

SOME EFFECTS OF 11-DEHYDRO-17-HYDROXY-CORTICOSTERONE
AND ADRENOCORTICOTROPIC HORMONE
UPON THE SCORBUTIC GUINEA FIG

by

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INTRODUCTION

The discovery that 11-dehydro-17-hydroxy-corticosterone will relieve the symptoms of rheumatoid arthritis (1), together with the well known fact that ascorbic acid (18) is intimately involved in the functional activity of the adrenal cortex suggested that the arthritic-like lesions in the joints of scorbutic guinea pigs may be due to the failure of the adrenal cortex to produce 11-dehydro-17-hydroxy-corticosterone which is commonly called cortisone.

The synthesis of cortisone in sufficient quantities for research work made it possible to study its effects on joint lesions of scorbutic guinea pigs.

The objective of this experiment was to test the validity of the hypothesis that the joint lesions in the scorbutic guinea pigs are not due directly to the lack of ascorbic acid, but due indirectly to the inability of the adrenal cortex to synthesize cortisone when ascorbic acid is not present.

Historical Background

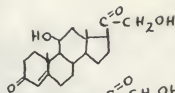
The Discovery of Cortisone. In 1855 Thomas Addison, a British physician, noticed and called attention to the relationship of the deterioration of the adrenal gland and the human disease now associated with his name. The first positive evidence that the adrenal glands produced a hormone which would

relieve the symptoms of Addison's disease did not come until 1927 when two independent groups of investigators, Hartman and Brownell (2), Swingle and Pfiffner (22), prepared potent extracts of the adrenal cortex. Hartman and Brownell called the active principle "cortin." This material, after being tested on laboratory animals, showed amazing results in relieving symptoms of Addisonians, even if moribund.

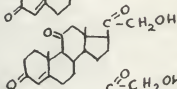
The production of this active extract stimulated the workers of three groups and their associates, E. C. Kendall, J. J. Pfiffner and O. Wintersteiner, and T. Reichstein (3) to try to prepare the compound responsible for this action.

Each of these groups quickly obtained several crystalline compounds which were designated, in the order of their isolation, by the letters of the alphabet. However, it was not until 1936 that Mason, Meyers, and Kendall (10) clearly established the physiological activity and effectiveness of their Compound E. Reichstein (3) in 1937 isolated his pure Compound H which was shown to be highly active and was named corticosterone. Various investigators have isolated 26 crystalline steroids from the adrenal cortex of which 5 have this marked cortical activity. In addition to these crystalline compounds there is an amorphorous residue of unknown composition which shows marked physiological activity in relieving some of the symptoms of Addison's disease. The 5 crystalline compounds are named as derivatives of corticosterone. They are:

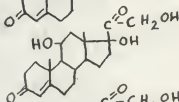
corticosterone



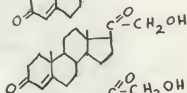
11-dehydro-corticosterone



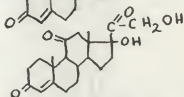
17-hydroxy-corticosterone



desoxy-corticosterone



11-dehydro-17-hydroxy-corticosterone



This last compound was designated "E" by Kendall and "F" by Reichstein and is the one having marked effect in relieving symptoms of rheumatoid arthritis, and is now called cortisone.

The isolation of pure crystals of cortisone and establishment of its structure stimulated intensive research by many workers that cumulated in the synthesis of cortisone in 1946 by L. H. Sarrett (12). By 1948 cortisone was available in sufficient quantity and pure enough for clinical study. Dr. Hench (1) at Mayo's Clinic tried cortisone on patients suffering from severe rheumatoid arthritis and met with startling success with this treatment. This compound has since been used successfully in treating many related conditions and much research is being carried on with it at the present time.

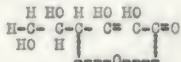
The Discovery of Adrenocorticotropic Hormone. Since the first observations of Smith (19) it has been well established that the size and the function of the adrenal cortex is under

the influence of the pituitary (6, 21, 23).

In almost all animals hypophysectomy causes adrenal cortical atrophy and hypophyseal implants or injections of hypophyseal extracts tend to enlarge the adrenal cortex. The substance which has this physiological action was isolated by Sayers (17) from the anterior lobe of the pituitary of swine, and by Li, Evans and Simpson (11) from the anterior lobe of the pituitary of sheep in 1943.

This material is a protein and has been given the name adrenocorticotropic hormone, usually referred to as ACTH. It has been found to be a potent anti-arthritic therapeutic agent, probably because it stimulates the adrenal cortex into producing and releasing additional cortisone. It was prepared in sufficient quantities to be available for limited research work in 1950.

Ascorbic Acid in the Adrenal Cortex. Before ascorbic acid (vitamin C) had been prepared in crystalline form, Kendall and co-workers (4) at Mayo's Clinic, while attempting to extract the active principle of the adrenal cortex, isolated several grams of a white crystalline material which was later proven to be ascorbic acid by Svirbely and Szent-Gyorgyi (20), Waugh and King (25) in 1932. This material has the chemical structural formula as below:



Much work (5, 14, 15, 25) has been done since this time on the relationships of ascorbic acid to the functions of the adrenal cortex. A relation of ascorbic acid to the adrenal cortical functions is indicated by the sudden drop of the ascorbic acid content when the adrenal cortex is stimulated by injections of ACTH (8). The vitamin C content of the normal guinea pig is about 400 mg per 100 gm of fresh adrenal cortical tissue and 80 to 90 percent of this material is lost in the first three hours after stimulating the cortex by ACTH. There is also a similar drop in the cholesterol content of the cortex, and it is thought that this compound, which has a structure similar to cortisone, may be its precursor. The drop in cholesterol and ascorbic acid takes place at the same time the adrenal cortex is stimulated to produce cortisone and implies that vitamin C may be involved in the transformation of cholesterol to cortisone. This was the hypothesis to be tested by these experiments.

Since this work has been started results of experiments bearing on this subject have been published by Schaffenburg, Mason and Corcoran (16).

EXPERIMENTAL PROCEDURE

Phases of the Experiments

This experiment was divided into two phases. In the first phase the effects of injecting cortisone on various lesions of the scorbutic guinea pigs were studied. In the second phase the action of ACTH was compared with the action of cortisone in the scorbutic guinea pigs.

Basal Ration

The same basal ration was used in both phases of this experiment. It consisted of hulled oats, soy bean meal, and dehydrated alfalfa pellets, fortified with minerals, vitamins A and D, and the water soluble vitamins, including vitamin B₁₂, to meet the needs of growing guinea pigs (9), but excluding vitamin C.

The positive control group received the basal ration plus adequate crystalline vitamin C.

The Animals Used

Young male guinea pigs, weighing between 225 and 350 gm were purchased from The Gopher State Caviary, St. Paul, Minnesota. They were kept, three in a cage, in guinea pig cages with wire bottoms. They were fed daily, but no attempt was made to equalize food consumption.

Treatment of the Animals

Weights were taken every four or five days. Notes as to the development of clinical symptoms of scurvy were made daily. In most cases the experiment continued until the scorbutic animals died. They were then posted by Dr. Herrick. In a few cases animals from various other groups were sacrificed for comparison purposes. Records were made of the macroscopic lesions observed by Dr. Herrick and the author.

Sections of tissues for microscopic examination were removed, and the results of this study are to be the subject of other theses.

Description of the Phases

Phase One. Phase One was divided into two experiments, the first starting on October 18, 1950 and the second starting on January 11, 1951.

Experiment One. In this experiment 24 guinea pigs were used. On arrival they were divided into three groups, 12 animals in the negative control group, 6 animals in the positive control group, and 6 animals in the group receiving cortisone. This distribution was made to equalize approximately the comparative weights of the animals in each group.

The negative controls, Group 1, received only the basal ration. The positive controls, Group 2, received the basal ration plus an adequate amount of ascorbic acid. The animals of Group 3 received the basal ration and after the fifth day

also a daily subcutaneous injection of a fine suspension of 5 mg of cortisone acetate in one ml of solution. The cortisone acetate was produced by Merck and Company, Inc., Rahway, New Jersey and is sold under the trade name "Cortone."

Experiment Two. Fifteen guinea pigs were used in this experiment. They were divided into three groups of five each; the negative controls, Group 4, the positive controls, Group 5, and the group receiving cortisone, Group 6.

The animals were treated similarly to those in the first experiment with the exception that Merck provided a more concentrated product of the cortisone acetate suspension in which the 5 mg dose was contained in 0.2 ml.

Phase Two. There was only one experiment in Phase Two, and it was carried on in this manner. Six guinea pigs were divided into two groups of three each. Both groups received the basal ration. The one group, denoted as Group 7, received 5 mg of the cortisone acetate after the basal ration had been fed for five days. The second group, Group 8, received the basal ration and 2 mg of ACTH in 0.5 ml of physiological salt solution every 12 hours. The ACTH was furnished by the Lederle Laboratories, Division of the American Cyanamid Company, New York, New York.

The animals were fed daily and weighed approximately every five days. At death they were treated in the manner previously described.

EXPERIMENTAL RESULTS

Results of Phase One - Experiment One

The data pertaining to weights and survival time are given in Tables 1, 2 and 3. The average results of these data are expressed in Fig. 1. Group 1 is the negative control group, Group 2 the positive control group and Group 3 the group receiving cortisone.

Group 1. All of the animals in Group 1 developed the usual clinical symptoms of scurvy. The stiffness in the joints appeared first at 7 days in animal Number 17, and all of the animals in this group showed this symptom of scurvy by 11 days.

It will be seen from Fig. 1 that the average weight of these animals began to drop by the ninth day and had dropped at the average time of death (18 days) to an average of 204 gm. This is a loss of at least one-fifth the average initial weight.

On autopsy all of these animals showed the usual macroscopic lesions of scurvy, such as swollen joints and hemorrhaging around the joints and in the viscera. There was also noted a lack of adipose tissue in the body when compared with normal guinea pigs posted at the same time.

Group 2. These animals developed normally and on post mortem examination showed no abnormalities. This showed that the basal ration was adequate for the development of young guinea pigs when supplemented with ascorbic acid.

Group 3. The animals receiving the injections of 5 mg of

cortisone acetate per day did not develop the sore joints typical of the scurvy guinea pigs in Group 1.

It will be seen from Fig. 1 that the animals increased in weight, at first, somewhat more rapidly than the positive control group. This could correspond possibly to the feeling of well-being reported by human patients when first receiving cortisone. About the fourth week of the experiment these animals started losing weight. Their weight drop was slower than that of Group 1. On autopsy it was observed that there was little hemorrhaging around the joints, but there was hemorrhaging around the ribs and in the lungs. These animals did not lose their fat deposits as those in Group 1. Their average survival time was 42 days and average weight at death was 239 gm. This represents a loss of about one-tenth of their initial body weight.

Results of Phase One - Experiment Two

When additional cortisone became available, Experiment One, using five animals in each group, was repeated. The same basal ration was used and the treatment of the animals was the same. In this experiment the negative control group was designated Group 4, the positive control group was called Group 5 and the animals that received cortisone were called Group 6.

The data pertaining to weights and survival time are given in Tables 4, 5 and 6, and the average results of these data are expressed in Fig. 2.

Group 4. Unfortunately the animals in the second experiment developed a respiratory infection shortly after the experiment

started. The combination of the lack of vitamin C and the respiratory infection may have caused the early death of the animals in Group 4. The average survival time of the animals of this group was only 13 days whereas the average survival time in the similar group of the first experiment where no infection was present was 18 days. Two of the animals, Numbers 41 and 43, did not develop the soreness of the joints before death, but the other three animals exhibited clearly this clinical symptom of scurvy. On autopsy the macroscopic lesions usually found in scurvy guinea pigs were not found in animal Number 43. However, since he died on the ninth day of the experiment it is possible that not enough time had elapsed for the lesions to develop.

The other four animals on autopsy did show the typical lesions of scurvy guinea pigs and were, if anything, in a worse condition than those of the similar group in Experiment One.

Group 5. The respiratory infection was very severe in the positive control group and one of the animals, Number 61, died on the ninth day. Animal Number 59 was caught in the cage wire, broke his leg, and for this reason was removed from the experiment. The other three animals seemed to recover completely, and they appeared completely normal when posted. It will be seen that these animals regained rapidly the weight lost during the time of the infection.

Group 6. The animals receiving cortisone were also affected by the respiratory infection. However, these animals did not die as quickly as those in Group 4. The first death occurred on the same day the last animal in Group 4 died. They did not lose

weight like the positive control group. Two of the animals recovered, one living 51 days and the other 69 days.

None of these animals showed the soreness of the joints exhibited by scurvy guinea pigs, but all of these animals showed on post mortem examination severe internal hemorrhaging.

Results of Phase Two

Sufficient ACTH was secured to give injections of 2 mg every 12 hours to a group of three guinea pigs. The animals receiving ACTH were compared with a group of three guinea pigs which received the same dosage of cortisone which had been found effective in preventing joint soreness in Phase One, Groups 3 and 6. The basal ration and treatment of the animals was the same as in Phase One.

As the basal ration had been thoroughly tested in the negative and positive control groups of Phase One, these groups were not repeated in this phase of the experiments.

The data pertaining to weights and survival time are given in Table 7, and the average results of the experiment are given in Fig. 3.

In this experiment the animals receiving cortisone were designated as Group 7, and those receiving ACTH as Group 8.

In this experiment the animals receiving cortisone showed striking differences from those receiving ACTH.

Group 7. These animals received 5 mg of cortisone acetate in a 0.2 ml injection daily. The experiment was concluded at

51 days and all three of the animals were alive at the time. However, all three were losing weight rapidly and were in the last stages of scurvy. They were typical of scurvy guinea pigs that received cortisone. They did not exhibit sore joints, but on post mortem examination they showed typical hemorrhaging in the viscera, around the joints and especially in the lungs.

Group 8. The animals receiving ACTH developed clinical symptoms of scurvy rapidly and two of them were dead within 12 days. The other, Number 53, survived for 27 days. This animal developed very sore joints, and during the last 12 days he would not move about the cage and seemed to be in severe pain when handled. The animals all showed the clinical symptoms of joint stiffness and on autopsy showed very severe hemorrhaging around joints and in the viscera. These animals suffered also a nervous disorder which resulted in trembling and led to spasms three to four hours before death.

A possible explanation of the extremely poor condition which developed in these animals might be due to the ACTH which depletes the adrenal cortex of its ascorbic acid supply much more rapidly than the scorbutic ration alone. This depletion of ascorbic acid would bring on the death of the animal more rapidly than if it were merely fed the scorbutic ration.

Due to the small number of animals used in this experiment too much significance was not placed upon this work. However, since the conclusion of this work, another student has repeated this phase of the experiment and obtained substantially the same results.

DISCUSSION

Phase One

Combining the results of Experiments One and Two, it is found that the average survival time of the negative control animals was 17 days, and that of the animals receiving cortisone was 37 days. It was also found that the animals receiving cortisone did not lose as much weight before death as did the negative controls. This weight differential is due probably to the fact that the animals receiving cortisone continued to consume some food until a day or so before death. Scurvy guinea pigs usually stop eating about the time sore joints develop. This might be due to the absence of hunger, or could be due conceivably to pain that results from the loosening of the teeth and pain of chewing due to sore maxillary joints. Another significant difference between the two groups was the lack of joint soreness of the animals receiving cortisone when compared with the negative control group. When gentle pressure was applied to the joints of a scurvy guinea pig, the animal would squeal and give other indications of pain. When the animals that received cortisone were treated in this manner, they reacted in a manner similar to normal guinea pigs.

The gait of the scorbutic animal was another indication of joint soreness. Instead of the normal running gait, the scorbutic guinea pigs hopped. The hopping gait, which involves a different motion of the hip joints, is an indication of soreness or stiffness of the joints of the scurvy guinea pigs.

Although the histological study of these animals was not a part of the work, it is interesting to note that there was a distinct difference between the scurvy guinea pigs and the animals receiving cortisone(26). The animals which received cortisone did not exhibit the typical microscopic lesions of the joints of scurvy guinea pigs.

These results lead to the conclusion that the adrenal cortex of the scorbutic guinea pig does not produce sufficient amounts of the cortical hormones to prevent the joint lesions. A probable explanation for this failure is that vitamin C is essential for the production of cortisone and, since the guinea pig can not synthesize vitamin C, there is not enough of this compound present in the scurvy guinea pig to elaborate adequate amounts of cortisone. This agrees with the hypothesis presented at the start of this paper.

Phase Two

Striking differences appear when the ACTH and cortisone injected guinea pigs are compared. Post mortem examinations of those animals which received cortisone showed they were fairly close to death at the time the experiment was terminated. Although they had been losing weight they were, from all external appearances, still normal animals. On the other hand, the animals receiving ACTH developed scurvy symptoms more rapidly than the negative controls of Phase One. Clinical symptoms of scurvy appeared about the fifth day of the experiment.

It is known that the injection of ACTH depletes the adrenal cortex of ascorbic acid within three to four hours, so the animals receiving the ACTH and no vitamin C in their diet should show the symptoms of scurvy more rapidly than the animals which did not receive ACTH.

In addition to the earlier development of scurvy, these animals also developed a nervous disorder described in the experimental results. This nervous disorder may be a symptom of what is known as the "General Adaptation Syndrome," (17) and could be caused by abnormal stress, by an excess dosage of ACTH or by a dosage of ACTH when the body can not respond in a normal manner.

When additional ACTH was made available, this work of Phase Two was repeated by another student.

These results indicate that the cortex of the scurvy guinea pig can not produce cortisone under the influence of ACTH. This appears to be true although the cholesterol content of the cortex has been found to be depleted by ACTH injections (11).

This raises the question of what becomes of the cholesterol mobilized in the cortex. It may be that the cholesterol is converted to one of the cortical steroids which is in a lower state of oxidation than cortisone.

SUMMARY AND CONCLUSIONS

1. Fourteen scorbutic guinea pigs were injected subcutaneously daily with 5 mg of cortisone acetate.
2. Three scorbutic guinea pigs were injected with 2 mg of ACTH at 12 hour intervals.
3. For comparison purposes, 19 guinea pigs were kept on the scorbutic basal ration.
4. Nine guinea pigs were used as a positive control and received adequate vitamin C.
5. Records were kept on the weights of the animals and of the appearance and development of the symptoms of scurvy. Special attention was paid to the development of soreness of the joints.
6. The guinea pigs were all posted and records were made of the observed macroscopic lesions.
7. Tissues were prepared for microscopic studies. The results of these studies are not included in this paper.
8. The average survival time of the 19 negative controls was 17 days, and their average weight at death was 206 gm.
9. The average survival time of the 14 animals receiving cortisone was 37 days, and their average weight at death was 228 gm.
10. The average survival time of the three animals receiving ACTH was 16 days, and their average weight at death was 211 gm.

11. The guinea pigs used as negative controls developed the usual symptom of scurvy, soreness of the joints. This symptom was not present in those guinea pigs which received cortisone but was present in the three animals receiving ACTH.

12. The post mortem examination results showed somewhat less hemorrhaging in the joints of the guinea pigs which received cortisone than in the joints of the negative controls. There were no major differences in the other tissues.

13. The results of this experiment seem to warrant the conclusion that the adrenal cortex of the scorbutic guinea pig is unable to produce sufficient cortical hormones to prevent joint lesions.

This would suggest that vitamin C, which can not be synthesized by the guinea pig, is essential to the production of these hormones.

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APPENDIX

Appendix One
Phase One - Experiment One

Table 1. Weight record of Group 1, negative control group.

Animal: number:	Number of days					: Survival : time	: Weight : at death
	0	4	8	12	16		
13	365	370	340	300	-	15	235 gm
14	285	290	350	320	277	19	225 gm
15	245	260	280	255	210	19	185 gm
16	280	305	340	310	261	19	225 gm
17	245	260	260	240	195	16	195 gm
18	225	240	260	225	-	15	188 gm
25	275	265	270	275	233	21	190 gm
26	300	315	305	300	262	20	215 gm
27	320	340	340	340	282	20	226 gm
28	240	260	265	265	233	19	200 gm
29	265	260	265	250	187	16	187 gm
30	245	260	265	270	216	20	173 gm

Table 2. Weight record of Group 2, positive control group.

Animal:	Number of days										
number:	0	4	8	12	16	21	26	30	35	40	45
31	315	350	370	390	409	442	428	431	414	433	478
32	270	305	290	270	283	282	280*				
33	305	315	330	340	334	355	363	371*			
34	246	260	260	290	295	312	314	322	319	347	367
35	265	295	315	330	340	350	340	312	287	272	310
36	240	245	240	240	238	235	227	216*			

* Posted for comparison with animals from other groups.

Table 3. Weight record of Group 3, animals receiving cortisone.

Animal:	Number of days										Survival:	Weight
number:	0	4	8	12	16	21	26	30	35	40:	time	at death
19	280	310	320	330	305	340	365*					
20	250	265	285	290	284*							
21	245	265	280	285	282	296	306	268	236	37		206 gm
22	325	355	365	380	375*							
23	285	315	345	350	341	380	367	348	327	301	43	261 gm
24	235	285	345	350	346	361	377	374	354	321	45	252 gm

* Posted for comparison with animals from other groups.

Phase One - Experiment Two

Table 4. Weight record of Group 4, negative control group.

Animal:	Number of days				Survival:	Weight
number:	0	4	11	14	time	at death
41	292	271	199		12	175 gm
42	299	273			10	182 gm
43	341	314			9	219 gm
44	254	282	263	235	15	230 gm
45	277	268	209	202	14	202 gm

Table 5. Weight record of Group 5, positive control group.

Animal:	Number of days										Sur-	Weight
number:	0	4	11	14	22	29	36	43	63	69:	vival:	at
										time	:	death
59	309	270	229	225							15	222 gm
60	268	261	289	288	317	359	401	418	460	516		
61	287	270									9	204 gm
62	287	263	300	282	336	370	367	371	409	450		
64	252	254	285	289	269	294	311	329	359	416		

Table 6. Weight record of Group 6, animals receiving cortisone.

Animal:	Number of days										Sur-	Weight
number:	0	4	11	14	22	29	36	43	63	69:	vival:	at
										time	:	death
47	257	266	238	231							17	178 gm
48	276	281	236	214							15	184 gm
49	341	363	366	358	299	318	355	317			51	243 gm
51	299	325	316	286							17	200 gm
52	292	265	285	306	315	341	314	325	297	281	69	281 gm

Phase Two

Table 7. Weight record of Group 7, animals receiving cortisone, and weight record of Group 8, animals receiving ACTH.

Animal: number:	Number of days							Survival: time	Weight at death
	0	5	12	19	26	45	51	:	:
Group 7									
54	203	205	215	210	230	210	173	*	
57	240	260	295	305	310	260	255	*	
58	380	390	420	398	380	350	280	*	
Group 8									
53	265	250						9	235 gm
55	300	315	350	317	230			27	208 gm
63	220	215	177					12	177 gm

* Experiment terminated at 51 days.

Appendix Two

These graphs show a comparison of the general condition of the groups at various times during the experiment.

The graphs were prepared in the following manner. The weights of the animals were averaged and plotted against time until the first animal died. This is represented by a solid line on the graph. Then the average weight at death and average time of death was plotted and a curve was completed to this point as a dotted line. The range of survival time and weight at death is shown by the horizontal and vertical lines through the point of average weight at death and average survival time.

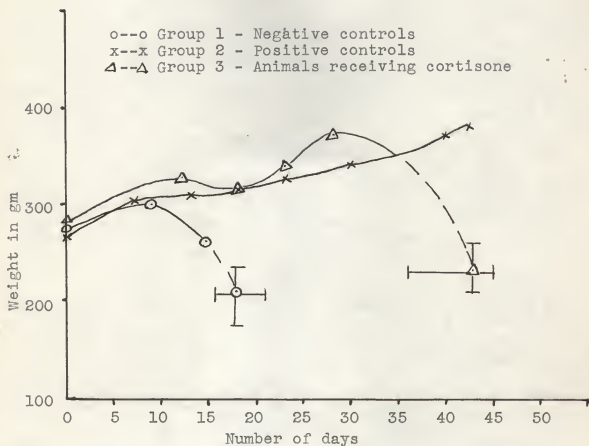


Fig. 1. Phase One, Experiment One; Comparison of the average weight and survival time of the various groups.

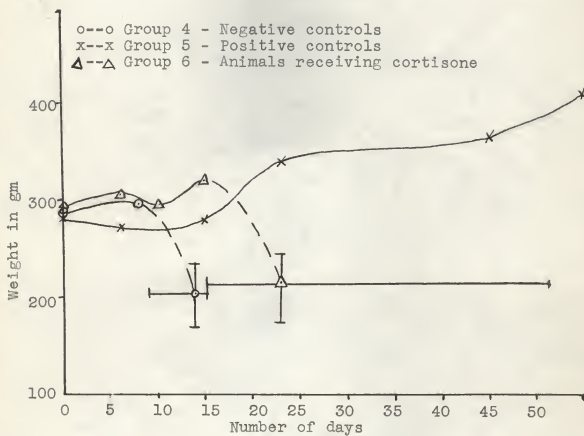


Fig. 2. Phase One, Experiment Two; Comparison of the average weights and survival time of the various groups.

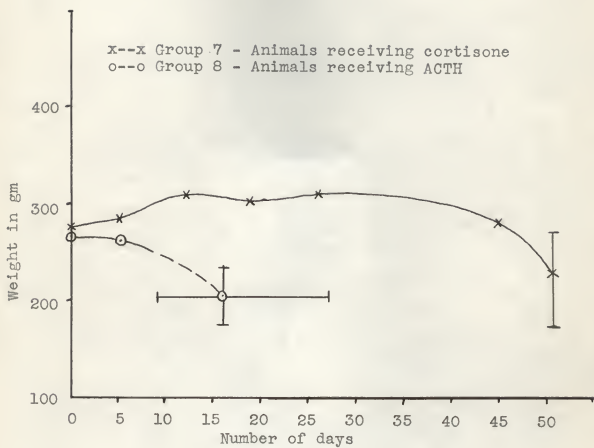


Fig. 3. Phase Two; Comparison of animals receiving cortisone and animals receiving ACTH.

SOME EFFECTS OF 11-DEHYDRO-17-HYDROXY-
CORTICOSTERONE AND ADRENOCORTICOTROPIC HORMONE
UPON THE SCORBUTIC GUINEA PIG

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The discovery that cortisone will relieve the symptoms of rheumatoid arthritis along with the fact that vitamin C is involved in the functional activity of the adrenal cortex suggested that the arthritic-like lesions in the joints of scorbutic guinea pigs might be due to the failure of the adrenal cortex to produce cortisone. The objective of this experiment was to test the hypothesis that the joint lesions of scorbutic guinea pigs are not due directly to the vitamin C deficiency, but indirectly due to the inability of the adrenal cortex to synthesize cortisone when ascorbic acid is not available.

The experiments were divided into two phases. In the first phase the effects of injecting cortisone on various lesions of scorbutic guinea pigs were studied. In the second phase the action of ACTH was compared with that of cortisone.

Those animals which received only the basal ration rapidly developed the typical symptoms of scurvy while the animals receiving the basal ration plus adequate vitamin C developed normally. This showed that the basal ration was adequate except for the lack of vitamin C. The animals receiving cortisone in addition to the basal ration did not develop the typical macroscopic joint lesions of scurvy. The animals receiving ACTH developed typical symptoms and lesions of scurvy even more rapidly than those animals merely receiving the basal ration. This could be because the ACTH accelerates the depletion of the vitamin C reserves.

These results led to the conclusion that the adrenal cortex does not produce sufficient amounts of the cortical hormones to prevent the joint lesions. A probable explanation for this is that vitamin C is essential to the production of cortisone. One theory is that since vitamin C is easily oxidized it acts as a part of an enzyme system in synthesizing this compound.