# THE REACTION OF THE ADRENAL CORTEX TO LOW ATMOSPHERIC PRESSURE*

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Numerous investigators have reported that anoxia produces an activation of the adrenal medulla,[4, 10, 11, 16, 25, 40, 41, 50, 57] but only recently has it been revealed that the adrenal cortex is also activated when an animal is exposed to low atmospheric pressure. Evans reported[17, 18] in 1934 and 1935 a striking increase in blood sugar and liver glycogen in rats exposed to one-half atmospheric pressure. This did not occur after extirpation of the adrenal cortex. He concluded, therefore, that upon exposure to anoxia the adrenal cortex is activated, and that its secretion caused the observed alterations in carbohydrate metabolism. FitzGerald[21] confirmed these findings. Giragossintz and Sundstroem[24] published a brief report in 1937, in which they stated that exposure of an animal to low pressures results in disturbances similar to those characteristic of adrenal insufficiency. They found adrenalectomized rats to require about 20 times the sea-level maintenance dosage of extract while exposed to a simulated altitude of 24,000 feet. Armstrong and Heim[1] observed marked hypertrophy of the adrenal glands in animals exposed daily to an altitude of 18,000 feet. Lewis, Thorn, Koepf, and Dorrance[43] have recently reported an extensive study of the relationship of acute anoxia to the adrenal cortex in which they confirmed, in part, the observations of Evans. They concluded that during the initial phase of anoxia there is an increased utilization of carbohydrate which stimulates the adrenal cortex, resulting in the observed alterations in carbohydrate metabolism.

We have reinvestigated the rôle played by the adrenal cortex in the adjustment of the organism exposed to low atmospheric pressure. We have studied in rats and dogs the effects of anoxia upon the adrenal size, the minimum required amounts of adrenal cortical

hormones, some aspects of carbohydrate metabolism, and renal function.

## Methods

Male albino rats weighing about 200 grams were used for the studies on adrenal hypertrophy, increased hormonal requirements, and carbohydrate metabolism, while the renal excretion studies were made on dogs. The rats were exposed to low atmospheric pressure in small decompression chambers equipped with constant pressure valves which kept the pressure at the desired value, without any appreciable variation. For a few minutes each day the pressure was raised to atmospheric while the cages were cleaned and fresh food and water provided. The experiments using dogs were carried out in a larger chamber, and since the exposure periods were limited to 6 hours, manual regulation of pressure was used.

Rats were adrenalectomized by the usual lumbar incisions under ether anesthesia. The dogs were adrenalectomized for us by Dr. Hebbel Hoff, and then were maintained with 6 cc. of adrenal cortical extract (Wilson) per day, which proved adequate as judged by the electrolyte excretion. Both the normal and the adrenalectomized rats were given tap-water and Purina dog chow. The intact as well as the adrenalectomized dogs were fed a synthetic diet.[13] This diet was of uniform composition, and since the quantity given was completely consumed, a constant intake of the substances under consideration was assured. Also, on this diet the feces were very scanty, reducing contamination of the urine to a minimum. Both groups had fresh water available at all times.

The following analytical procedures were used: blood sugar, the Folin[22] modification of the Folin-Wu method,[23] on blood deproteinized by the Somogyi copper method; liver glycogen, the method of Cori[12] as modified by Long (personal communication); chloride, the modified Volhard-Harvey titration (ref. 52, p. 833); potassium, Harrison and Darrow;[28] sodium, the Butler and Tuthill[9] modification of the Barber and Kolthoff method.[2] All colorimetric determinations were made with a photoelectric colorimeter of the Evelyn type.[20]

## Adrenal hypertrophy

Table 1 shows the results of exposing rats to 20,000 feet altitude for from 1 to 14 days. The maximum hypertrophy of the whole adrenal gland occurs within the first two days, after which no further enlargement takes place. These results confirm those of Armstrong and Heim.[1] Sundstroem (unpublished data) observed a 30 per cent increase in adrenal weight when the pressure was maintained at 20,000 feet, while at 24,000 feet the adrenal weight increased

100 per cent, which makes it appear likely that the degree of hypertrophy is a function of the degree of anoxia.

Rats exposed to 20,000 feet altitude rapidly lose weight for the first 3 days, after which the body weight slowly increases. Mulinos and Pomerantz[49] demonstrated that 7 days of starvation, resulting in a 32 per cent loss of body weight, caused a 17.6 per cent increase in the size of the adrenals. (See also ref. 69.) Underfeeding, on the other hand, resulting after 70 days in a 36 per cent loss of body weight, caused a 15.3 per cent decrease in the size of the adrenals.

TABLE 1

HYPERTROPHY STUDIES

| Procedure | No. of animals | Weight at start gm. | Weight at end gm. | Per cent loss of weight | Adrenal weight gm. | Adrenal/body weight percentage |
|---|---|---|---|---|---|---|
| Control ................. | 21 | 160-329* | | | 21.1-43.2 | 0.010-0.016 |
| | | 227** | | | 29.6 | 0.013 |
| Exposed 20,000 feet 1-14 days .............. | 23 | 176-296 | 161-291 | 1.3-28.4 | 28.5-57.3 | 0.013-0.032 |
| | | 227 | 199 | 13.7 | 39.3 | 0.020 |
| Exposed 20,000 feet 2-3 days ................ | 9 | 186-278 | 164-220 | 3.6-28.4 | 28.5-49.0 | 0.017-0.030 |
| | | 217 | 181 | 16.4 | 38.2 | 0.021 |
| Exposed 20,000 feet 2-3 days, 2 cc./day adrenal cortical ext. | 6 | 178-223 | 142-188 | 14.2-20.5 | 27.6-30.8 | 0.015-0.020 |
| | | 205 | 169 | 17.6 | 28.5 | 0.017 |

\* Range.
\*\* Average.

Since all of our animals exposed to low oxygen tension lost weight, it may be argued that the adrenal hypertrophy is simply due to starvation. However, there is no correlation between percentage loss in body weight and the degree of adrenal hypertrophy. Also, in the decompression series there is only a 13.7 per cent body weight loss compared to the 32 per cent body weight loss in the starvation group of Mulinos and Pomerantz, yet the starvation group shows but a 17.6 per cent hypertrophy of the adrenals compared with the 32.9 per cent increase in adrenal size in the decompression series. Since the animals at high altitude begin to eat on the second day, and after the third day they maintain their weight constant, or gain in weight, the underfed group reported by Mulinos and Pomerantz

would be a more valid standard of comparison than their starvation group. In the underfed series the adrenals were seen to atrophy. Accordingly, the enlargement observed in our decompression series becomes even more striking. Sundstroem found in his animals a decrease in the size of all other organs examined, indicating a definite specificity of the effect on the adrenals under these conditions. And finally, the fact, mentioned above, that the degree of hypertrophy appears to be a function of the degree of
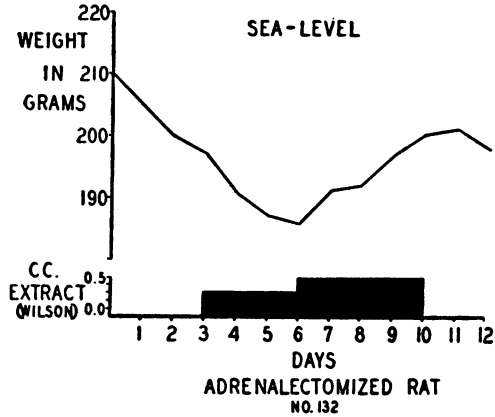


Fig. 1

anoxia makes it perhaps conceivable that underfeeding may play a rôle in the adrenal hypertrophy reported in this series, but it is certainly only a minor part of the total picture.
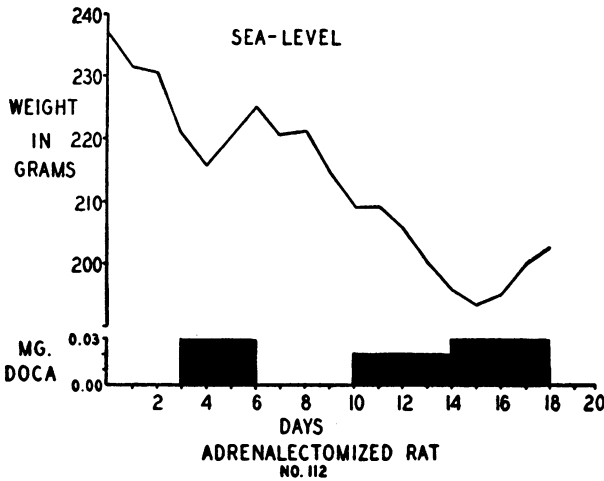


Fig. 2

Adrenal hypertrophy has been reported to result from a wide variety of stimuli, all of which place an inordinate stress upon the organism.[34, 37, 58, 59, 70] Exposure to high altitudes (over 20,000 feet) can certainly be classified as a stress. The adrenal enlargement observed, due to low atmospheric pressure is, therefore, consistent with the adrenal reaction to the various other stress stimuli.

The promptness with which adrenal hypertrophy can be detected

upon exposure of an animal to anoxia agrees with the fact demonstrated by Ingle that adrenal hypertrophy can be seen within 12 hours to result from continuous work.[37]

It is well known that the administration of the whole extract to normal rats causes an atrophy of the adrenal cortex.[39] Selye and his co-workers[59] also showed that certain adrenal steroids successfully combatted the artificially produced "alarm reaction." Further, the adrenal hypertrophy produced by continued work can be prevented by the administration of cortin.[34, 38] Accordingly, it was to be expected that the hypertrophy observed as a result of low atmospheric pressure could also be prevented by adequate quantities of extract.

Table 1 shows that at the end of two days, the time at which the adrenals of untreated normal animals showed the maximum hypertrophy, the adrenals of animals receiving 2 cc. of extract per day did not vary significantly from the normal unexposed rats. Thus, it is possible to prevent hypertrophy due to low atmospheric pressure by the administration of cortical extract.



Fig. 3

### Increased hormonal requirements

The finding that exposure to low atmospheric pressure produces adrenal hypertrophy which can be prevented by the administration of adrenal cortical extract indicates that under these conditions there is an increased demand by the body for the secretion of the adrenal glands. Consequently, it is to be anticipated that an adrenalectomized animal exposed to anoxia would require a greater quantity of extract for maintenance, than an unexposed adrenalectomized animal.
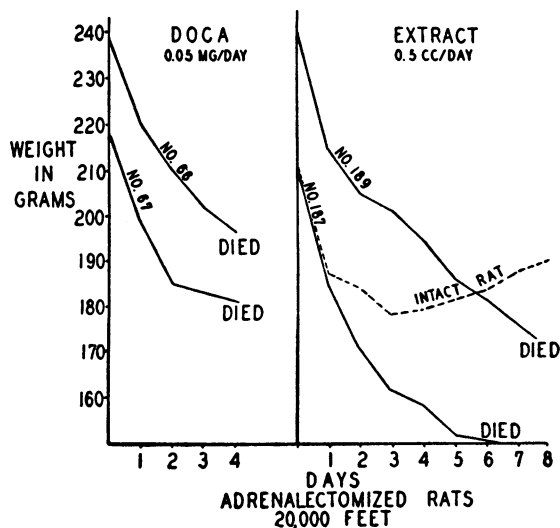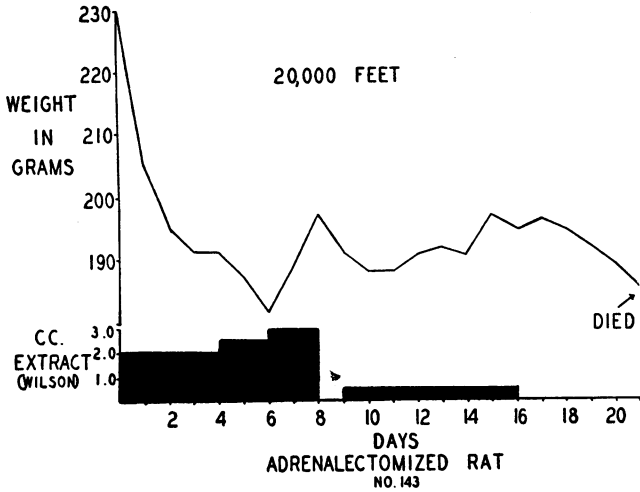
The minimum amount of adrenal cortical extract (Wilson), or desoxycorticosterone acetate (doca) required to produce a steady gain in weight in adrenalectomized rats was found to be 0.5 cc. of extract per day, which agrees well with the observations of D'Amour and Funk,[14] and 0.03 mg. of doca per day. Figures 1 and 2 show typical weight curves using this method.



FIG. 4

Figure 3 shows the result of injecting this quantity of extract, or doca, during exposure to 20,000 feet altitude. No adjustment to this environment was made. The animals progressively lost weight, and invariably died. It was found that 3 cc. of extract or 1 mg. of doca per day were required to maintain adrenalectomized animals while exposed to 20,000 feet altitude in a condition in which their weight curves were comparable to those observed for normal animals.
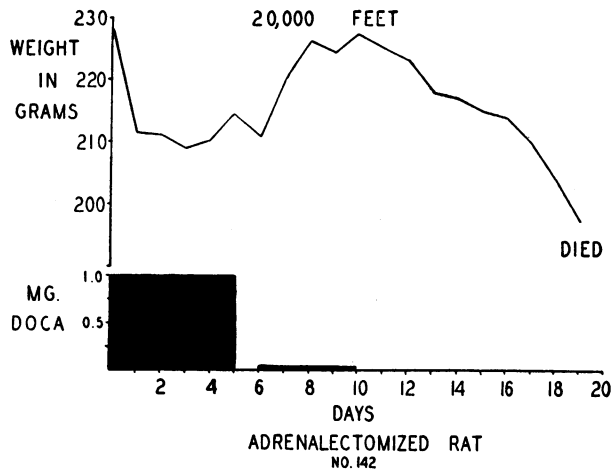


FIG. 5

It is well-known that tolerance to exposure to reduced pressure

increases with the time of exposure.[3, 8, 15, 27, 56, 62]    In view of this fact, it was of interest to determine whether the amount of extract, or doca, required to maintain an adrenalectomized animal decreased after several days of exposure to anoxia.    Figures 4 and 5 show clearly that such is actually the case.    Five adrenalectomized animals were maintained on large quantities of extract during the

TABLE 2

CARBOHYDRATE STUDIES

| Procedure | Altitude ft. | No. of animals | Blood sugar mg. % | No. of animals | Liver glycogen % |
|---|---|---|---|---|---|
| Intact, fed | 0 | 14 | 84-99*<br>92** | 6 | 1.00-4.98<br>3.32 |
| Intact, 24-hr. fast | 0 | 6 | 62-68<br>65 | 3 | 0.11-0.16<br>0.14 |
| Intact, 24-hr. fast | 20,000 | 9 | 74-108<br>89 | 2 | 2.40-2.65<br>2.53 |
| Intact, 48-hr. fast | 0 | 7 | 58-67<br>62 | 2 | 0.58-0.60<br>0.59 |
| Intact, 24-hr. fast + 24-hr. fast | 20,000 | 6 | 55-67<br>63 | 4 | 1.29-3.47<br>2.67 |
| Adrex, fed 1 cc. extract/day | 0 | 10 | 79-92<br>87 | — | — |
| Adrex, 24-hr. fast 1 cc. extract/day | 0 | 6 | 56-64<br>60 | — | — |
| Adrex, 24-hr. fast 1 cc. extract/day | 20,000 | 10 | 56-85<br>74 | 3 | 0.10-0.83<br>0.35 |
| Adrex, 24-hr. fast 3 cc. extract/day | 0 | 5 | 66-78<br>74 | 3 | 0.05-0.14<br>0.09 |
| Adrex, 24-hr. fast 3 cc. extract/day | 20,000 | 7 | 72-93<br>78 | 5 | 0.69-2.44<br>1.34 |
| Adrex, 24-hr. fast 5 cc. extract/day | 0 | 4 | 74-86<br>81 | — | — |
| Adrex, 24-hr. fast 5 cc. extract/day | 20,000 | 4 | 77-85<br>81 | — | — |
| Intact, acclimated fed | 20,000 | — | — | 5 | 2.40-3.90<br>2.97 |
| Intact, acclimated 24-hr. fast | 20,000 | — | — | 5 | 0.09-0.21<br>0.15 |

* Range.
** Average.

period of acclimatization, after which the dosage was reduced to the quantity required to maintain an adrenalectomized animal at sea-level, and in every case the animals continued to gain weight. When the injections were stopped all of the animals died, indicating that the adrenal tissue had been completely removed at operation. The same procedure was repeated on 5 adrenalectomized animals using doca, and again it can be seen that after acclimatization had occurred there was no further demand of the body for increased quantities of the adrenal hormone.
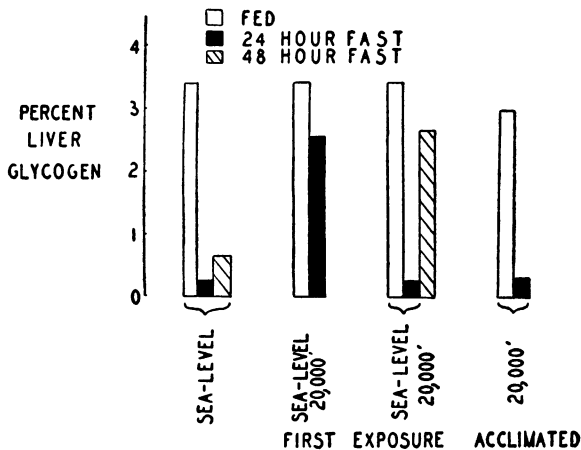
Upon first exposure to high altitude the adrenalectomized animals required about 6 times more extract, and 30 times more doca, than the adrenalectomized animals at sea-level. These figures are not believed comparable, however, since the doca was given in oil, whereas, the extract was in a 10 per cent alcohol solution, and hence, the rates of absorption were much different.



FIG. 6

## Alterations in carbohydrate metabolism

With but few exceptions[31, 51] there is general agreement that extracts of the adrenal cortex are capable of elevating blood sugar and liver glycogen in either fed or fasted normal animals as well as in adrenalectomized animals.[5, 6, 7, 32, 46, 53, 55, 60, 61, 72]  Evans, Fitz-Gerald, and Lewis and his collaborators have attributed the alterations in carbohydrate metabolism observed in an animal exposed to anoxia, to the direct effect of increased secretion from the adrenal cortex.   Our experiments indicate that this conclusion needs modification.

The results of our studies on carbohydrate metabolism are summarized in Table 2.   Figure 6 shows the well-known effect on liver

glycogen of a 24-hour fast at sea-level. If the animal is fasted for this period while exposed to reduced pressure there is a striking difference in the re-sulting liver glycogen level. After a 24-hour fast at sea-level to lower the liver glycogen, subsequent exposure to 20,000 feet altitude for 24 hours while continu-ing to fast results in a marked increase in liver glycogen. This confirms the work of Evans, except that we observe a failure of the blood sugar to become elevated again after preliminary lowering by fasting for 24 hours at sea-level. The cause of this discrepancy has not yet been ascertained.
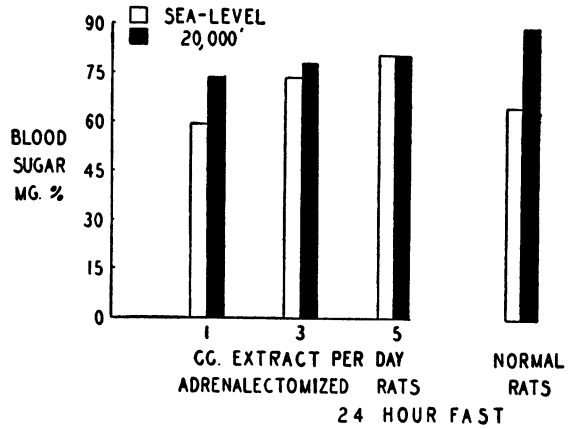


FIG. 7
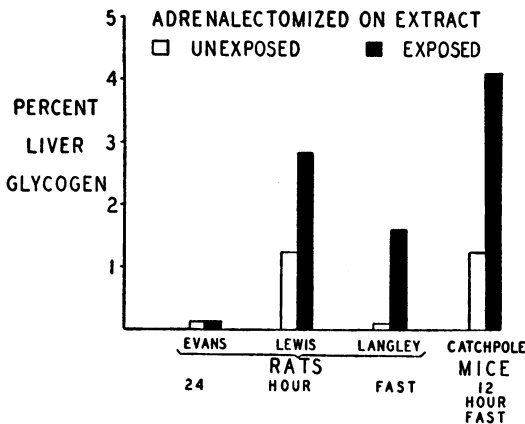
Figs. 7 and 8 show clearly that the blood sugar and liver glyco-gen values are invaria-bly *higher* in adrenal-ectomized rats exposed to low atmospheric pres-sure than in unexposed adrenalectomized ani-mals when both are maintained on a con-stant amount of extract. Catchpole (unpublished data) has observed the same phenomenon in a large series of mice. Lewis and his co-workers report similar results in rats.



FIG. 8

These data must be interpreted to mean that there is either an increased rate of gluconeogenesis due to factors other than increased

adrenal secretion, or a diminished carbohydrate utilization, for the following reasons: (1) The amount of extract required to maintain an adrenalectomized animal upon first exposure to reduced pressure *is not* adequate to raise the fasting blood sugar and liver glycogen values of an adrenalectomized animal at sea-level to the level observed in an intact animal fasting at 20,000 feet altitude. (2) This quantity of extract *is* adequate to raise the fasting blood sugar and liver glycogen values of an adrenalectomized animal exposed to 20,000 feet to approximately the level observed in an intact animal at 20,000 feet altitude. (3) Both Evans and Lewis have reported marked increases in the muscle glycogen of animals exposed to anoxia, but Long, Katzin, and Fry[46] have insisted that even very large quantities of cortical extract do not increase the muscle glycogen values in either normal or adrenalectomized animals.

The work of Houssay,[35, 36] Long and collaborators,[45, 46, 47, 48] Russell,[54, 55] Britton and Silvette,[5, 6, 7, 60, 61] and of Evans[19] has elucidated the interrelationship between the pituitary, adrenal cortex, and pancreas in controlling carbohydrate metabolism. As yet, the effect of anoxia on the activity of the pituitary and pancreas has not been investigated. Our results clearly indicate that augmented adrenal cortical secretion, due to exposure to anoxia, is inadequate to explain the observed carbohydrate changes; accordingly, it is conceivable that the pituitary or the pancreas may also be involved. Russell[55] has demonstrated an interesting synergistic action between the pituitary and cortical hormones. The carbohydrate alterations observed in an animal exposed to low atmospheric pressure are highly suggestive of a similar action.

It has been demonstrated that after acclimatization takes place there is no longer an increased demand for the cortical extract. Figure 6 shows the effect of fasting rats at 20,000 feet after they have been acclimatized by continuous exposure for 6 days. The liver glycogen now falls to the same low level observed in a fasting rat at sea-level, which is in marked contrast to the value observed in a fasting animal upon first exposure to high altitude.

Since it has been shown that after acclimatization has occurred the adrenal gland probably secretes its normal quantity of hormone, these data may be interpreted as further evidence of the dependence of the altered carbohydrate metabolism on increased secretion of the adrenal cortex, but the exact interrelationship of anoxia, the adrenal cortex, and carbohydrate metabolism awaits further elucidation of

the rôle played under these conditions by the pituitary and pancreas, as well as by the altered acid-base balance.

## Renal excretion

Upon exposure to low atmospheric pressure hyperventilation takes place which decreases the blood carbon-dioxide tension. To compensate for this disturbed acid-base balance the kidneys increase their output of base.[15, 27]   Since the adrenal cortical hormone plays a specific rôle in renal function[29, 30, 31, 33, 44, 64, 65, 66] it was suspected that the augmented adrenal activity demonstrated above may be concerned with this compensatory activity of the kidneys.

Figure 9 shows the result of exposing a normal dog to 20,000 feet altitude for 6 hours. It can be seen that there is a marked increase in the excretion of potassium, chloride, and
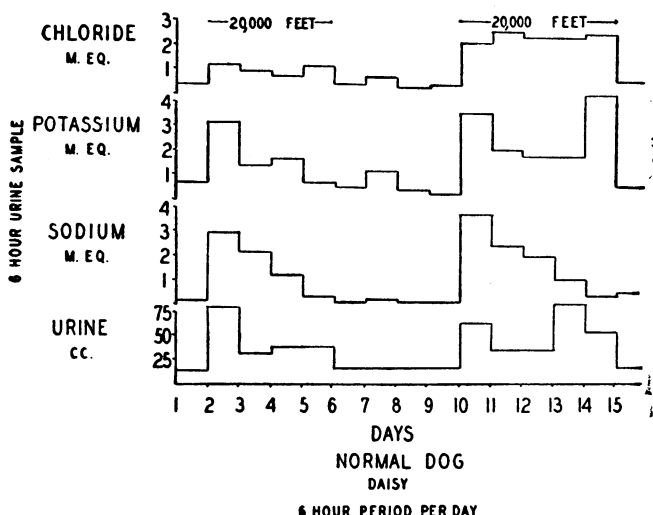


Fig. 9

sodium on the first day of exposure.   The decreased effect of anoxia on subsequent days is particularly striking in the case of the sodium excretion.   This demonstrates the fact that this feature of acclimatization to low atmospheric pressure can be brought about by discontinuous, as well as by continuous exposure.[68]

After adrenalectomy the renal excretion of these substances is quite different from that observed previously in the intact animal, except in the case of potassium, which is excreted more rapidly under both circumstances (Fig. 10).   The striking increase in sodium and chloride no longer occurs.   It is apparent, therefore, that the

increased excretion of sodium and chloride observed in the normal animal exposed to 20,000 feet altitude is due to the activity of the adrenal cortex, whereas increased potassium output seems to be independent of the adrenal glands.

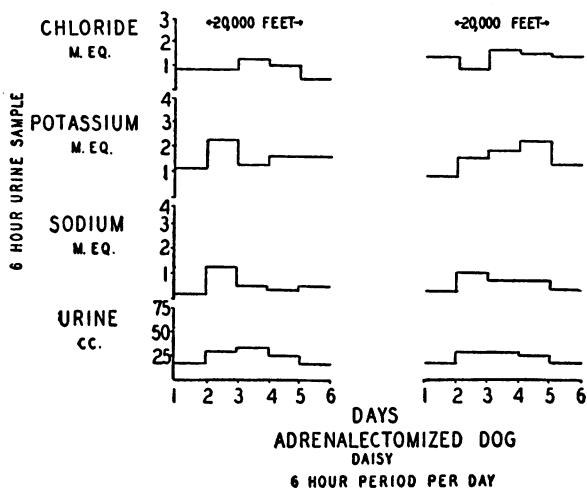The fact that the adrenal hormone produces, under these conditions, a sodium diuresis in the intact animal is particularly significant in view of the recent work of Thorn, Engel, and Lewis,[64] who demonstrated that certain fractions of the adrenal extract cause an increased excretion of sodium in contrast to the sodium retention which occurs following injections of the whole extract. This observation suggests that the adrenal cortex is capable of secreting certain components of the whole extract independently of the others.



FIG. 10

## Discussion

Selye[58, 59] has shown that a variety of conditions results in hypertrophy of the adrenal glands which he has interpreted to indicate an increased demand by the body for the cortical hormone. This is part of what he has termed the "alarm reaction." Selye states that when stress is placed upon an organism the normal output of the adrenal glands is inadequate; therefore this discrepancy between demand and supply results in a temporary state of relative adrenal insufficiency. The adrenal cortex now becomes activated and meets the increased demand; however, after a prolonged period of stress the cortex becomes exhausted, and the animal once again develops symptoms of adrenal insufficiency. Exposure to low atmospheric

pressure might also be classified as a stress, and the above data which indicate that the adrenal cortex is activated under these conditions could be "explained" in a similar manner.   However, to say that a stress gives rise to an increased demand for cortical hormone, which the adrenal gland meets by increasing its activity, is merely a description, and not an explanation.   It is first important to ascertain the sequence of physiological events following exposure to a stress which produces the increased need for cortical hormone, and it is then essential to know how the changes resulting from this increased secretion aid the organism in adapting to the new environment.

Lewis and his collaborators state that the effect of the adrenal cortical "carbohydrate-regulating" factor might be a favorable reaction, since during exposure to low oxygen tension there is an increased utilization of carbohydrate.   In our opinion, there seems to be no adequate evidence that exposure to anoxia increases the utilization of carbohydrate.   The data presented by Lewis, as well as those presented here, are suggestive of decreased utilization of carbohydrate.   Since an adrenalectomized animal on a constant dosage of extract shows higher carbohydrate values after fasting at reduced pressures than after fasting at sea-level, it is difficult to see how there can be an increased utilization of carbohydrate under these conditions.   The increase in blood sugar and liver glycogen observed in an adrenalectomized animal exposed to anoxia must either be attributed to decreased utilization of carbohydrate or to an increased production due to factors other than the cortical secretion.   In addition, it has been shown that an adrenalectomized animal can be maintained at 20,000 feet on doca, a compound which is believed to have very little gluconeogenic action.[5, 26, 42, 67, 71]   The activity of the kidneys in compensating for the alkaline shift caused by the hyperventilation in response to anoxemia suggests that the adrenal-renal relationship is important in the adaptation of the organism to reduced pressures.   In fact, it has been shown that if the partial pressure of carbon dioxide is kept high, the carbohydrate effects of anoxia are markedly diminished.[43]   Polonovski[52a] studied blood sugar and the renal excretion of base in subjects exposed to a simulated altitude of about 17,000 feet.   His results are entirely consistent with ours. He then compared these values with those observed under the same conditions in subjects who had ingested sugar before exposure.   It is most interesting to note that in the latter group the elimination of base was decreased to approximately normal values, but the high

blood sugar levels, observed in an untreated subject exposed to anoxia, were also decreased to normal after the ingestion of sugar. Polonovski concluded from these experiments that the beneficial effect of taking sugar is most likely due to its effect in modifying the disturbed acid-base equilibrium caused by the loss of carbon dioxide.

Whether or not an adrenalectomized animal can compensate for the disturbed acid-base balance to a degree comparable to that observed in the normal animal is an important question, and is now under investigation.

## Summary

1. Rats exposed continuously to 20,000 feet altitude show adrenal hypertrophy which reaches a maximum within 2 days. The hypertrophy may be prevented by injection of adequate quantities of adrenal cortical extract.

2. Adrenalectomized rats exposed to this altitude require greatly increased quantities of cortical extract, or "doca" (desoxy-corticosterone acetate) for maintenance during the process of acclimatization. After acclimatization has occurred, the rat may be maintained on the sea-level dosage of either extract or doca while exposed to 20,000 feet altitude.

3. The observed carbohydrate changes are dependent upon the presence of the adrenal cortical hormone, but the increased adrenal cortical activity cannot be considered to be the sole cause of these alterations. After rats have been acclimatized by continuous exposure for 6 days at 20,000 feet the liver glycogen values upon subsequent fasting at this pressure no longer remain elevated.

4. Normal dogs exposed to 20,000 feet altitude show a marked increase in sodium, chloride, and potassium excretion. Following adrenalectomy the increase in potassium excretion upon exposure to anoxia continues to occur, but the striking increases in sodium and chloride excretion are no longer observed.

## Conclusions

Exposure of an animal to 20,000 feet altitude produces an activation of the adrenal cortex. This activation appears to be essential for adaptation to this environment. After acclimatization has occurred at this altitude, adrenal activity tends to return to normal. The adrenal cortex does not appear to be activated by decreased carbohydrate levels under these conditions. The observed carbohydrate alterations cannot be attributed solely to adrenal

cortical activation.    This is not meant to imply that the carbohydrate changes are unimportant, or without value to the organism in meeting the stress of the environment, but the rôle of the adrenal cortex in anoxia appears to be more intimately concerned with the disturbed acid-base balance resulting from hyperventilation.

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