

THE FRIEDMAN TEST TECHNIQUE AND INTERPRETATION

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The Friedman test¹ was devised principally to aid in the early diagnosis of pregnancy. The test can also be used for diagnostic purposes in a number of other conditions in which there may be reason to suspect an excess of gonadotropic hormone in the urine.² This is especially true in conditions of pituitary dysfunction due to a primary pituitary hyperactivity or secondary pituitary hyperactivity resulting from hypogonadism including the menopause and where there is chorionic epithelium in the body. In cases of pituitary tumor the test is useful not only in estimating the degree of hyperactivity of the gland, but also in checking the decrease in pituitary activity once roentgenotherapy has been started. The use of Friedman tests at frequent intervals when patients are being treated with roentgenotherapy for pituitary tumor often indicates a reactivation of the glandular tumor after a period of quiescence. The degree of the positive reaction, found so often at the onset of the menopause, may be of considerable value in governing ovarian therapy in order to relieve the symptoms due to the secondary pituitary hyperactivity.

Although the test is primarily qualitative, with care it can be used in a roughly quantitative manner. In order to accomplish this, certain features of the reaction which are herein described require special attention.

The Friedman test is done at the Cleveland Clinic according to directions received in a personal communication from Dr. Maurice Friedman in 1931. Slight modifications having to do with the collection of the urine and not with the actual technique of the test were instituted by Dr. E. Perry McCullagh.

TECHNIQUE

The urine: One of the modifications made by Dr. McCullagh was the collection of a concentrated morning specimen of urine for the test instead of using a routine specimen. The fluid intake is restricted to six ounces from 4 p. m. on the day preceding the collection of the specimen until it is collected the following morning. All urine voided during the evening and night is discarded and only the first morning specimen is saved for the assay. Except in cases where there is a disturbance in the water metabolism, the specific gravity of a morning specimen under these circumstances should be above 1.020.

The urine is refrigerated for some hours before it is injected; this causes a precipitation of phosphates and urates which are filtered out. Cloudy urine is never injected. If the urine be alkaline, it is acidified

with hydrochloric acid until it is acid to litmus paper. The urine is warmed to approximately body temperature before it is injected.

The animals: With the exception of the chinchillas, all varieties of rabbits used have been used quite satisfactorily.

It has been found that rabbits that have had young are preferable to virgins. In virgin rabbits quite a large percentage have ovaries which are inactive and apparently remain so throughout life. Such animals, of course, cannot be used. If an animal has had young, one would infer that the ovaries function normally. If the rabbit is tested with pregnancy urine before she is used as a test animal and if a reaction is noted, one is doubly confident of the reliability of readings of future tests. We have tested virgin rabbits with pregnancy urine over a period of years, using the technique described above and some never give a positive reaction while others give a positive reaction on one specimen but not on another.

Method: Using a nonpregnant adult female rabbit, 4 cc. of acid urine are injected intravenously three times daily for two days. The marginal ear vein and a 23 gauge needle are used. Forty-eight hours after the first injection the animal is opened under ether anesthesia and the ovaries examined.

In using this test, the following points must be kept in mind:

1. Alkaline urine is never injected.
2. If unusually large quantities of acid are required to neutralize the urine, it is frequently found to be so toxic that it kills the test animal. Under these circumstances, it is therefore usually best to obtain another specimen. However, the test can occasionally be successfully completed by making two injections an hour and a half apart, using 2 cc. at each injection.
3. The urine must always be refrigerated and filtered and if it is cloudy after filtration, it should not be used since it usually results in the death of test animals.
4. The urine should be injected slowly; two cc. per minute.
5. Handle the rabbits gently in order to prevent injuries to the lumbar nerves thus causing paralysis of the posterior portion of the body.
6. Specimens of urine from women who are being treated for pelvic inflammatory disease usually kill rabbits on the first injection.
7. Test rabbits should be kept in strict isolation, contrary to the opinion of some workers. False coitus or even mechanical stimulation of the vulva will produce ovulation and hence ruptured follicles and corpora lutea.
8. The rabbits can be used reliably for another test ten days after a positive reaction has been obtained even though ruptured or hem-

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orrhagic follicles, or fresh corpora lutea were present at the last test. The ruptured follicles will have disappeared in that time. Hemorrhagic follicles do not disappear, but recede to a small and firm black spot that is *not raised above the surface of the ovary*. If there is any doubt about the freshness of a hemorrhagic follicle, it should be pierced with a needle; a fresh one will ooze blood, while in an old one the blood has coagulated.

Fresh corpora lutea may easily be distinguished from atretic corpora lutea by the network of fine capillaries which cover the surface, the nodular appearance, and the distinct elevation above the surface. The color is also a distinguishing characteristic. Fresh corpora lutea in the rabbit are not yellow as the name implies, but are pinkish yellow. Old corpora lutea are chalk-white; they have lost the surface capillaries and are not distinctly elevated above the surface of the ovary.

9. Immediately upon opening the rabbit it is advisable to note the amount of congestion of the uterine horns. Handling causes rapid congestion of the organs.

INTERPRETATION

An excess of gonad-stimulating hormone, if it be great enough, produces a positive Friedman reaction. By a positive Friedman reaction is meant the production of either ruptured or hemorrhagic follicles, or fresh corpora lutea. The reaction that may occur in other parts of the reproductive tract is not taken into consideration. An excess may be excreted in a number of conditions other than pregnancy and in both male and female.

For five years an arbitrary method has been used in this institution for recording the results of Friedman tests. It was found that all the significant changes in the genital tract of a female rabbit could be recorded in a tabular manner. The degree of reaction is noted in plus signs, one to four signs being used. A typical positive reaction is indicated in the following table. The degree of reaction can be compared with the normal activity of the organs which also is indicated.

| | <i>Normal</i> | | <i>Normal</i> |
|----------------------------------|---------------|----------------------------------|---------------|
| Swelling of Uterus <u>+++</u> | 0 to + | Mature Follicles <u>+</u> | 0 to ++ |
| Congestion of Uterus <u>++++</u> | 0 to + | Ruptured Follicles _____ | 0 |
| Congestion of Oviducts _____ | 00 to + | Hemorrhagic Follicles <u>+++</u> | 0 |
| Congestion of Ovaries _____ | 0 | Fresh Corpora Lutea _____ | 0 |

DISCUSSION

As mentioned previously, there are different types of positive reactions; likewise there are different types of negative reactions.

According to the table above, one can see that a marked reaction may occur in the uterine horns, oviducts, and ovaries without any marked follicular activity in the ovaries. An abnormal amount of swelling of the uterine horns and an abnormal amount of venous congestion in the uterine horns, the oviduct, and the ovaries, although they do not constitute a positive Friedman reaction, are considered to be due to an excess of sex-stimulating hormone in the urine. The normal size and degree of congestion of the uterine horns and ovaries of the rabbit must be determined by experience.

The type of congestion and swelling of the uterine horns in positive Friedman reactions can be correlated with the reaction in the ovaries in most cases in aiding in accounting for the excess.

The injection of urine from pregnant women will produce a type of congestion in the uterine horns of the animal that is not simulated in a positive reaction caused by other conditions. The amount of swelling and congestion gives the uterus a velvety, transparent appearance, even though the color of the horns may be a purplish-black. This is accompanied by distinct convolutions of the uterine horns into a series of closely associated u-shaped figures. It is the opinion of the writer that in pregnancy the reaction in the ovaries varies in accordance with the duration of the pregnancy. During the first trimester, positive tests may be entirely different. Pregnancies of four weeks or less, *as a rule*, produce positive reactions indicated only by ruptured follicles. Pregnancies of five and six weeks usually produce both ruptured and hemorrhagic follicles. After six weeks of pregnancy and up to the seventh month, positive reactions, *as a rule*, are characterized only by hemorrhagic follicles. After the seventh month ruptured follicles and fresh corpora lutea predominate over hemorrhagic follicles. In most positive reactions in very early and late pregnancy, no hemorrhagic follicles are found. There are, of course, exceptions but they are few.

Positive Friedman reactions have been found during the menopause, in the presence of pituitary basophilism, hypogonadism in both males and females, diabetes mellitus, pituitary tumor, myopia, keratoconus, migraine, hyperthyroidism, prostatic hypertrophy, and testicular tumor, in some conditions of hyperpituitarism such as acromegaly, in some instances of hypertension, and in the presence of tumors containing chorionic epithelium. A positive reaction due to any of these conditions can usually be distinguished from that due to pregnancy by the characteristic appearance of the uterine horns rather than by the reaction in the ovaries. The uterine horns may be swollen and greatly congested

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but they do not have the velvety appearance nor are they convoluted as is characteristic of the uterine horns in the positive reaction of pregnancy.

SUMMARY

1. A review of the technique for the Friedman test has been made and attention called to various points in the technique which might prove difficult for the beginner.

2. The nature of the reaction in the oviducts and the uterine horns as well as that in the ovaries is discussed. It is shown that, by using these observations, the scope of the Friedman test can be considerably enlarged.

REFERENCES

1. Friedman, Maurice H.: Mechanism of ovulation in rabbit; demonstration of humoral mechanism, *Am. J. Physiol.*, 89:438-442, (July) 1929.
2. Hirsch-Hoffman, H. U.: Über die Ausscheidung der Hormone des Hypophysenvorderlappens im Harn bei endokrinen Erkrankungen, *Klin. Wchnschr.*, 11:94-97, 1932.