

It is seen that the 3 partially benzoylated antigens have no invariably common fractional identity, in spite of the presence of an equal number of benzoyl "coefficients" in each antigen. Moreover, the heterophile relationships suggested by titration with one antiserum are not the same as those suggested by a parallel titration with an antiserum of different specificity, both antisera presumably containing the same antibenzoyl fractional antibody or function.

These data are almost impossible to harmonize with the suggested theory that each protein is but a mechanical "carrier" of independent superficial unit "determinants". They can be harmonized, however, with the classical postulate that each protein-crystalloid complex functions as a single antigenic unit.

## 6396

**Emetic and Fatal Doses of Digitalis at High Altitudes.**

A. J. LEHMAN AND P. J. HANZLIK.

*From the Department of Pharmacology, Stanford University School of Medicine, San Francisco.*

For over a hundred years, there has been some knowledge of changes in effects of drugs at high altitudes. However, some scientific studies, according to a summary of Loewy,<sup>1</sup> indicate conflicting tendencies. Nevertheless, it would seem that changes in certain pharmacological actions might be expected from known or assumed changes in circulatory and respiratory functions, although the degree or character could not be exactly predicted, owing to the adjusting influences of compensatory mechanisms. The interest attached to any possible changes is both fundamental and practical, the latter especially with reference to dosage, toxicity and unexpected actions in medication of persons at high altitudes. Macht<sup>2</sup> has recently claimed that digitalis is more toxic at high altitudes in the Blue Ridge Mountains, Rocky Mountains, and the Tyrolean Alps than at Baltimore. The continued studies of digitalis along different lines in this laboratory prompted us to include determinations at high altitudes of the emetic and fatal doses in pigeons and of fatal doses in cats. The results obtained are generally consistent with Macht's

---

<sup>1</sup> Loewy, A., *Physiologie des Höhenklimas*, 1932, 414, Springer, Berlin.

<sup>2</sup> Macht, *Am. J. Physiol. (Proc.)*, 1931, **97**, 540.

claims, and indicate the desirability of similar investigations with other drugs.

The plan of our experiments was as follows: A potent tincture of digitalis which has been assayed for several years by the pigeon method<sup>3</sup> was used. The pigeon-emesis method was used to great advantage, since it was possible to repeat the test on the same pigeons, first at one altitude and then at the other. Thus, any changes were due solely to altitude, exclusive of individual variations, which offer greater difficulties in fatal-dose methods. However, the fatal doses for pigeons were also determined, thus providing a check on the results with emetic doses.

Actually, 2 large groups of pigeons were used. One group was used for determining the emetic doses, and their distribution, at San Francisco. A week later, *i. e.*, after recovery, the same was done at Tioga Pass in the Sierra Nevada Mountains. After keeping these pigeons another week at Tioga, the fatal dose was determined. Using another group of fresh pigeons, the emetic doses were first determined at Tioga and a week later at San Francisco; after another week at San Francisco, the fatal dose was determined. The usual procedure for determining the intravenous fatal dose in cats was used, the cats being anesthetized with barbital intraperitoneally. Two groups of 8 cats each were injected, one at San Francisco and the other at Tioga. The estimated altitudes and barometric pressures were: San Francisco, 0 and 760 mm.; Tioga Pass, 10,000 ft. (3000 + M.), and 526 mm., a decrease of 234 mm.

The results with the 2 corresponding groups of pigeons were put together in Table I as they were practically the same.

TABLE I.  
Emetic and Fatal Doses of Digitalis in Pigeons at Different Altitudes.

| Elevation                  | Digitalis: mg. per kilo body weight |    |    |    |    |    |              |    |    |     |     |     |     |     |  |
|----------------------------|-------------------------------------|----|----|----|----|----|--------------|----|----|-----|-----|-----|-----|-----|--|
|                            | 5                                   | 10 | 15 | 20 | 25 | 30 | 60           | 90 | 98 | 105 | 120 | 135 | 143 | 150 |  |
|                            | % Emesis*                           |    |    |    |    |    | % Mortality† |    |    |     |     |     |     |     |  |
| San Francisco<br>(0)       | 0                                   | 0  | 29 | 50 | 54 | 75 | 0            | 0  |    | 0   | 40  | 57‡ | 80  | 100 |  |
| Tioga Pass<br>(10,000 ft.) | 0                                   | 25 | 63 | 67 | 75 | 96 | 0            | 20 | 40 | 67§ | 80  |     |     | 100 |  |

\*24 pigeons for each dose; †at least 5 pigeons for each dose; ‡12 pigeons; §7 pigeons.

*Emetic Doses in Pigeons.* A total of 288 tests with 6 doses of digitalis, ranging from 5 to 30 mg. per kilo body weight, were made in 144 different pigeons. The results in the table show conclusively that all doses, except the 5-mg. dose which was ineffective at both

<sup>3</sup> Hanzlik, *J. Pharm. Exp. Therap.*, 1929, **85**, 363.

altitudes, caused a greater number of pigeons to vomit at Tioga than at San Francisco; actually, from 17 to 34%, median 21%, more vomited at Tioga. The M. Em. D. was 25 mg. per kilo at San Francisco, and 15 mg., or about 40% less, at Tioga. If compared with the dose of 20 mg. per kilo which caused 50% of pigeons to vomit at sea level, the M. Em. D. at Tioga was still 25% less. Nearly all the pigeons vomited after 30 mg. per kilo of digitalis at Tioga, but only 75% at San Francisco. Thus, a greater potency of digitalis at the high altitude was demonstrated by data on the distribution of emetic doses and the minimum emetic dose. In general, a 1% increase in number of pigeons vomited for each fall of 11.6 mm. barometric pressure, or rise of 418 feet in altitude; somewhat similar was the variation in emetic potency. It follows that for an equal degree of pharmacological activity at sea-level, the dosage of digitalis at an altitude of 10,000 feet should be reduced from 1/4 to 2/5.

*Fatal Doses in Pigeons.* The fatal doses of digitalis were determined in 74 pigeons. The results essentially confirmed those with emetic doses. The mortality was greater for each dose tried at Tioga, except the dose of 60 mg. per kilo, which failed to kill at both altitudes. The surely fatal dose at both altitudes was 150 mg. per kilo. The mortality was about 40% (median) greater at Tioga for comparable doses, the differences being even more striking with doses of 98 and 105 mg. per kilo. The M. F. D. at San Francisco was 135 mg. per kilo, and 105 mg., or about 22.2% less, at Tioga. The mortality was increased 1% for each 7 mm. fall of barometric pressure, or 252 feet rise in altitude. It follows that for greater safety in medication with digitalis at high altitudes the dosage should be definitely less than at sea-level.

*Fatal Doses in Cats.* The 16 cats used gave the following fatal doses of digitalis in mg. per kilo body weight: at San Francisco, median 108, range 87 to 190, and at Tioga, median 127, range 57 to 170. Accordingly, the extreme doses at the high altitude were less than those at sea-level in agreement with the tendency in pigeons. However, the median doses showed the reverse tendency, due probably to the greater variations in the cats and the small number used than was the case with pigeons. A comparable number of cat-tests was obviously out of the question, whereas the pigeon-tests were made on a large and significant scale with the greatest ease and convenience, which illustrates some decidedly practical advantages in the pigeon method. For the present, the results of the cat-tests

must be regarded as less conclusive than those of the pigeon-tests. Macht's results were obtained with cats, but he gives no data.

*Conclusions.* The emetic and fatal doses of digitalis in significant numbers of pigeons were found to be 40 and 22% less, respectively, at an altitude of 10,000 feet than at sea-level. A similar tendency was shown by the extremes in fatal doses for cats, but the results were inconclusive, due probably to greater variations in cats and smaller numbers used. The higher potency of digitalis at high altitudes reflects changes in state of the emetic and circulatory functions at high levels and indicates the desirability of reducing the dosage of the drug at high levels so as to avoid undesirable and toxic reactions.

### 6397

#### Artificial and Hereditary Suppression of Sacral Vertebrae in the Fowl.\*

C. H. DANFORTH.

*From the Department of Anatomy, Stanford University.*

An understanding of the action of hereditary factors in regulating structural expression is likely to be facilitated by finding ways of reproducing the same effects by other than genetic means. To this end, the conditioning of either of 2 allelomorphic forms irrespective of the genotype is a principal desideratum. The present note records the few fragmentary data obtained from an attempt in this direction. Suppression of several of the sacral and caudal vertebrae in the fowl producing the condition known as "rumplessness" has long been known, and has been studied by Du Toit,<sup>1</sup> Dunn,<sup>2</sup> and Landauer,<sup>3</sup> who have described the anatomy and genetics of the condition. The latter authors have also pointed out the occurrence of occasional spontaneous non-hereditary cases which differ little, if at all, from those of the hereditary type. Owing to the extreme rarity of the sporadic cases (not over 1 in 1000, according to Dunn), it has hitherto seemed improbable that much could be learned of their genesis.

---

\* Aided in part by a grant from the Rockefeller Fluid Research Fund of Stanford University.

<sup>1</sup> Du Toit, P. J., *Jenaische Z. f. Naturwissensch.*, 1913, 49.

<sup>2</sup> Dunn, L. C., *J. Hered.*, 1925, 16.

<sup>3</sup> Landauer, Walter, *J. Hered.*, 1928, 19.