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THE THERAPEUTIC APPLICATION OF OVARIAN EXTRACT.* (Preliminary Report.)

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Organotherapy, or the therapeutic use of extracts from animals organs, has existed in some form since earliest times. It remained, however, for Brown-Sequard (1) in 1889 to put organotherapy on, at least, a working physiologic basis. This author promulgated the following theory. "All glands, provided or not with secretory ducts give to the blood useful principles whose absence is felt after their extirpation or destruction by disease." He reported excellent results with testicular extract in the rejuvenation of old men and, carried away by the idea that he had discovered the fountain of youth, Brown-Sequard had anathemas hurled at him by the scientific world, all because he claimed more than he could prove. Organotherapy suffered a blow from which it took years to recover. Nevertheless there was some good wheat among all the chaff.

The literature on the use of animal extracts in the treatment of disease, is voluminous. Ever since Brown-Sequard established his theory of the internal secretions, investigators in all lands have been working to reduce it to a firmer physiologic basis. Much of the best research work, along this line, has been done by the French. It will be impossible, however, in this short paper to touch on but a few of the more important of these investigations and only those concerning the use of ovarian extract in the treatment of disorders following artificial or physiologic menopause. Almost all the experiments upon animals have been made to test, first the toxicity of ovarian extract upon the male and, secondly to determine what metabolic changes are produced in the organism after castration. Animals are, as a rule, available only for experimental purposes when one can make use of some objective symptom. The symptoms of the menopause, either artificial or physiologic, are nearly all subjective, such as flashes of heat and cold, insomnia, extreme nervousness, etc. It has been noted, however, by many investigators that ovarian extract is poisonous to the male, to the pregnant female and causes certain metabolic changes that appear in the urine. These objective symptoms have been made use of in animal experiments.

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Curatulo and Tarulli, (2) conducted a series of experiments on bitches, in which they examined the urine before and after castration. They found that removal of the ovaries was followed by a diminution in the excretion of phosphorus. These authors conclude that:

1. The ovaries, like the other glands, according to Brown-Sequard's theory, continually pour into the blood an internal secretion, whose chemical composition is as yet unknown, which favors the oxidation of phosphorus-containing organic substances which build up the bones. It follows that by removal of the ovaries a retention of organic phosphorus is brought about, which removal results in a greater accumulation of calcium and magnesium phosphate and the restoration of the normal firmness of the bones." This fact has been made use of in the treatment of osteomalacia.

2. The elimination of nitrogen presents slight oscillations.

3. Carbonic acid expired and oxygen inspired diminish perceptibly up to a certain point then their quantity remains stationary.

4. The body weight increases gradually.

5. In injecting a medium dose of ovarian extract, the amount of phosphates eliminated is greater than exists before castration. With larger doses, the phosphates increase considerably.

6. The extirpation of the uterus and ovaries at the same time does not provoke modification other than those that take place after extirpation of the ovaries alone.

Ferre and Bestion (3) conclude after a series of experiments on animals, to determine the toxicity of ovarian extract, as follows:

1. That ovarian extract has a specific action.

2. That it is less toxic for normal females than for normal males.

3. That it is as toxic for pregnant females as for males.

4. That it is toxic under the same conditions for castrated females, for young females and in those whose ovaries have not yet functionated.

Other laboratory workers have reported the results of their animal experimentation and they agree in general with those just given. Many clinical reports have been made as to the efficacy of ovarian extract. Mention will be made of only a few. Krusen (4) used ovarian extract in a series of cases and met with varying results. He concludes as follows:

1. The employment of ovarian extract is practically harmless.

2. In amenorrhea and dysmennorrhea no good results secured.

3. Best results in artificial menopause.

4. No appreciable results in natural menopause.

5. No definite or exact reliance can be placed upon the drug as it often proves valueless when positively indicated.

6. In cases where relief was obtained, it was due to mental suggestion rather than to the physiologic action of the drug.

Jacobs (5) in reporting 244 cases gives the following tabulated results:

Definite cures	116
Transitory cures	48
Betterment	61
Failures	19

244

Mosse (6) gives his results in 41 cases as follows:

Complete cures	6
Rapid betterment	25
Transitory.....	5
Failures	5

41

Cases of amenorhea, dysmenorrhea, chlorosis, and menorrhagia, treated with ovarian extract, have been reported with varying success.

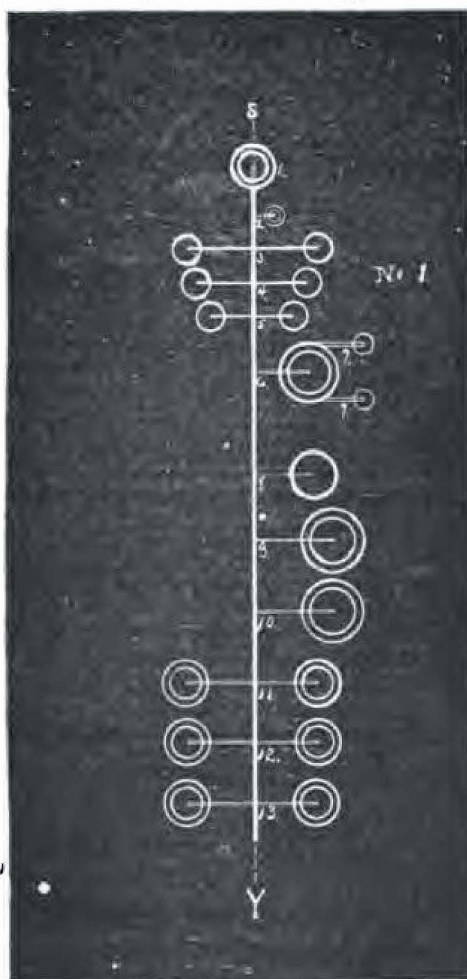


Chart No. 1.

S-Y—The sympathetic chain. 1—Pituitary or Hypophysis cerebri. 2—Pineal gland or Epiphysis cerebri. 3—Parotid gland. 4—Submaxillary gland. 5—Sublingual gland. 6—Thyroid. 7—Parathyroids. 8—Thymus. 9—Spleen. 10—Pancreas. 11—Adrenals. 12—Kidneys. 13—Ovaries (testes). (Schematic.)

A most important fact and one that I hope you will keep firmly fixed in your minds is that, in the use of any extract of whatever organ,

the extract should be carefully and properly prepared. That many of the reported failures are due to a poorly prepared extract, I am most firmly convinced. The glandular tissues are most delicate and require the most careful handling. I have known of fresh ovaries desiccated in a bake-oven, ground into powder and this so-called powdered ovarian extract used in the treatment of disorders of artificial menopause. The same amount of saw-dust would produce as good results. Extremes of heat and cold, concentrated chemicals, exposure to the air, etc., will soon render glandular tissue per se inert. Only careful preparation and preservation will produce an active, ideal, physiologic extract.

Before taking up my experimental work, I would digress a moment to mention briefly the question of the reciprocal action of glands with an internal secretion. For a number of years, I have been convinced that all glands with a so-called internal secretion are more or less intimately connected. They exist in a sort of cosmic relation. (Chart 1.) Recently in Von Noorden's clinic in Vienna (7) some experimental work has been done that to a large extent supports this view. Experiments were performed on animals to show the inter-relation of the thyroid, pancreas and adrenals. Hyper- and hypo-function of each gland was produced and the result noted on the other two. (Chart 2.) Only the

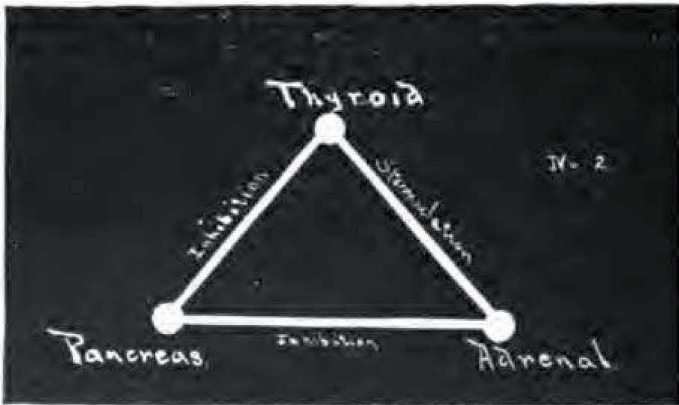


Chart No. 2.

(Schematic.) The authors (1. c.) were able to demonstrate that between the adrenals (chromafine system) and the thyroid a mutual stimulation existed, between the adrenals and pancreas and between the thyroid and pancreas, an inhibition. The inhibition was greater than the stimulation. For example, hyperfunction of the pancreas produced inhibition of both the thyroid and adrenals (chromafine system) hence an hypofunction of these two latter glands. Hyperfunction of the thyroid produced stimulation of the adrenals and inhibition of the pancreas, which latter caused also a stimulation of the adrenals by removing some of the inhibition from the latter. Other results might be noted. It was further demonstrated that this stimulation and inhibition was produced through the sympathetic fibers.

other day a case was reported in the Berliner klinische Wochenschrift (8) that adds additional weight to the theory of the reciprocal action of glands with an internal secretion. The patient entered the clinic suffering from amenorrhea. Examination showed atrophic ovaries with a tumor of the adrenals. The X-ray confirmed a tumor of the hypophysis as symptoms of acromegaly began to develop. Hypophyseal tablets were given with little or no effect. The author thinks that ovarian extract should have been tried owing to the pathologic condition

of the ovaries. The tumor so-called of the hypophysis was no doubt an hypertrophy. The trouble started in the adrenals, thus a lessened function of these glands was instituted and the equilibrium destroyed. The ovaries lacking something, furnished by the adrenals, atrophied, while the hypophysis, endeavoring to make up the deficiency, hypertrophied. Of course this is only a theory but it shows what possibilities there are in organotherapy on account of this reciprocal action.

To return to the subject in hand, the animal experiments undertaken were an attempt to establish:

1. Whether the ovarian extract was toxic to the male.
2. Whether castration changes the output of P2 O5 in the urine and if so, whether this can be brought back to normal by the injection of ovarian extract.

(Charts 3A, 3B, and 4.)

Cage ID	Anim. #	Sex-Weight	Operation	Date	† Date	No. of Inj.	PM Diagnosis	Remarks
	1	Male-350gr	Control	Jan. 14 '29	Apr. 2 '29	31	Killed	Weight-Feb. 20 '29 - 320grms
	2	285	25m. Ov. Ext. No. 11 (Type)		Mar. 2 '29	47	exam. male	Weight - 29 '29 - 310
	3	300	B.	Jan. 17 '29		3	By Peritonitis	Jan. 18 '29 - 310
	4	300	B.			3		370
	5	300	A.			3		370
	6	285	B.			3		370
	7	350	C.			3		370
	8	350	25m. Ov. Ext. No. 11			3		370
	9	370	B.			3		370
	10	370	CG		Jan. 18 '29	4		

Chart No. 3A.

Summary—All pigs in this series were injected as above indicated. All died in three days and showed, on post-mortem, beginning peritonitis, except pig No. 2. All pigs showed loss of weight, except pig No. 8. The extract used in the above was freshly prepared under sterile conditions.

Cage ID	Anim. #	Sex-Weight	Operation	Date	† Date	No. of Inj.	PM Diagnosis	Remarks
	1	Male-350gr	Control	Jan. 14 '29	Apr. 2 '29	42	Killed	Weight-Feb. 18 '29 - 420 Grams
	2	360	25m. Ov. Ext. No. 11 (Type)	Jan. 14 '29	Feb. 18 '29	45	?	370
			300					
			300					
			300					
	3	360	25m. Ov. Ext. No. 11 (Type)	Jan. 14 '29	Feb. 25 '29	55	?	370
			300					
			300					
			300					
	4	355	25m. Ov. Ext. No. 11 (Type)	Jan. 14 '29	Jan. 18 '29	18	?	370
			300					
			300					
			300					
	5	375	25m. Ov. Ext. No. 11 (Type)	Jan. 14 '29	May 18 '29	127	?	Feb. 18 '29 315
			300					
			300					
			300					

Chart No. 3B.

Summary—The pigs in this series were injected with the extract as above with no fatal results. All died from other causes. Both Extract No. 11 and Extract No. 12 were old.

Chart No. 4				Urine 24 Hrs.		P. O. in Grams			
Animal	Observation	Water 24 Hrs.	Weight	Am't.	Sp. G.	Total	per hour	per c.c.	
Rabbit No. 1	15	105 cc.	2.5 Kg.	114 cc.	1027	0.24060	0.01025	0.00210	
"	No. 2 before	17	73 cc.	3.09 Kg.	169 cc.	1033	0.120910	0.004925	0.000730
"	" after	24	102 cc.	2.50 "	115 "	1024	0.064710	0.002700	0.000560
"	" under	16	49 cc.	2.55 "	169 "	1024	0.043805	0.001825	0.000260
"	No. 3 before	21	106 cc.	2.50 Kg.	137 cc.	1041	0.122405	0.005095	0.001590
"	" after	25	64 cc.	2.50 "	131 cc.	1024	0.044990	0.001810	0.000345
"	" under	19	51 cc.	2.50 "	200 cc.	1022	0.059865	0.002475	0.000275
"	No. 4 before	26	72 cc.	2.25 Kg.	92 cc.	1027	0.024145	0.000995	0.000360
"	" after	18	32 cc.	2.30 "	105 cc.	1024	0.023175	0.000945	0.000355
"	" under	6	23 cc.	2.10 "	110 cc.	1013	0.021620	0.000890	0.000315
"	No. 5 before	22	55 cc.	2.40 Kg.	72 cc.	1024	0.024405	0.001015	0.000375
"	" after	25	46 cc.	1.70 "	81 cc.	1024	0.016980	0.000710	0.000255
"	" under	6	41 cc.	2.00 "	68 cc.	1020	0.022720	0.000940	0.000330

Chart No. 4.

Summary—The chart is, to a large extent, self-explanatory. The 24-hour urine was collected daily at the same time (7 a. m.) from each rabbit. The amount for 24 hours was measured, its specific gravity (Sp. G.) taken, its color noted, whether clear or cloudy, its reaction taken, and it was tested for albumin, sugar and bile. The sediment was centrifugated, examined under the microscope and the findings recorded. A careful record was kept of the amount and the kinds of food, also of the amount of water, that each animal ingested in 24 hours. The animals were weighed every few days and the weight recorded. A daily quantitative estimation of P2 O5 was made by the uranium acetate method, and the amount in grams recorded. From the total amount, the amount per hour and the amount per c.c. were easily obtained. In the above chart, only the average amount of the total number of determination, is given. For example, on rabbit No. 2 before castration, 17 daily determinations were made and 73 c.c. is the average amount of water ingested in 24 hours for 17 days, 169 c.c. the average amount of urine passed every 24 hours for 17 days, etc. The animal was then castrated and another series of observations started. The results of rabbit No. 1 are given only for comparison, as the animal died soon after castration.

The amount of P2 O5 excreted in rabbit No. 2 is less after castration. Under treatment with the extract, the amount of P2 O5 excreted is still less. This can easily be explained as small doses of an old extract were injected. The extract was practically inert. In No. 3, larger doses of a fresher extract were injected. The amount after castration was diminished, but increased under treatment. The increase was not marked. In No. 4 the results were more marked. Large doses of a fresh extract caused an increased excretion of P2 O5 greater than existed before castration. The amount per c.c. also increased proportionately. This was not the case in No. 3, showing that the increased excretion was only relative, being dependent upon the increased excretion of urine (200 c.c.). No. 5 shows a lessened excretion of P2 O5 after castration, with an increase almost back to normal after injection of the extract. The amount per c.c. was also proportionate. Extract Corpora Lutea only was used. Extract of the entire ovary and extract of the residue will be used in a later series of experiments.

Case No. 1. A patient, of Dr. E. E. Shifferstine, of Tamaque, Pa., is 36 years old, married, nullipara. Her family, personal and menstrual history are negative. On March 12, 1908, she was operated upon and both tubes and ovaries and the uterus removed. About three weeks after the operation, the patient began to experience, flashes of heat, insomnia, severe nervousness, and pain in the small of the back. The symptoms were all increased at the time when her menses should appear. In other words, she had a regular monthly exacerbation of these symptoms. Treatment was commenced with Ext. Corp. Lutea Gr. V t.i.d. The symptoms at once disappeared and the patient has been much improved. She has had only a slight return of the symptoms, which yield readily to treatment with the extract.

Case No. 2. A patient of Dr. F. E. McClure gives the following history. She is 47 years of age, Para IV, and with the exception, that one sister and one brother died of tuberculosis, her family history is negative. For the past five years she has suffered with enlarged thyroid and all the attending symptoms.

Her menstrual history is negative. On November 3, 1908, she was operated upon, when a partial thyroidectomy was done. On November 14, 1908, the appendix and a cyst of the right ovary were removed. Both ovaries were found to be small and atrophic. Since the latter operation, the patient suffered with flashes of heat and cold, insomnia, extreme nervousness, etc., all indicative of physiological menopause. On April 3, 1909, treatment was commenced with Ext. Corp. Lutea gr. V. t. i. d. The patient reported almost immediate relief and on April 14, 1909, she was given Ovarian Residue gr. V. t. i. d. with no return of the symptoms. From April 20th to May 1st, 1909, neither was given. The patient noticed a slight return of the symptoms on May 3, 1909. Ext. Corp. Lutea again given, gr. V t. i. d. and immediate relief obtained.

Case No. 3. Also a patient of Dr. F. E. McClure. This patient is 48 years of age, married, Para IV., with a negative family history. The patient began to fail mentally 15 years ago and four years ago was operated upon when both ovaries, tubes and the uterus were removed. The maniacal symptoms were not lessened but in addition she had all the symptoms of passing through the menopause, only that these symptoms were markedly increased. On September 15, 1908, the patient was given Ext. Corp. Lutea gr. V t. i. d., in addition to the usual treatment instituted in these cases. The patient was kept on the extract until March 1, 1909, and is at present (May 1), free from the symptoms incident to the menopause. Her mental condition is also much improved.

Case No. 4. A patient of Dr. G. E. Chene. She is 41 years old, widow, Para II., with a negative family and menstrual history. She was well up to three years ago, when she began to have symptoms indicative of the physiological menopause. These symptoms, such as severe insomnia, various parasthesias, occipital headache, etc., have increased each year. She was given Ext. Corp. Lutea gr. X t. i. d. The symptoms were at once relieved. The patient is still under treatment.

Case No. 5. A patient of Dr. T. A. McGraw, Jr. She is 36 years old, Para II., one abortion at 3 months 9 years ago. Family and menstrual history negative. Eight years ago one ovary (right) was removed. On November 30, 1908, she had an appendectomy, supra-vaginal hysterectomy and resection of the left ovary. A very small piece of the left ovary, apparently healthy, was left in situ. About 2½ months later the patient began to suffer greatly from hot flashes, pain in the back, severe insomnia, extreme nervousness, etc. On February 20, 1909, she was given Ext. Corp. Lutea gr. V t.i.d. On February 27, 1909, the treatment was stopped and all the symptoms, which had disappeared under treatment, returned. She was immediately put on the treatment again and the symptoms again disappeared. On March 10, 1909, unbeknown to the patient, she was given Ovarian Residue gr. V t. i. d. On March 25th she reported that all the old symptoms had returned and that the medicine seemed to do her no good. She was at once given capsules of Ext. Corp. Lutea gr. V t. i. d. No later report received.

Case No. 6. Also a patient of Dr. T. A. McGraw, Jr. She is 22 years old, married, Para I. Family and menstrual history negative. On January 2, 1909, a double salpingo-oophorectomy was performed. Seven weeks after the operation the patient complained of hot flashes and slight nervousness. Given Ext. Corp. Lutea gr. V t. i. d. In three weeks she noticed an improvement. One month later she reported that she had been without the capsules for two weeks and that the hot flashes and nervous symptoms had returned. She was given the Ovarian Residue gr. V t. i. d. Returned in a week still suffering from hot flashes, etc. Treatment with Ext. Corp. Lutea again started. No later report received.

Case No. 7. An inmate of the Eastern Michigan Asylum, is 39 years of age, single nullipara. Her mother died in the asylum and the patient has been inclined to brood over her condition. Menstrual history practically negative. Some slight attacks of pain in the right inguinal region are the only symptoms. On April 1, 1907, the patient was operated and both ovaries removed. Soon after, she suffered with flashes of heat and cold, insomnia, pain in the abdomen and lower extremities. On April 24, she was given gr. V. Extract Corpora Lutea t. i. d. The patient has had less soreness in abdomen, less nervousness, able to sit quietly for longer periods, has an improved appetite, in short there has been a general improvement. She is still under treatment.

Case No. 8. Also an inmate of the Eastern Michigan Asylum, is 38 years of age, married, Para V, one abortion at two months, three years ago. One brother insane, otherwise family history is negative. The patient, a Russian, was married at the age of 20. Menstrual history negative. Four years ago the patient was operated upon, when, as she says, a double oophorectomy was performed. Since then she has suffered with occasional flashes of heat, frequent flashes of cold, slight attacks of insomnia and with little or no pain. On April 28, 1909, the patient was given Ext. Corp. Lut. gr. V t. i. d., which treatment she is still taking. The physicians at the asylum report that the patient, at present, feels stronger, says the flashes of heat and cold are less frequent and that she feels more cheerful and better in every way.

As will be noted from the title, this is only a preliminary report of the work upon the use of ovarian extract. The research work upon animals will be carried further in the hope that more light may be thrown upon the question of the internal secretion of the ovary. It is to be hoped that further use of the extract will be made on clinical cases so that some definite conclusions may be drawn. If this short paper shall inspire other research workers to investigate this most fertile field of the internal secretions, the labor in its preparation shall not have been in vain.

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