THE EFFECTS OF GONADOTROPIC HORMONES IN THE TREATMENT OF EXPERIMENTAL TUBERCULOSIS*

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(Received for publication, October 30, 1936)

Whether the influence of pregnancy on the course of pulmonary tuberculosis is beneficent or malign is a problem which has baffled many clinicians and still remains unsettled. The early clinicians noted improvement during gestation and even recommended pregnancy as a therapeutic for tuberculous girls. However, at the beginning of this century the prevalent attitude was that pregnancy was very much to be avoided in the tuberculous woman. In recent years, this point of view has again been considerably modified. Although certain authors report aggravation of the tuberculous process during pregnancy in a percentage of instances varying anywhere from 10 to 100 per cent (1–3), a strong body of evidence is accumulating that pregnancy has no harmful effect in tuberculous women providing the disease is not too advanced or active and progressive (4–8).

It is apparent that conflicting points of view still prevail when pregnancy is considered together with its sequelae, parturition and puerperium. A much greater unanimity of opinion is encountered when the period of gestation is considered apart from the severe incident of delivery. Most observers find an amelioration of tuberculous disease during the course of gestation. Even those authors who hold that pregnancy is to be avoided in the tuberculous woman admit an improvement of the tuberculous condition during the early months of pregnancy. For example, Floyd (9) speaks of "a seeming improvement or arrest of the tuberculous process frequently noticed after the first months of pregnancy." Robinson (10) concludes that although parturition involves a special risk for the phthisical woman, the patient may show an apparent improvement during pregnancy; this beneficial effect usually disappears in later pregnancy.

* This study was supported in part by a grant from the Josiah Macy, Jr., Foundation.

The explanations that have been offered for the amelioration of symptoms in the tuberculous during pregnancy have been manifold. Sabourin (11) stresses the absence of catamenial intoxication; Ingraham (12), the care and rest that the patient receives during pregnancy. Fishberg (13) considers the possible beneficial rôle of congestion of the respiratory mucous membranes. Brachman (14) believes that the elevation of the diaphragm during gestation puts the lung at partial rest.

On the other hand, various theories have also been advanced in explanation of the possible harmful effect of pregnancy on tuberculosis. Jameson (15) regards the alteration of capillary permeability incident to the gravid state as a possible cause. Metabolic changes of pregnancy that have been considered in this connection include hypercholesterolemia (16), demineralization, and increased basal metabolism (15).

Studies in the experimental animal have not led to any definite conclusions. A favorable effect of pregnancy on experimental tuberculosis in guinea pigs has been reported by Müller (17), Jameson (15), Burke (18), and Bogen (19). However, Herrmann and Hartl (20) came to a contrary conclusion. Schmidt-Lange (21) criticizes the work of Herrmann and Hartl, and in an extensive series of experiments, he was unable to determine an unfavorable effect of pregnancy on the course of tuberculosis in guinea pigs.

A phase of the problem which appears to have been inadequately considered is the change in endocrine balance which is such a prominent feature of pregnancy (*cf.* Krause (22)). Presumptive evidence for increased hormone secretion exists in the characteristic hypertrophy which occurs in the pituitary, thyroid, and adrenal cortex. There is also evidence of hyperfunction of the parathyroid and pancreas. The placenta contributes its quota of hormones. However, exact quantitative estimates indicating increased hormone secretion have been obtained only for the estrogenic and gonadotropic hormones. The appearance of the gonadotropic hormone in the urine is so characteristic of human pregnancy that it is universally used as a diagnostic test for gestation (Ascheim-Zondek test (23)).

We undertook to investigate the effect of the gonadotropic hormone on experimental tuberculosis, in order to determine whether this hormone might be a factor in the increased resistance displayed by pregnant women.

In part of our experiments we employed blood serum from a 4 months pregnant mare. The serum (Squibb) was first titrated for gonadotropic hormone, by injecting small amounts into mice, and found to contain more than 1300 mouse

units per liter. Such serum, of course, contains all the hormones characteristic of pregnancy, especially the estrogenic follicular hormone, theelin, which increases throughout the course of gestation. We also studied the effect of the isolated gonadotropic hormone. For this purpose we utilized two proprietary preparations of this substance, antuitrin-S (Parke, Davis) and follutein (Squibb), both obtained from human pregnancy urine. Glandular anterior pituitary extract (Squibb), which contains growth-promoting, thyrotropic, and gonadotropic principles, was also included in this study, as was the placental extract, emmenin (Ayerst, McKenna and Harrison).[1]

After completion of the experiments here reported, we learned of certain Italian publications on related studies. Addessi (24) injected whole urine of pregnant women in tuberculous rabbits and found that the tuberculous process was accelerated. Of course, the repeated injection of whole urine introduces many factors in addition to the pregnancy hormones. Vercesi and Merenda (25) used isolated preparations of the gonadotropic and estrogenic hormones and concluded that these hormones do not aggravate tuberculosis in guinea pigs. However, only 5 animals were treated with the gonadotropic hormone and the infecting dose of tubercle bacilli was so great as to cause rapid generalization of disease and death within an average of 22 days. Repetti (26) could not detect any effect of the estrogenic hormone, folliculin, on tuberculosis in guinea pigs.

EXPERIMENTAL PROCEDURE

Rabbits and guinea pigs were the experimental animals employed, and only those which did not react to tuberculin were used. Weekly weight records were obtained throughout the course of the experiments. However, no useful correlation could be made between the weight curves and extent of disease. All animals were injected subcutaneously in the groin with a weighed amount of bovine tubercle bacilli (B1) in saline suspension. With the exception of the first experiment, hormone administration was begun the day of infection and was continued daily, omitting Sundays. In each experiment a group of infected animals remained untreated to serve as controls. At various intervals after infection one animal from each group was sacrificed and a comparative study was made of the extent of macroscopic tuberculosis. The estimate of the severity of the infection was based on the number, nature, and distribution of lesions in the susceptible organs, and was expressed in a scale of from 0 to 4+. The system of grading was essentially the same as employed by Petroff and Steenken (27): 0

[1] We are greatly indebted for the generous supply of hormones to Parke, Davis and Co., E. R. Squibb and Sons, and Ayerst, McKenna and Harrison.

indicates no tuberculous involvement; 1+ indicates a very few scattered tubercles in one or two of the susceptible organs; 2+ indicates a moderate number of tubercles in one or more organs; 3+ indicates somewhat generalized distribution in all organs or, in some instances, extensive active disease in one organ; 4+ indicates severe progressive generalized tuberculosis. Sections of the spleen, lymph glands, liver, kidneys, and lungs were fixed in Zenker's solution and studied microscopically. The histopathology of lesions in the treated animals did not appear to vary from that of controls.

The Effect of Antuitrin-S, Follutein, and Anterior Pituitary Extract on Experimental Tuberculosis in Rabbits

In our first experiment we utilized 24 young female rabbits, divided into 4 groups of 6 animals each. One group received no hormone treatment and served as controls. The remaining 3 groups received subcutaneous injections of one of the following hormones daily, except Sundays: (*a*) antuitrin-S, 0.75 cc., or 75 rat units; (*b*) follutein, 0.3 cc., or 75 rat units; (*c*) anterior pituitary extract, 2.0 cc., or 20 rat growth units. Antuitrin-S and follutein are both standardized according to their content of gonadotropic hormone, *i.e.*, ability to produce mature follicles, hemorrhagic follicles, and corpora lutea in ovaries of immature rats. Anterior pituitary extract is standardized according to its growth-promoting principle. The three experimental groups were pretreated for 10 days with the stated dose of hormone, and together with the control group were then infected subcutaneously with 0.01 mg. of a pathogenic bovine strain of tubercle bacillus (B1). Hormone treatment was continued until the animals were autopsied, at 74 to 114 days after infection. In general, when an animal died in one group, an animal from each of the other groups was also killed for comparative study. In each animal, the involvement of the susceptible organs was recorded on a 0 to 4+ scale, and a general estimate of the extent of the disease in the animal was obtained according to the system outlined above; and, finally, an average for the tuberculous involvement of each group as a whole was calculated (Table I).

It soon became evident that the animals of this experiment which were treated with the gonadotropic principle developed distinctly less tuberculosis than had the anterior pituitary-treated group and the controls. In every instance these animals showed less disease than those with a comparable survival period in the latter 2 groups. No tuberculosis whatsoever was found in the liver, spleen, or lymph glands of any animal treated with gonadotropic hormones. As the experiment progressed, it was apparent that the antuitrin-S-treated rabbits were slightly less diseased than the follutein-treated animals. One rabbit in the antuitrin-S group showed no tuberculosis in any

organ, although it survived for 92 days after infection. In another, which lived for 74 days, the infection in the lung was discernible only by microscopic examination. In the group which survived for 107 days, the antuitrin-S-treated animal showed only 1+ tuberculosis in the lungs, while the corresponding anterior pituitary-treated animal showed not only the involvement noted in the table, but also disease in the omentum, peritoneum, and pleura. The corresponding

TABLE I

Effect of Various Hormones on Tuberculosis in Female Rabbits

Time infected	Antuitrin-S 0.75 cc.						Follutein 0.3 cc.						Anterior pituitary 2.0 cc.						No hormone					
	Lung	Kidney	Liver	Spleen	Lymph glands	General estimate	Lung	Kidney	Liver	Spleen	Lymph glands	General estimate	Lung	Kidney	Liver	Spleen	Lymph glands	General estimate	Lung	Kidney	Liver	Spleen	Lymph glands	General estimate
days																								
74–80	1	0	0	0	0	1+*	1	0	0	0	0	1+*	4	0	4	4	0	4+	4	0	0	0	0	3+
90	2	2	0	0	0	2+	2	0	0	0	0	2+*			†				2	4	4	4	0	4+
91–93	0	0	0	0	0	0*	2	2	0	0	0	2+*	4	0	0	0	0	3+*	2	0	1	1	0	3+
104	1	0	0	0	0	1+	0	1	0	0	0	1+	4	0	4	4	0	4+*	4	1	1	0	0	4+
107	1	0	0	0	0	1+	4	3	0	0	0	4+	4	4	0	0	4	4+*	4	4	4	2	4	4+
114	3	1	0	0	0	3+	3	0	0	0	0	2+	4	1	4	1	0	4+	4	4	4	4	0	4+*
Average tuberculous involvement.....						1.3+						2+						3.8+						3.7+

Degree of tuberculous involvement recorded as 0 to 4+.

Rabbits injected subcutaneously with 0.01 mg. B1. Hormone treatment begun 10 days before infection and continued daily except Sundays.

* Indicates animal died spontaneously; death was usually due to intercurrent infection.

† This animal died 27 days after infection as a result of injury to spine, hence is not included in table.

control had tuberculosis of the diaphragm and pericardium, as well as in the more susceptible organs.

The average degree of tuberculous involvement of the various groups is recorded as: antuitrin-S 1.3+, follutein 2+, anterior pituitary extract 3.8+, and controls 3.7+. Of course these average values cannot be taken to indicate actual quantitative ratios for the different groups since they are based upon a series of relative, not

absolute numbers. Nevertheless they may serve to give some idea of the comparative involvement of each group as a whole. The conclusion that the gonadotropic hormones have retarded the progress of disease is borne out by the consideration that in every one of the six sets of comparative autopsies, the animals treated with the gonadotropic hormones showed less disease than did the corresponding control animals.

The Effect of Antuitrin-S, Follutein, and Anterior Pituitary Extract on Experimental Tuberculosis in Male Guinea Pigs

In this experiment the same three hormone preparations were tested on guinea pigs instead of on rabbits. Male animals were employed for this experiment as a convenient way of avoiding the possible complication of pregnancy. The gonadotropic hormones employed are known to affect the gonads of the male as well as the female. Anterior pituitary extract (growth hormone) also is effective in both male and female animals. We used 24 albino male guinea pigs, weighing 450 to 500 gm., none of which reacted to tuberculin. All the animals were infected with 0.001 mg. B1 (bovine tubercle bacilli), subcutaneously. They were then divided into 4 groups of 6 each. The first group was treated with antuitrin-S, 0.4 cc., or 40 rat units; the second with follutein, 0.16 cc., or 40 rat units; the third with anterior pituitary extract, 1.0 cc., or 10 rat growth units; while the fourth group was kept untreated for control purpose. The dosage was half that used in the rabbit experiment, but, considering the difference in weight of the animals, was proportionately larger. Hormone treatment was begun on the day of infection, and was continued daily except Sundays. The animals were sacrificed in groups of 4, at 35, 36, 37, 38, 39, and 41 days after infection. We chose a short survival period since it is known that the administration of hormones has a maximum stimulating effect for only a few weeks. It is believed that the administration of hormones over a long period of time may even have a harmful effect on the glands of internal secretion, due to overstimulation followed by a period of depression (Zondek (28)), or possibly because of the production of antihormones (Collip and Anderson (29)).

Again, in this experiment, the gonadotropic principle gave the best results, that is to say, animals treated with antuitrin-S and follutein had less tuberculosis than those treated with anterior pituitary extract and non-treated controls. Antuitrin-S again seemed much more effective than follutein in inhibiting the progress of the disease. In every instance, the antuitrin-S-treated animal showed considerably less disease than the corresponding animals in the other groups. The antuitrin-S-treated animal which survived for 37 days showed no

tuberculosis on gross examination, and microscopic study revealed only a slight involvement of one lymph gland. 5 of the 6 guinea pigs treated with this hormone were recorded as 1+ in the general estimate of disease, in striking contrast to the more or less generalized tuberculosis found in the other groups of animals. It is interesting to note that in this experiment the anterior pituitary-treated animals showed as much disease as the controls, and in some instances distinctly more. The values for average involvement were: antuitrin-S 1.2+, follutein 3.2+, anterior pituitary extract 4+, controls 3.8+ (Table II).

The Effect of Antuitrin-S and Anterior Pituitary Extract on Experimental Tuberculosis in Male Guinea Pigs

In order to confirm our results, we repeated our second experiment with certain modifications. We used a smaller infecting dose, 0.0001 mg. of bovine tubercle bacilli (B1) injected by the same subcutaneous route. The hormones were administered as before except that follutein was not used, as this preparation had previously proved less effective than antuitrin-S.

Twelve male guinea pigs, weighing from 500 to 700 gm., all non-tuberculin reactors, were infected. They were then divided into 3 groups of 4. The first group was treated with antuitrin-S, 0.4 cc., or 40 rat units, and the second with anterior pituitary extract, 1 cc., or 10 rat growth units; while the third group served as controls. In each group, one animal was sacrificed at 35 days after infection, one at 39, one at 40, and one at 41.

The efficacy of antuitrin-S was again strikingly demonstrated. The antuitrin-S-treated animals were in every instance less severely involved than the corresponding controls. The average involvement of the antuitrin-S-treated group was only slightly more than half that of the anterior pituitary-treated animals, and less than half that of the controls (Table III). Of the individual animals, the only 2 with involvement estimated at 1+ appeared in the antuitrin-S-treated group. Noteworthy is the absence of lesions in the spleen and lymph glands of all 4 antuitrin-S-treated animals. The other 2 groups showed extensive involvement of these organs in most instances.

In an attempt to determine whether temporary hormone treatment would influence survival time, another group of 12 guinea pigs was infected and treated in exactly similar fashion. Treatment was dis-

TABLE II

Effect of Various Hormones on Tuberculosis in Male Guinea Pigs

Time infected	Antuitrin-S 0.4 cc.					Follutein 0.3 cc.					Anterior Pituitary 1.0 cc.					No hormone				
	Lung	Liver	Spleen	Lymph glands	General estimate	Lung	Liver	Spleen	Lymph glands	General estimate	Lung	Liver	Spleen	Lymph glands	General estimate	Lung	Liver	Spleen	Lymph glands	General estimate
days																				
35	1	1	0	0	1+	0	2	0	0	2+	4	4	4	4	4+	4	4	4	0	4+
36	0	1	0	0	1+	4	1	4	0	4+	2	4	4	0	4+	4	4	4	0	4+
37	0	0	0	2	1+	3	4	4	4	4+	4	4	4	4	4+	4	4	4	0	4+
38	0	2	1	1	2+	3	1	2	1	3+	4	4	4	1	4+	4	4	4	4	4+
39	0	1	0	0	1+	3	2	2	0	3+	4	4	4	3	4+	4	2	4	4	4+
41	0	1	0	0	1+	3	4	2	1	3+	4	4	4	0	4+	2	4	3	0	3+
Average tuberculous involvement.....					1.2+					3.2+					4+					3.8+

Degree of tuberculous involvement recorded as 0 to 4+.

Guinea pigs injected subcutaneously with 0.001 mg. B1. Hormone treatment begun day of infection and continued daily except Sundays.

TABLE III

Effect of Various Hormones on Tuberculosis in Male Guinea Pigs

Time infected	Antuitrin-S 0.4 cc.					Anterior pituitary 1.0 cc.					No hormone				
	Lung	Liver	Spleen	Lymph glands	General estimate	Lung	Liver	Spleen	Lymph glands	General estimate	Lung	Liver	Spleen	Lymph glands	General estimate
days															
35	0	1	0	0	1+	0	4	0	0	2+	4	4	2	0	4+
39	0	1	0	0	1+	4	4	3	4	4+	4	3	0	0	3+
40	4	1	0	0	3+	4	3	3	4	4+	4	4	4	4	4+
41	1	1	0	0	2+	1	4	3	2	3+	4	1	4	4	4+
Average tuberculous involvement.....					1.8+					3.3+					3.8+

Degree of tuberculous involvement recorded as 0 to 4+.

Guinea pigs injected subcutaneously with 0.0001 mg. B1. Hormone treatment begun day of infection and continued daily except Sundays.

continued at 41 days after infection, and the animals survived from 149 to 305 days. It appeared that hormone treatment did not lengthen survival time nor lessen eventual involvement, but one is not justified in drawing conclusions from such a small group of animals, many of which died of intercurrent infection.

The Effect of Antuitrin-S, Pregnant Mare Serum, and Emmenin on Experimental Tuberculosis in Female Guinea Pigs

The results with the gonadotropic hormones were considered of such significance as to warrant a more comprehensive study of the hormone factors of pregnancy in relation to resistance to tuberculosis. We decided to use serum from a pregnant mare, since such serum contains all the hormones of pregnancy, and probably in their optimal proportions. We thought that even more favorable results might be obtained with such serum than with the gonadotropic principle alone. As previously mentioned, the serum we employed was obtained when the mare was 4 months pregnant. At this time the serum is rich in gonadotropic principle, estrogenic principle, and other hormones of pregnancy. We also included in this experiment another hormone characteristic of pregnancy, namely, the placental hormone, emmenin. This hormone is distinctive in that it is very successfully given *per os*.

In this experiment female guinea pigs were employed. It was thought that the administration of these hormones to female animals might provide a closer analogy to the situation in the pregnant woman. Proper precautions were taken to exclude pregnant animals from this experiment. 35 female guinea pigs, weighing 400 to 550 gm., were injected subcutaneously with 0.001 mg. of bovine tubercle bacilli (B1). They were then divided into 5 groups, as follows: the first 2 groups served as controls, one remaining untreated and the second receiving normal mare serum daily to serve as controls for the animals receiving pregnant mare serum; the third group received antuitrin-S, 0.4 cc., or 40 rat units; the fourth was treated with pregnant mare serum, 0.5 cc., or 0.7 mouse unit; and the fifth was treated with emmenin, 0.5 cc., or 5 oral day units. The hormones were administered daily except Sundays, by subcutaneous injection except in the case of emmenin, which was given twice daily *per os*. One animal from each group was killed at 28, 32, 35, 36, 37, 38, and 39 days after infection.

The value of gonadotropic hormone treatment was again apparent. In 5 of 7 instances the antuitrin-S-treated animal showed distinctly

TABLE IV

Effect of Various Hormones on Tuberculosis in Female Guinea Pigs

Time infected	Antuitrin-S 0.4 cc.					Pregnant mare serum 0.5 cc.					Emmenin 1.0 cc.					Normal mare serum 0.5 cc.					No hormone				
	Lung	Liver	Spleen	Lymph glands	General estimate	Lung	Liver	Spleen	Lymph glands	General estimate	Lung	Liver	Spleen	Lymph glands	General estimate	Lung	Liver	Spleen	Lymph glands	General estimate	Lung	Liver	Spleen	Lymph glands	General estimate
days																									
28	0	1	1	2	1+	0	1	0	1	1+*	0	4	2	4	4+	3	4	4	4	4+	3	4	3	3	4+
32	1	2	4	1	3+	2	1	2	2	2+	3	4	4	4	4+	1	3	1	3	3+	2	2	3	4	3+
35	0	1	1	2	1+*	1	0	3	3	3+	0	3	1	3	3+	1	4	3	3	3+	1	4	4	4	4+
36	0	1	1	2	1+	1	3	3	3	3+	1	2	4	4	4+	2	1	2	3	2+	1	2	4	3	3+
37	1	3	2	2	2+	0	1	1	3	1+	4	4	4	4	4+	3	4	1	3	3+	3	3	4	4	4+
38	0	0	1	3	1+	0	2	3	2	2+	1	3	3	4	3+	2	3	3	3	3+	2	2	3	4	3+
39	2	3	3	3	3+	1	1	1	1	1+	2	3	4	4	4+	1	2	2	4	3+	3	2	3	2	3+
Average tuberculous involvement.....					1.7+					1.9+					3.7+					3+					3.4+

Degree of tuberculous involvement recorded as 0 to 4+.

Guinea pigs injected with 0.001 mg. bovine tubercle bacilli (B1), subcutaneously. Hormone treatment begun on day of infection and continued daily except Sundays.

* Animal died of intercurrent infection.

less tuberculosis than did the corresponding control. In the other 2 instances the animals of both groups were equally involved. The pregnant mare serum gave approximately similar results. In 6 instances the animals treated with pregnant serum manifested less disease than the corresponding untreated animals and, in 5 instances, less than the guinea pigs treated with normal serum. The average degree of involvement was 1.7+ for the antuitrin-S group and 1.9+ for the pregnant serum group, values significantly lower than for all other groups. When considered from the point of view of animals showing minimal (1+) tuberculosis, these same 2 groups are again outstanding—the number for each group being: antuitrin-S 4, pregnant mare serum 3, all other groups 0 (Table IV).

Daily injection of normal mare serum did not result in any appreciable lessening of disease, although in 3 instances the treated animal showed slightly less involvement than the non-treated control. The average value is therefore slightly lower than for the non-treated controls.

The emmenin-treated guinea pigs fared worst of all the groups. In comparison to the non-treated controls the animals in this group showed more extensive disease in 3 instances, and less disease in only one instance. The average value for the group as a whole indicates somewhat more severe involvement than the controls.

DISCUSSION

It is apparent from these experiments that the gonadotropic hormone obtained from the urine of pregnant women exerts a favorable influence on the progress of experimental tuberculosis in both male and female animals. Of all the animals treated with antuitrin-S (6 rabbits and 17 guinea pigs), only 2 guinea pigs failed to show less tuberculosis than did the corresponding controls. Follutein, which contains the same hormone, also proved of some value in retarding the progress of disease, but was not as effective as antuitrin-S. It appears possible that the poorer results obtained with follutein may be due to the high concentration of glycerol present in this preparation. Long and Vorwald (30) have shown that injection of glycerol enhances the multiplication of tubercle bacilli in rats.

Pregnant mare serum, which is a rich source of gonadotropic

hormone, also proved very efficacious in retarding tuberculosis. In the one series in which it was tested, it gave results very nearly as good as did antuitrin-S. But it may be added that this serum which contains all the hormones of pregnancy did not prove superior to the use of the gonadotropic principle alone.

Anterior pituitary extract, containing growth, sex, and thyrotropic principles, proved of no value in retarding the progress of the disease, and in many instances animals treated with this hormone showed more tuberculosis than did the controls. One is reminded here of the lowered resistance to tuberculosis displayed by man during the period of most active growth—presumably the time when the secretion of growth hormone is greatest.

Placental extract (emmenin) given by mouth was likewise entirely ineffective in preventing progress of the disease, which in some instances was more invasive in the treated animal than in the control.

The results obtained suggest that the gonadotropic principle which appears during pregnancy may be an important factor in the increased resistance displayed by the pregnant tuberculous woman. The breakdown of this resistance that occurs during the later stages of pregnancy may perhaps be correlated with the diminution of this hormone, which begins after about the 5th or 6th month and ends with the entire disappearance of the hormone a few days after delivery.

The mechanism whereby the gonadotropic hormone influences tuberculosis remains to be determined. Experiments are planned in castrated rabbits to decide whether the hormone acts necessarily through a stimulation of the sex glands.

SUMMARY

Experimental tuberculosis in rabbits and guinea pigs was favorably influenced by the administration of antuitrin-S, pregnant mare serum, and, to a lesser extent, follutein. No retardation of disease was obtained by the use of either anterior pituitary extract or emmenin.

The results suggest that the gonadotropic hormone may be a factor in the temporary amelioration of symptoms observed in tuberculous women during pregnancy.

The authors wish to thank Dr. Earl T. Engle for his valuable advice throughout these experiments.

BIBLIOGRAPHY

1. Frischbier, G., *Beitr. Klin. Tuberk.*, 1931, **79,** 108.
2. Rist, E., *Brit. Med. J.*, 1927, **2,** 247.
3. Bernard, L., *Paris méd.*, 1923, **47,** 22.
4. Schultze-Rhonhof, F., and Hansen, K., *Ergebn. ges. tuberk.-Forsch.*, 1931, **3,** 223.
5. Ornstein, G. G., and Kovnat, M., *Am. Rev. Tuberc.*, 1935, **31,** 224.
6. Castlen, C. R., *Am. Rev. Tuberc.*, 1936, **34,** 340.
7. Forssner, H., *Acta gynec. Scand.*, 1925, **3,** 256.
8. Jennings, F. L., and Mariette, E. S., *Am. Rev. Tuberc.*, 1932, **25,** 687.
9. Floyd, C., *New England J. Med.*, 1935, **212,** 379.
10. Robinson, A. L., *J. Obst. and Gynec. Brit. Emp.*, 1931, **38,** 338.
11. Sabourin, C., *J. Pract.*, 1918, **32,** 561.
12. Ingraham, C. B., *Am. J. Obst. and Gynec.*, 1932, **23,** 1.
13. Fishberg, M., Pulmonary tuberculosis, Philadelphia, Lea & Febiger, 1932, **2,** 179.
14. Brachman, D. S., *Am. J. Obst. and Gynec.*, 1935, **29,** 880.
15. Jameson, E. M., Gynecological and obstetrical tuberculosis, Philadelphia, Lea & Febiger, 1935.
16. Krönig, B., and Schneider, K., in Mohr, L., and Staehelin, R., Handbuch der innerin Medizin, Berlin, Julius Springer, 1919, **6,** 158.
17. Müller, V., cited by Fishberg (13).
18. Burke, H., cited by Jameson (15).
19. Bogen, E., cited by Jameson (15).
20. Herrmann, E., and Hartl, R., *Z. Hyg. u. Infectionskrankh.*, 1907, **56,** 230.
21. Schmidt-Lange, W., *Arch. Hyg.*, 1935–36, **115,** 221.
22. Krause, A. K., *Am. Rev. Tuberc.*, 1935, **31,** 254.
23. Ascheim, S., *J. Am. Med. Assn.*, 1935, **104,** 1324.
24. Addessi, G., *Ann. ostet. e ginec.*, 1931, **53,** 1289.
25. Vercesi, R., and Merenda, P., *Riv. med.-soc. tuberc.*, 1933, **10,** 42.
26. Repetti, M., *Ann. ostet. e ginec.*, 1935, **57,** 1489.
27. Petroff, S. A., and Steenken, W., Jr., *J. Immunol.*, 1930, **19,** 79.
28. Zondek, B., Hormone des Ovariums und des Hypophysenvorderlappens, Berlin and Vienna, Julius Springer, 1931.
29. Collip, J. B., and Anderson, E. M., *Lancet*, 1934, **1,** 76.
30. Long, E. R., and Vorwald, A. J., *Am. Rev. Tuberc.*, 1930, **22,** 636.