are to be called positive. The test is positive when a reaction is obtained in the tube containing serum and placenta, while the other two tubes fail to react. A reaction in either of the two other tubes show either that they originally contained dialyzable, reacting substances, that the tubes were defective, or that contamination has been introduced, since bacterial action also produces digestion.

When the serum plus placenta tube alone reacts, if the tube is not shown to be defective, and asepsis has been good, it means that the serum has exerted a digesting effect on the placenta, and that the products have passed through the membrane into the water. According to Abderhalden, that serum is from a pregnant patient, otherwise the reaction would be negative, since the serum of a nonpregnant patient is not supposed to have the necessary digestive ferments.

After the test all glassware, as well as the dialysis tubes, are to be thoroughly washed and resterilized, and kept clean until a new test is to be performed. The tubes may be kept in sterile water under a layer of toluene. Each tube may be used for several tests, but from time to time its state of permeability is to be retested.

Abderhalden has performed more than 200 tests, personally, mostly on normal pregnant women. He has reported thirty cases involving differential diagnosis between tubal pregnancy and adnexal swellings. In all cases the biological test agreed with clinical findings, except in one case where, though the dialysis test was positive, a salpingitis was found at operation. In this case dialysis was positive both before and after operation. The patient had missed a period, there was colostrum in the breasts, and the uterus was enlarged. The clinical diagnosis was also ectopic pregnancy. He believes in this instance that the salpingitis may have been subsequent to an infective abortion.

Franz and Jarisch, though using the earlier technic and fish skin condoms, never found the dialysis test in error. They, however, found that chorioepithelioma and cancer of the cervix gave a positive reaction with placenta. Franz, using the now abandoned technic, supported Abderhalden's findings regarding the pregnant patients. He obtained a pregnancy reaction in one case that had a cancer of the cervix.

Schlimpert and Hendry examined 316 cases. They met with a great many difficulties in the first part of this work. In seventy-nine cases they used the latest modified technic. In thirty-nine nonpregnant cases all gave negative tests. The sera of twenty-eight pregnant women all reacted positively, even one who had gone over her period but four days and subsequently presented the clinical diagnosis of pregnancy. Of ten puerperal women, nine reacted positively; eight were in the early puerperium, one in her thirteenth day; the one which reacted negatively had confined four weeks previously.

Lindig had no pregnancy which failed to react, yet does not consider the test specific since he finds that in pregnancy, carcinoma and in other tumors, the reaction occurs with equal distinctness whether placental, carcinomatous, or tumor substance is used in the dialysis tubes. Abderhalden assails his results because he used powdered placenta, and asserts that when the properly prepared placenta is used, reaction is obtained only in case the patient is or has recently been pregnant.

Veit considers the Abderhalden reaction a valuable diagnostic method and relates that on the basis of a negative dialysis test,

in a case where pregnancy could not otherwise be eliminated, he operated and enucleated a myoma from the uterus. He has seen positive value in the differential diagnosis of ectopic pregnancy.

Henkel, from an experience in forty cases, had no failure in diagnosis. The serum of an eclamptic failed to digest an eclamptic placenta, however. The reaction was positive in a case which at operation revealed an ectopic pregnancy on one side and an inflammatory tumor of the opposite appendages.

Ekler had constantly negative results in twenty-five nonpregnant individuals while in thirty-seven pregnant women he always obtained the reaction. Most of his pregnancies were in the first week; four were ectopic pregnancies and six were incomplete abortions.

Frank and Heimann, though using fish bladders and the Biuret reaction, never had an error in dialysis, except twice when defective membranes had been used, aside from two cases which reacted positively and were operated as ectopic pregnancy when they had postabortive infection. Later, in an article regarding their experience in the diagnosis of carcinoma they relate that in spite of following the latest technic, in which tissue is rid of reacting substances just prior to the performance of the test, that the sera of carcinomatous subjects react with either carcinomatous or placental substance. Their carcinomatous test-tissue was obtained from carcinoma of the uterus. In sixteen cases of ovarian carcinoma fourteen reacted positively to both placental and carcinomatous tissue, while two were negative. Cancer of the uterus was constantly positive to both test substances. One man who was apparently normal reacted to carcinomatous tissue. In three doubtful cases of carcinoma of the uterus positive reactions were verified by operation. They say that they always get a positive result in pregnancy, though pregnancy will react to carcinoma tissue and carcinoma to placental tissue.

A. Meyer relates that a negative dialysis test was obtained before operation in a clinically positive case of ruptured ectopic pregnancy; while in a clinically questionable case which by operation showed an unruptured pregnancy on one side and a ruptured sac on the other, the Abderhalden reaction was positive. He asks whether the first case failed to furnish enough placenta to produce a reaction, or if the death of the ovum had produced the negative reaction.

Markus using the earlier technic found positive reactions in all of fifteen pregnant and puerperal women and three ectopic pregnancies while eighteen nonpregnant women gave negative results, though five carcinomatous women gave positive reactions to placenta.

Obeying the latest enunciations of Abderhalden he got twenty positives in twenty pregnant women, one of whom was only ten days past her expected period. Eleven carcinomatous individuals were tested to placental tissue; seven were absolutely negative, four faintly positive. Eight carcinoma patients were tested to cancer of the uterus tissue; five gave a positive, while three gave a negative result; these three had carcinoma of the intestinal tract. Of seven pregnancies five reacted negatively to carcinoma tissue and two faintly positive.

Engelhorn tried the dialysis method, using placental substance in 108 cases. Of sixty pregnant patients forty-nine were positive and eleven, who were in the last weeks of pregnancy, were negative. Of forty-eight nonpregnant individuals, thirty-one were positive and seventeen negative. Of twelve pregnant women tested with cancer tissue, ten reacted positively. Of eleven nonpregnant individuals eight were positive and three were negative, though one was a carcinoma patient. With ovarian substance three nonpregnant women reacted positively, while of three pregnant women one was positive and two were negative. With fetal lives he got both positive and negative tests in both pregnant and nonpregnant cases. Engelhorn consequently does not regard the Abderhalden test as of diagnostic importance.

Behne, using placental tissue and the earlier technic with special tubes and ninhydrin examined forty pregnant women in the last few weeks and got positive reactions in all but one. In thirty sick individuals who were not pregnant he found thirteen reactors and seventeen nonreactors. Nearly all who reacted had a suppurating genital condition. Following the most recently elaborated details, he tested sixty sera to placental substance. Among twelve pregnant women, eight gave the test and two, though near term, did not react. Of four ectopic pregnancies controlled by operation three cases were positive and one was negative. Of fifteen infection cases tested at varying periods of from seven days to three and a half months after confinement, thirteen reacted and two failed to react. Of twenty-six women who were not gravid and had not been so for a long time, one-half were positive, one-half negative. Three men suffering from advanced tuberculosis all reached positively.

Freund and Brahm have performed 141 pregnancy tests on 135 patients, on six cases having done two tests each. The optic test was performed 134 times, the dialysis test ninety-nine times. The clinical findings agreed with the optic reaction in the 134 cases but ninety-seven times or 72.4 per cent. and with the ninety-nine

dialysis tests but sixty-six times or 66.7 per cent. In ninety-two of the dialysis tests a control optic test was run; agreement occurred in sixty-one instances, in the remainder no harmony existed. They could not notice excessive rotation in their seventeen eclampsia cases. Of three ectopic pregnancies only one reacted positively while of four inflammatory adnexal swellings one reacted positively to dialysis and negatively to the polarization method.

Abderhalden with the optic method relates that in what is now a large experience he has had no failures. He apparently repudiates the joint article of Abderhalden, Freund and Pincussohn, in which numerous failures to get a positive reaction during pregnancy are related, among which are fourteen failures in fourteen patients in the ninth and tenth months of pregnancy.

Williams and Pearce met with great difficulties in the use of the fish skin condoms and with the Biuret reaction, but later with diffusion shells and ninhydrin they got constant positive results in twenty-eight pregnant and eight postpartum cases, one of which latter gave a faintly positive reaction twenty-five days after labor, while the two controls were negative. Using pregnant sera, they found, however, that the serum of pregnancy reacts with tissues other than placenta (kidney, breast, uterus) and with other than human tissues (dog's kidney). Also sera of various sick and healthy individuals gave the reaction with placenta and other tissues. Just as satisfactory results as by dialysis were obtained by mixing tissue and serum in tubes and after incubating for twenty-four hours, testing the filtrate obtained on coagulation by heat and acetic acid with ninhydrin. Inactivation of the serum caused a great diminution in the intensity of the reaction, but did not cause it to disappear. They found that the reaction power may persist in a serum for a week, if properly kept.

McCord, using a dessicated placental powder of his own manufacture and celloidin thimbles as dialyzing tubes, asserts that in 204 tests the findings were in 95 per cent. of cases correct. The 5 per cent. of failures he attributes to errors in technic.

Epstein testing sera to carcinomatous tissue obtained a positive in all but one of thirty-seven cancer patients, while only one of forty-seven cancer-free cases reacted. When placental substance was used only one of eighteen pregnant women gave a negative test.

Rübsamen relates only one error of diagnosis in 100 tests performed on ninety-four cases. In fifty-six cases both the optical and dialysis methods were used. Among thirteen eclamptics the sera of ten digested placenta; while no reaction was obtained in

three severe cases. He feels that the method offers a means of making a prognosis. In emaciated subjects he advises that only 1 c.c. of serum be used in the test.

Stange reports that in seventy-eight examinations the test was never in error.

Schiff found agreement between test and clinical diagnosis in all of forty-seven cases which he examined. He tested twelve pregnant women to cancer tissue and all reacted negatively.

Schafer made 123 dialysis examinations sixty-five of which were controlled by polarization. Of sixty-two cases of pregnancy, two failed to react. He had eleven nonpregnant individuals react positively most of whom were carcinoma and fibroid subjects. Of the sixty-five optical tests one positive reaction was given by a uterine fibroid and a negative test was given by a pregnancy. Two pregnancies and two carcinoma cases reacted to both cancer and placental tissue.

In seventy tests Lichtenstein found only one instance where the test did not agree with the clinical diagnosis. In this case a negative test was given by a pregnancy where the ovum had been dead three to four weeks.

Jellinghaus and Losee reported on 563 dialysis tests. They have reported their cases divided into six series according to the technic used. In the last series which nearest conforms to Abderhalden's claims they got 5.5 per cent. of negative reactions in eighty-nine pregnant sera and 8 per cent. of positive reactions in forty-nine nonpregnant sera.

One year ago when Abderhalden still advocated the use of fish skin condoms and the Biuret reaction, feeling that the sources of possible error in the method as then used were too great to yield promising results and thinking that possibly the ferment action of the blood might not be specific to placental albumin one of us began to test the activity of the serum of pregnant and nonpregnant humans to ordinary commercial peptones.

Twenty c.c. of 2 per cent. sterilized aqueous solution of Witte peptone was mixed with 10 c.c. of blood serum in a sterile flask. Of this mixture 10 c.c. was withdrawn immediately and titrated for amino-acids according to the formalin method of Sorensen-Ronchesi. After incubation of the remaining portion for twenty-four hours the titration was again performed. The difference in titer represents in terms of 1/10 normal KOH the increase of amino-acids as the result of digestion.

	Immediately.	24 hrs. later.	Difference.
	c.c.	c.c.	c.c.
Normal pregnancy at term	2.05	3.25	1.2
Normal pregnancy at term	1.85	2.1	1.25
Normal pregnancy at term	1.4	2.1	0.7
Normal pregnancy at term	2.1	2.4	0.3
Normal pregnancy at term	2.0	2.3	0.3
Normal pregnancy at term	1.9	2.7	0.8
Normal pregnancy at term	2.05	2.3	0.25
Normal pregnancy at term	2.0	2.7	0.7
8 1/2 months' pregnancy	2.05	2.3	0.25
Hysteria (menses regular)	2.0	2.7	0.7
Hysteria (menses regular)	2.05	2.7	0.65
30 days after hysterectomy	2.1	2.75	0.65

In four other cases instead of peptone solution placenta was dessicated and powdered and a 1 to 200 suspension was made and tests made in the same manner as already described.

	Immediately.	24 hrs. later.	Difference.
	c.c.	c.c.	c.c.
Pregnant at term	0.9	1.1	0.2
Pregnant at term	1.1	1.1	0.0
Hyperemesis gravidorum third month	1.0	0.95	0.05
Nonpregnant	0.9	0.9	0.0

From the titration experiments with peptone it will be seen that the peptolytic activity of the blood varied in intensity, but that the variation could not be brought into correlation with the gravid or nongravid state of the patient, but depended upon factors not ascertained. From the four cases in which placental suspension was used no proteolytic activity could be demonstrated by an estimation of the amino-acids. If digestion of the placenta occurred it was either not carried to the amino-acid stage, or was not measurable by the method used. The few experiments as performed did not yield promising results so that this part of the work was abandoned.

Abderhalden continued to publish positive results with the dialysis method and when the use of ninhydrin and diffusion shells was advocated we took up the test. We used the dialysis tubes No. 579, 16 mm. in diameter. Seidenpeptone not being procurable, we used wittepeptone and normal horse serum to test our tubes. The tests were performed with the strictest adherence to each new elaboration of the test as discovered by Abderhalden from time to time. Full regard to asepsis was paid and the facilities for work were satisfactory in every way.

By the technic in which the placenta was not reboiled and retested just prior to the test, eleven cases were examined, of whom four were pregnant and seven nonpregnant. Each of the four pregnant women gave a positive reaction. Of the seven nonpreg-

nant individuals only two failed to react. Of the five who reacted positively two were males with syphilis; one woman had been operated one week earlier for tuberculous peritonitis, the uterus and appendages having been removed one year previously; one woman clinically nonpregnant but who had not menstruated for months, suffered from multiple ulcers of the rectum, probably syphilitic.

Since rendering the placenta free of reacting substances before testing, we have tested seventeen individuals. Of five women who were not pregnant, one reacted positively. This patient had periods of amenorrhea from some cause not ascertainable. Of seven pregnant women from all periods, two reacted negatively in the 6th and 14th weeks respectively, who subsequently developed positive signs of pregnancy. The women from the 14th week subsequently gave a second negative test. Of five puerperal women, two who had been delivered thirteen and twenty days prior to the test reacted negatively, the other three women were from the earlier puerperium and reacted positively. The dialysis tubes used in the adverse tests had previously and subsequently given positive reactions. Positive tests occurring when not expected can be explained on the basis of an error in technic, while a negative test is not so easily explained.

A review of the literature and an experience with the test, together with the use of other means of testing the digestive activity of the blood, leads one to question the specificity of the test of Abderhalden; though, since the need of such a reaction is great the test should be further tried, and its results accurately reported.

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PEOPLE'S GAS BUILDING.