size but, in all cases, were much larger than the B-mouse tumors and weighed an average of 0.678 g each.

The mice of group B, with average tumor weights of 0.028 g when they were sacrificed, weighed, on the average, 14.3 g on implantation, 16.4 g on the fifth day (22 October) after injection of nitrogen mustard, and 17.5 g on the day before they were sacrificed (31 October). The control mice of group C, with average tumor weights of 0.678 g when they were sacrificed, weighed, on the average, 14.3, 17.0, and 17.7 g on 8 October, 22 October, and 31 October, respectively.

Although the findings strongly suggest that the single dose of 0.2 mg of the nitrogen mustard achieved a complete cessation of growth of the implant, experiments have yet to be performed to determine whether actual regression of a tumor of appreciable size can be achieved and whether the small static tumors of the B mice are viable.

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References and Notes

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5. I am indebted to F. Bergel and J. A. Stock for their kindness in providing reference samples of the DL-, D-, and L-forms of the compound and to Howard Smith for synthesizing quantities of the DL-mixture and the L-isomer. Sally Williams and John Zemp assisted with the implantations and the injections. This work was carried out with assistance from the Cancer Institutional Grant, administered by Stanford University on behalf of the American Cancer Society.
6. This dosage approximates 14 mg/kg body weight.

16 November 1955

Increased Frequency of Births in the Morning Hours

It is generally felt that the incidences of day and night births are practically identical. Supporting this feeling is Guthmann's paper on the subject in which he combined 26,707 cases of his own with 95,087 culled from earlier literature (*1*). The resulting 121,794 cases showed that 49.1 percent of the births occurred during the day (6 A.M. to 6 P.M.) and 50.9 percent at night (6 P.M. to 6 A.M.).

The results reported here show a similar ratio between day and night—49.9 and 50.1 percent, respectively, among 33,215 births; but such an artificial division of the day into two 12-hour periods distorts the picture entirely. By dividing the day into hourly periods, and tabulating the births for each hour, one finds a very marked and statistically significant peak in the morning hours. Using his own cases, Guthmann also found a peak in the morning hours, but this finding seems to have been neglected.

Excluding Caesarian section, second or third twins, and mid- and high-forceps delivery, human births at five hospitals in three different cities were classified by time of delivery. There were 33,215 such births: 8760 from the Edward W. Sparrow Hospital, Lansing, Mich., during a 3-year period; 2532 from the St. Lawrence Hospital, Lansing, during a 1-year period; 10,546 from the W. C. A. Hospital, Jamestown, N.Y., during an 8-year period; 9421 from the Jamestown General Hospital during a 9-year period; and 1956 from the Warren (Pennsylvania) General Hospital during a 2½-year period.

The 8 consecutive hours of greatest frequency of birth, the 8 consecutive hours of lowest frequency of birth, and the 8 remaining hours were compared with one another. Thus, three statistical populations were established, and the means were compared. Such comparison was made for each of the five hospitals individually, and for the total.

Combining the data from all five hospitals (Table 1) and using the formulas

$$\frac{\text{S.D.}}{\sqrt{8}} = \text{Standard deviation of mean} \quad (1)$$

and

$$\text{S.D. of difference between means} = \sqrt{(\text{S.D. mean}_1)^2 + (\text{S.D. mean}_2)^2} \quad (2)$$

gave the following results. (i) There was a mean of 1561 births (S.D. 47) for each hour during the peak hours of 3 A.M. to 11 A.M. (ii) There was a mean of 1213 births (S.D. 66) for each hour during the low hours of 3 P.M. to 11 P.M. (iii) There was a mean of 1375 births (S.D. 65) for each hour during the remaining hours of 11 A.M. to 3 P.M. and 11 P.M. to 3 A.M. (iv) During the peak hours, 28.7 percent more births occurred than during the low hours. The standard error of the difference of the means of the two groups was 28; hence the difference is extremely significant statistically (12 σ), the odds being 1 in approximately 6×10^{32} that this difference is due only to chance. By taking three standard deviations of the difference between the means of the peak and low hours, one obtains a meaningful range of 21 to 36.9 percent. (v) The peak hour was 5 A.M.; it showed 48 percent more births than the low hour of 7 P.M.

Analysis of the data from each hospital individually was even more striking than the analysis of the total. Each of the five

Table 1. Number of births each hour of the day in five hospitals.

Time	No. of births
Group A (3 A.M. to 11 A.M.)	
3	1590
4	1560
5	1632
6	1547
7	1470
8	1588
9	1585
10	1515
Group B (11 A.M. to 3 P.M and 11 P.M. to 3 A.M.)	
11	1422
12	1418
1	1480
2	1416
11	1355
12	1297
1	1281
2	1335
Group C (3 P.M. to 11 P.M.)	
3	1134
4	1276
5	1180
6	1213
7	1103
8	1267
9	1298
10	1253

hospitals showed a statistically significant difference between the means of the 3 A.M.-to-11 A.M. and the 3 P.M.-to-11 P.M. periods. The number of standard deviations in each group is as follows: (i) Sparrow Hospital, 11 σ; (ii) St. Lawrence Hospital, 4.5 σ; (iii) Warren General Hospital, 3.25 σ; (iv) W. C. A. Hospital, 7 σ; (v) Jamestown General Hospital, 10 σ.

By taking the odds in each of these five and multiplying them together, one can estimate that the likelihood of the differences between the peak and low groups being due to chance is 1 in about 10^{69}.

I did a similar analysis of Guthmann's 26,707 cases and found that the period from 2 A.M. to 10 A.M. showed 7.8 percent more births than the period from 2 P.M. to 10 P.M. This difference was statistically significant (4 σ) and, although it is not great, it tends to corroborate the findings presented here. The periods are not identical with mine because Guthmann's cases were tabulated in periods of 2 hours.

To argue that there are "only 33,215" cases here and hence not enough to prove the point is to ignore the fact that each of the five hospitals alone showed similar peak and low hours that were statistically significant. The same results in many smaller groups are more significant than a certain result in one large group.

It may be felt that the inclusion of low-forceps deliveries disguises the true situation. However retabulation of the 10,546 W. C. A. Hospital cases showed the same statistically significant peak and low hours in both the 5039 spontaneous and the 5507 low-forceps deliveries, just as was seen in the total for each hospital and in the grand total.

It is interesting that Charles (*2*) and also Guthmann (*1*) noted a daily disproportion in the frequency of the onset of labor. Charles found that 62 percent of labors began between 9 P.M. and 9 A.M., the midpoint of this period being 4 hours before the midpoint of the peak period of birth given here.

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9 November 1955

Adrenal Cortex and the Parotid Secretion of Sodium-Depleted Sheep

The isolation of aldosterone (*1*) has stimulated inquiry into the role of the adrenal gland in the changes occurring in the activity of electrolyte-secreting tissues as a result of sodium ion (Na^+) depletion (*2*). The necessity of adequate techniques of bioassay has been emphasized accordingly (*3*).

It has been reported elsewhere (*4*) that sheep with a modified Pavlov-Glinski fistula of the parotid duct lost 2 to 4 lit of hypertonic alkaline saliva each day (composition: Na^+, 170 to 180 mequiv/lit; K^+, 5 to 15 mequiv/lit; Cl^-, 8 to 15 mequiv/lit; HCO_3^-, 120 to 150 mequiv/lit; HPO_4^{--}, 15 to 40 mequiv/lit; $Na^+/K^+ = 18$ to 25). If the fistula loss of Na^+ was not replaced, these sheep became rapidly depleted of large quantities of Na^+, and the Na^+/K^+ ratio of the saliva decreased commensurately

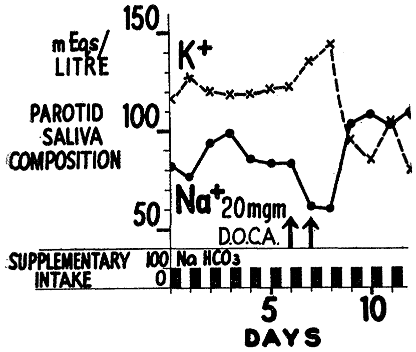

Fig. 1. Parotid fistula No. 7. Effect of DOCA on electrolyte composition of parotid saliva of a sheep moderately depleted of Na^+.

from 18 to 0.1. Since the $Na^+ + K^+$ total remained virtually constant, and the anion pattern was little changed, the saliva retained its hypertonicity and alkalinity.

At the outset, a tentative hypothesis was that the change in Na^+/K^+ ratio was mediated by the activity of the adrenal cortex, responding in some way to Na^+ depletion by enhanced production, presumably of aldosterone, which in turn affected the electrolyte output of the sheep's parotid gland. The following experiments were carried out (*5*).

Desoxycorticosterone (DOCA) was administered to a normal sheep with a parotid fistula. The animal, which had been moderately depleted of Na^+ during the previous 15 days, was secreting saliva of altered pattern (Na^+, 76 to 100 mequiv/lit; K^+, 115 to 128 mequiv/lit). On 2 successive days 20 mg of DOCA was injected intramuscularly, and a definite alteration of salivary Na^+/K^+ ratio resulted (Fig. 1). If, however, the same dosage of DOCA was given when the animal was grossly depleted of Na^+ (salivary pattern $Na^+/K^+ = 30/170 = 0.18$), there was less than 5 mequiv/lit effect on the concentrations. Thus DOCA was shown to produce an effect on the salivary electrolyte pattern. But was the adrenal cortex the regulator of the change seen during Na^+ depletion?

Sheep with unilateral parotid fistulas were bilaterally adrenalectomized.

1) If adequate Na^+ replacement was given, the sheep could be maintained in good condition indefinitely on a daily dose of DOCA (5 to 10 mg) and cortisone (25 mg). DOCA was the more critical component. The volume and electrolyte pattern of parotid saliva were normal.

2) If adrenal-hormone supplement alone was withdrawn, the usually observed fall in plasma Na^+/K^+ ratio and large Na^+ loss in the urine occurred (Fig. 2). However, despite the negative Na^+ balance (136 mequiv), there was no characteristic fall in the salivary Na^+/K^+ ratio. In fact this ratio rose (Fig. 2). The animal's condition rapidly deteriorated. When the adrenal hormones were replaced, the salivary Na^+/K^+ ratio fell to a level consistent with the existing degree of Na^+ depletion.

3) If the DOCA supplement was increased (40 mg/day), the salivary Na^+/K^+ ratio fell from 17 to 2.0 in 5 days.

4) If Na^+ replacement was withheld, and the usual maintenance-hormone supplement continued, a state of adrenal insufficiency developed within 2 to 4 days. Despite the Na^+ depletion, there was little or no change in the salivary Na^+/K^+ ratio.

5) If, however, Na^+ was withdrawn during a period of constant but increased

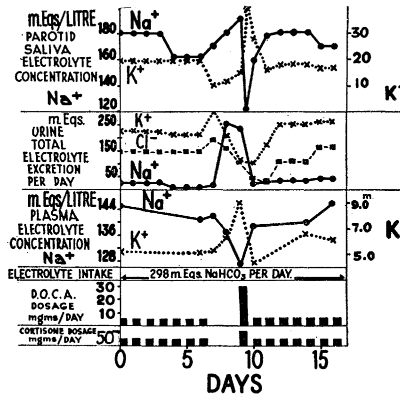

Fig. 2. Adrenalectomy No. 1. Effect on parotid saliva, urine, and plasma of withholding DOCA and cortisone from a bilaterally adrenalectomized sheep with a parotid fistula. The daily Na^+ supplement was given throughout the experiment.

DOCA dosage (20 mg/day), the salivary Na^+/K^+ ratio fell to that seen during Na^+ depletion in a nonadrenalectomized sheep. Figure 3 shows that the increased DOCA dosage lowered the salivary Na^+/K^+ ratio, and that an equilibrium state was reached before the Na^+ withdrawal. The pattern returned to this equilibrium ratio upon restoration of Na^+ balance. Hence, adrenal steroids do alter the sheep's salivary electrolyte pattern, and it is a necessary condition that they be provided in excess of basal-maintenance dose if this electrolyte pattern is to vary commensurately with Na^+ depletion as in a normal animal.

However, the finding in item 5 of an unequivocal response to Na^+ depletion on a constant DOCA dosage suggests that the "cause" of this parotid behavior in the normal animal is the simultaneous interaction of at least two factors. Probably the adrenal secretion is one contributory condition in a set of jointly

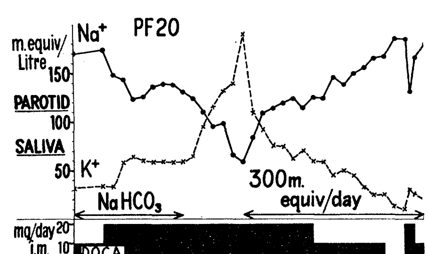

Fig. 3. Parotid fistula No. 20. Na^+ depletion (515 mequiv) in a bilaterally adrenalectomized sheep with a parotid fistula. Na^+ depletion caused a clear-cut fall in the Na^+/K^+ ratio of parotid saliva, in addition to that caused by increased DOCA dosage. After the recovery period, DOCA alone was withheld for 2 days (days 31 and 32) and, in this circumstance, the Na^+/K^+ ratio of saliva rose, despite a negative Na^+ balance of 300 mequiv.