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Hormones And Hemopoiesis I. Posterior Pituitary

Extract And Erythrocyte Count

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Introduction

The evidence seems clear that hemopoiesis is influenced by the hormones of the body¹. Also, there is general agreement that erythropoiesis is modified by virtue of a secondary hormonal effect upon general metabolism rather than a direct and specific hemopoietic action^{2,3,4,5,6}. However, a number of points remain unclarified. One area which has received scant attention is the hematologic effects of minimal hypo- and hyperactivity of the endocrine organs. Secondly, only brief study has been made of the relationship be-

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tween the posterior hypophyseal secretions and erythropoiesis.

This report is designed to analyze the relationship of small doses of posterior pituitary extract upon hemopoiesis as measured by changes in the circulating erythrocyte count.

Review of the Literature

Both lower animal^{2,4,5,6,7,8,9,10,11,12} and human³ studies indicate that a moderate to severe anemia follows experimental and clinical hypopituitarism. Dodds and his group^{13,14} observed severe macrocytic anemia with marked reticulocytosis and hyperchromia in guinea pigs and rabbits given large doses of posterior pituitary extract. These findings have been observed by other investigators^{15,16,17}. Davis¹⁸ noted that the daily administration of small amounts of posterior pituitary extract to both normal and splen-

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ectomized dogs and rabbits induced polycythemia in approximately one to three weeks. Limited observations indicate that extirpation of the intermediate and posterior lobes does not produce an anemia¹⁹.

Method of Investigation

Forty male and female human subjects were studied with regard to the effect of small doses of posterior pituitary extract upon the circulating red blood cell count. Included in the group were ten male and 30 female subjects with a mean age of 50.9 and a standard deviation of 13.8 years. The participants in this experiment were chosen from a group of 683 persons as possible cases of mild posterior pituitary disease. An anthropometric technique, described elsewhere²⁰, constituted the method for classifying these individuals in the posterior pituitary group.

At the start of the experiment, all subjects were subsisting on a similar diet (low-refined-carbohydrate high-protein) as previously reported²¹. Each participant in this study was given either 1/400 or 1/800 grain posterior pituitary extract orally once daily for periods ranging from three to 27 days. The posterior pituitary extract was prepared from 1/10 grain posterior pituitary extract (Armour) by appropriate dilution. It is of interest to mention that the doses utilized in this study are approximately 40 to 80 times smaller than the amounts generally prescribed for patients suffering with diabetes insipidus²².

There are, admittedly, elaborate techniques now available for the determination of erythropoiesis. Until very recently the only methods included the measurement of peripheral erythroid values, reticulocyte response, and bone marrow activity. These techniques, though not completely satisfactory, are certainly simple and practical. For purposes of this study only the circulating red cell count will be considered. Attention will be directed to the hemoglobin levels²³, hematocrit²⁴, mean corpuscular volume²⁵, mean corpuscular hemoglobin²⁶, and mean corpuscular hemoglobin concentration²⁷ in subsequent reports.

Results

The data will be reported in two broad categories: (1) general characteristics for the entire group, and (2) subgroup analyses for the purpose of evaluating sex, and the effect of dose and duration of medication.

General Characteristics

Figure 1 graphically depicts (for the entire series of 40 subjects) the erythrocyte counts initially (on the abscissa) and the difference from the initial count (on the ordinate) after 3 to 23 days with posterior pituitary extract.

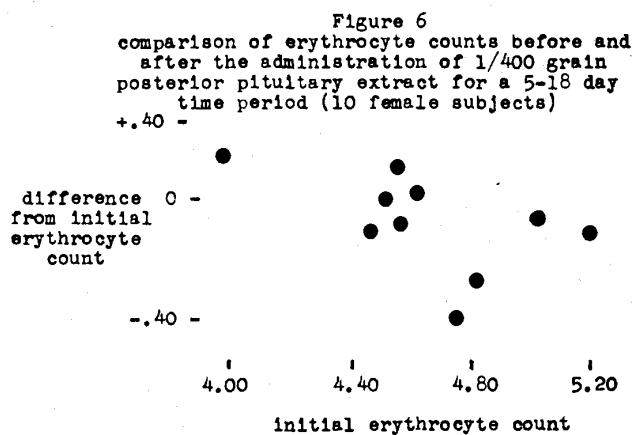
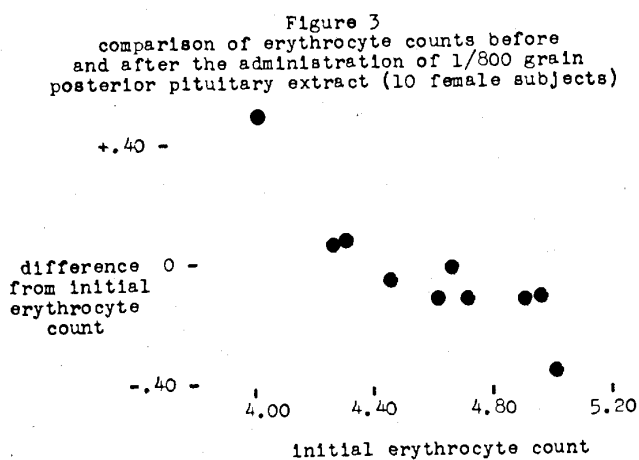
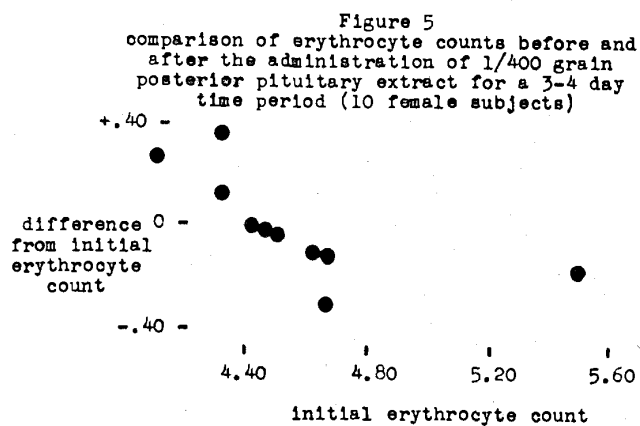
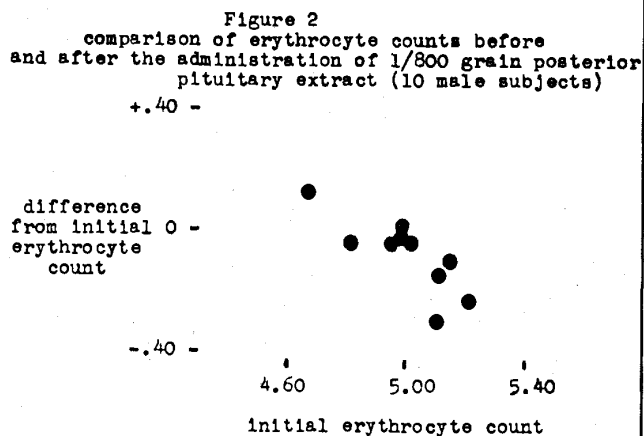
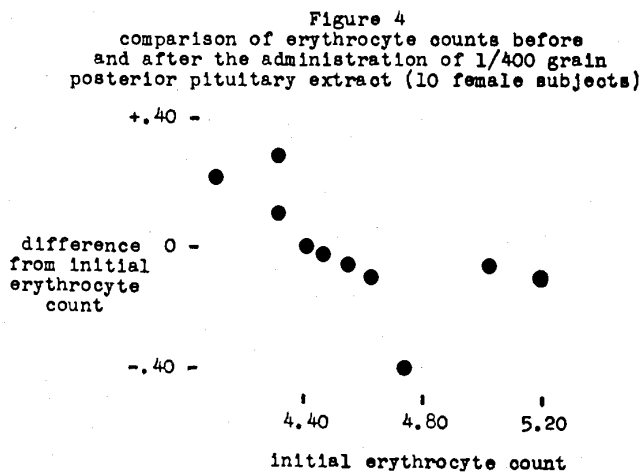
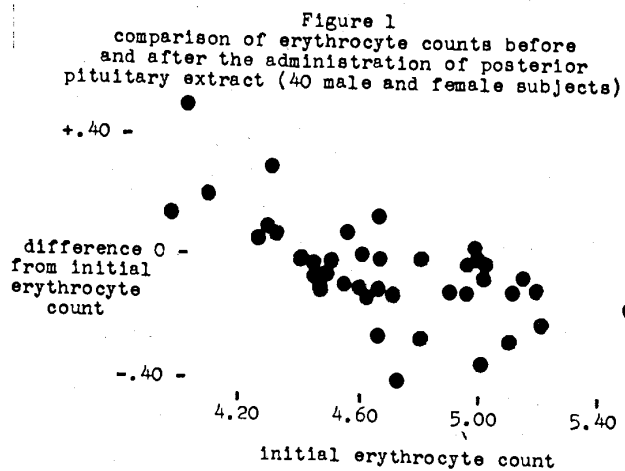
Simple inspection of Figure 1 suggests that the erythrocyte count changes with posterior pituitary extract administration. It appears that the highest red blood cell counts (>5,000,000) all seem to decrease. Also, it seems that the lowest erythrocyte counts (<4,300,000) all rise. A statistical analysis of these findings indicates a coefficient of correlation of $-.619$ and a $P < .001$. Thus, there seem to be significant changes in the erythrocyte count after posterior pituitary extract administration.

Subgroup Analyses

Sex Analysis: The group of 40 subjects included ten male and ten female patients who were given the same amount of posterior pituitary extract daily (1/800 gr.). Thus, a separate analysis was made of the changes in the erythrocyte count in the two sexes with the same medication regime.

Table 1 includes the original data. An examination of the ten male subjects given 1/800 grain posterior pituitary extract daily (Figure 2) shows that the subjects with red counts above 5,000,000 all decreased while, in the main, those below 5,000,000 rose. Thus, it would appear that the pattern previously noted for the entire group of 40 subjects obtains for the ten male subjects. These data were statistically studied and the coefficient of correlation of $-.804$ was found significant at the 5 per cent level.

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TABLE 1
EFFECT OF 1/800 GRAIN POSTERIOR PITUITARY
EXTRACT UPON THE ERYTHROCYTE COUNT

patient number	age	sex	number of days of therapy	initial red cell count	final red cell count	difference in red cell count
206	68	M	3	5.10	5.00	-.10
083	27	M	4	5.15	5.10	-.05
268	43	M	4	4.65	4.80	+.15
471	68	M	4	5.10	4.85	-.25
493	59	M	5	4.95	4.95	.00
082	65	M	5	4.80	4.80	.00
541	59	M	6	5.20	5.00	-.20
605	39	M	8	4.98	5.00	+.02
174	61	M	15	5.00	5.00	.00
069	---	M	17	4.97	5.00	+.03
153	44	F	2	4.65	4.65	.00
366	46	F	4	4.30	4.40	+.10
292	40	F	4	4.45	4.41	-.04
373	40	F	4	4.70	4.60	-.10
219	50	F	6	4.60	4.50	-.10
341	49	F	6	5.00	4.65	-.35
283	30	F	7	4.25	4.33	+.08
638	58	F	9	4.90	4.80	-.10
663	46	F	11	4.95	4.85	-.10
522	45	F	14	4.00	4.50	+.50

Included also in Table 1 is the original information derived from a study of ten female subjects also given 1/800 grain of posterior pituitary extract daily. Basically, the pattern previously described for the male group obtains for the ten female subjects (Figure 3). In other words, the highest red cell counts (>4,700,000) decrease while the lowest ones (<4,400,000) rise with this particular hormonal regime. Also, a high coefficient of correlation was shown (-.879) and a $P < .025$. There is, however, one big difference in a comparison of the male and female groups. It should be recalled that the male red counts seem to migrate toward 5,000,000. A more detailed study of the female group demonstrates that the shift is toward 4,500,000.

Dose Analysis

Table 2 summarizes the findings in ten females subjected to 1/400 grain of posterior pituitary extract per day for three to 18 days. Table 2 also includes the data from ten females administered 1/800 grain of posterior pituitary extract per day for two to 14 days. Thus, an opportunity is provided to study the

relationship of the changes in the erythrocyte count with different dosages.

An examination of Figure 4 shows the pattern previously described for the entire group and for the male and female groups independently. In other words, the highest red cell counts decrease and the lowest ones increase under the regime of 1/400 grain. The findings are essentially the same following the administration of 1/800 grain of posterior pituitary extract (Figure 3). The coefficient of correlation for the group receiving 1/400 grain is $-.618$ with a P value of $>.05$. The coefficient of correlation for the group receiving 1/800 grain of posterior pituitary extract is $-.879$ and significant ($P < .025$).

TABLE 2
EFFECT OF POSTERIOR PITUITARY EXTRACT
(DIFFERENT DOSES) UPON THE ERYTHROCYTE
COUNT

patient number	age	sex	dosage	number of days of therapy	initial red cell count	final red cell count	difference in red cell count
476	69	F	1/400	3	4.45	4.44	-.01
602	41	F	1/400	3	4.40	4.40	.00
287	68	F	1/400	3	4.30	4.40	+.10
274	58	F	1/400	4	4.08	4.30	+.22
092	32	F	1/400	4	4.30	4.60	+.30
225	40	F	1/400	4	4.60	4.50	-.10
122	---	F	1/400	7	5.19	5.10	-.09
507	72	F	1/400	8	4.73	4.34	-.39
604	40	F	1/400	18	4.55	4.48	-.07
500	32	F	1/400	13	5.00	4.95	-.05
153	44	F	1/800	2	4.65	4.65	.00
366	46	F	1/800	4	4.30	4.40	+.10
292	40	F	1/800	4	4.45	4.41	-.04
373	40	F	1/800	4	4.70	4.60	-.10
219	50	F	1/800	6	4.60	4.50	-.10
341	49	F	1/800	6	5.00	4.65	-.35
283	30	F	1/800	7	4.25	4.33	+.08
638	58	F	1/800	9	4.90	4.80	-.10
663	46	F	1/800	11	4.95	4.85	-.10
522	45	F	1/800	14	4.00	4.50	+.50

Duration Analysis

Table 3 summarizes the data for a group of ten females subjected to 1/400 grain of posterior pituitary extract for three to four days. Included also in this same chart are the findings from a group of ten females administered

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1/400 grain of posterior pituitary extract for five to 27 days. Thus, an opportunity is afforded to study the changes in the red cell count based upon the duration of therapy.

An examination of Figure 5 shows that the red cell counts in the higher brackets decrease while those in the lower groups increase during three to four days with 1/400 grain of posterior pituitary extract. The coefficient of correlation proved to be $-.664$ with a $P > .05$. Figure 6 graphically depicts the changes in the red cell count following five to 27 days under the same regime of 1/400 grain of posterior pituitary extract in ten females. A statistical analysis of these data indicates a coefficient of correlation of $-.492$ and a $P > .10$.

Discussion

It is rather interesting, from an examination of Tables 1-3 and Figures 1-6 that the relationship between posterior pituitary extract and erythrocyte count is not linear. In other words, this particular hormone does not consistently elevate or reduce the circulating red cell count. Rather, the evidence indicates a relatively narrow physiologic parameter of homeostasis. Apparently, the administration of posterior pituitary extract seems to attempt to right deviations from this very narrow range. Thus, it can be observed that relatively low and high red cell counts increase and decrease respectively. It is particularly pertinent that the changes seem to be very small. Thus, it appears that the erythrocyte count is very sensitive to this particular hormone. Mention should be made that these findings are not in agreement with earlier reports^{18,19}.

A second point worthy of mention is the seemingly different physiologic range or point in the two sexes. More detailed examination of Table 1 and Figures 2 and 3 disclose that the tendency to reach homeostasis in the male is at 5,000,000 circulating red blood cells. In contrast, the hypothetic norm in the female appears to be in the area of 4,500,000.

One point which remains unanswered is whether the changes which have been noted

TABLE 3
EFFECT OF 1/400 GRAIN POSTERIOR PITUITARY EXTRACT FOR DIFFERENT TIME PERIODS UPON THE ERYTHROCYTE COUNT

patient number:	age	sex	number of days of therapy	initial red cell count	final red cell count	difference in red cell count
210	63	F	3	4.65	4.55	-.10
002	54	F	3	5.50	5.35	-.15
393	65	F	3	4.65	4.40	-.25
476	69	F	3	4.45	4.44	-.01
602	41	F	3	4.40	4.40	.00
287	68	F	3	4.30	4.40	+.10
274	58	F	4	4.08	4.30	+.22
092	32	F	4	4.30	4.60	+.30
236	36	F	4	4.48	4.45	-.03
225	40	F	4	4.60	4.50	-.10
299	60	F	5	4.50	4.50	.00
336	72	F	5	4.55	4.65	+.10
085	65	F	6	3.95	4.10	+.15
122	---	F	7	5.19	5.10	-.09
088	21	F	7	4.60	4.62	+.02
507	72	F	8	4.73	4.34	-.39
664	64	F	9	4.45	4.35	-.10
500	32	F	13	5.00	4.95	-.05
604	40	F	18	4.55	4.48	-.07
430	50	F	27	4.80	4.55	-.25

are more significant in one or the other sex, at one or the other dosage, and in those receiving posterior pituitary extract for a relatively short or long period of time. These relationships have been analyzed statistically. The general statement can be made that none of the differences of the means proves to be statistically significant.

Two explanations have been proposed for the effect of posterior pituitary extract upon erythropoiesis. First, the posterior hypophyseal lobe may affect blood destruction possibly by way of the reticuloendothelial system¹⁴. Second, the anemia may be the result of hemodilution and eventual hemolysis due to water retention^{16,17}. The latter possibility seems more tenable since dehydration prior to pituitrin administration prevents the anemia^{17,18}.

In order to obtain information regarding the possibility of blood changes in parallel with urinary alterations, the female patients were placed into two groups. The first group included those subjects in whom the red blood

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cell count migrated with posterior pituitary administration toward 4,500,000 per cu. mm. Table 4 summarizes the patients' case numbers, sex, initial and final erythrocyte counts, and the initial and final specific gravities of morning urine samples. Figure 7 pictorially depicts the specific gravity relationships at the start of the study and following a variable number of days of posterior pituitary extract administration. The coefficient of correlation proved to be $-.619$ (significant at the five per cent level).

A chart (Table 5) summarizes the information for those subjects with red blood cell counts which did not migrate toward 4,500,000 per cu. mm. These data are graphically represented in Figure 8. The coefficient of cor-

relation was found to be $-.595$ and not statistically significant ($P > .10$).

It would, therefore, seem that the hematologic changes observed in this report may be due, in part, to hemodilution and hemoconcentration.

Summary

1. This report describes the effect of small doses (administered daily and orally) of posterior pituitary extract upon the circulating erythrocyte count.
2. The evidence suggests that the number of red blood cells decreases and increases toward a homeostatic point or range.
3. There is corollary data to indicate that the

TABLE 4
MORNING URINARY SPECIFIC GRAVITY BEFORE AND AFTER POSTERIOR PITUITARY EXTRACT IN FEMALE PATIENTS IN WHOM THE ERYTHROCYTE COUNT AFTER THERAPY MIGRATED UP OR DOWN TOWARD 4,500,000 PER CU. MM.

patient number	initial red cell count	final red cell count	difference in red cell count	initial specific gravity	final specific gravity	difference in specific gravity
002	5.50	5.35	-.15	1.006	1.019	+.013
225	4.60	4.50	-.10	1.008	1.013	+.005
210	4.65	4.55	-.10	1.012	1.015	+.003
299	4.50	4.50	.00	1.008	1.009	+.001
122	5.19	5.10	-.09	1.011	1.012	+.001
366	4.30	4.40	+.10	1.018	1.018	.000
633	4.95	4.85	-.10	1.021	1.020	-.001
274	4.08	4.30	+.22	1.021	1.020	-.001
500	5.00	4.95	-.05	1.005	1.004	-.001
219	4.60	4.50	-.10	1.008	1.006	-.002
085	3.95	4.10	+.15	1.014	1.012	-.002
341	5.00	4.65	-.35	1.011	1.008	-.003
283	4.25	4.33	+.08	1.024	1.021	-.003
522	4.00	4.50	+.50	1.028	1.022	-.006
373	4.70	4.60	-.10	1.022	1.015	-.007

TABLE 5
MORNING URINARY SPECIFIC GRAVITY BEFORE AND AFTER POSTERIOR PITUITARY EXTRACT IN FEMALE PATIENTS IN WHOM THE ERYTHROCYTE COUNT AFTER THERAPY MIGRATED AWAY FROM 4,500,000 PER CU. MM.

patient number	initial red cell count	final red cell count	difference in red cell count	initial specific gravity	final specific gravity	difference in specific gravity
236	4.48	4.45	-.03	1.008	1.018	+.010
153	4.65	4.65	.00	1.008	1.016	+.008
476	4.45	4.44	-.01	1.016	1.019	+.003
664	4.45	4.35	-.10	1.003	1.005	+.002
336	4.55	4.65	+.10	1.010	1.010	.000
088	4.60	4.62	+.02	1.020	1.018	-.002
602	4.40	4.40	.00	1.013	1.010	-.003
292	4.45	4.41	-.04	1.021	1.018	-.003

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Figure 7
comparison of morning urinary specific gravity before and after posterior pituitary extract in female patients in whom the erythrocyte count after therapy migrated up or down toward 4,500,000 per cu. mm.

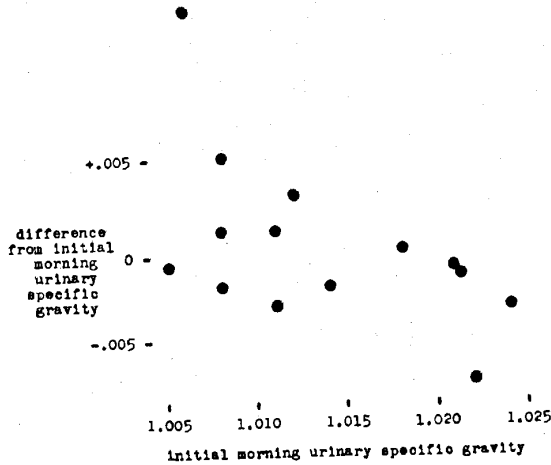
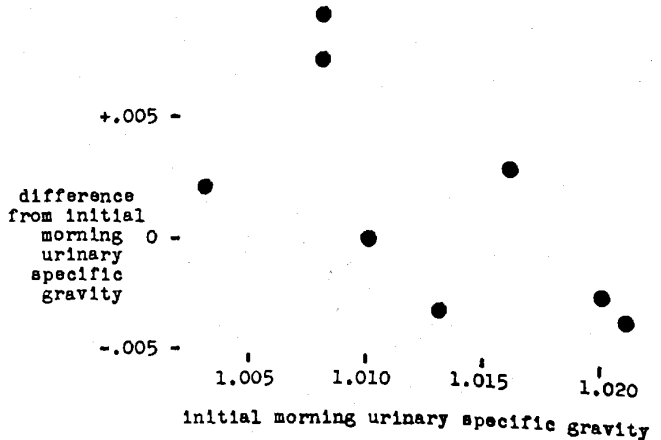


Figure 8
comparison of morning urinary specific gravity before and after posterior pituitary extract in female patients in whom the erythrocyte count after therapy migrated away from 4,500,000 per cu. mm.



physiologic erythrocyte count in the two sexes is different; 5,000,000/cu. mm. and 4,500,000/cu. mm. for the male and female respectively.

4. The observed changes are not significantly different in the two sexes, in those with small (gr. 1/800) versus relatively large (gr. 1/400) doses, and with difference in duration of therapy (3-4 versus 5-27 days).
5. Presumptive evidence is offered to indicate changes in urinary specific gravity in parallel with the alterations in the erythrocyte count.

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