pered by a maze of mathematical symbols. To accomplish such a feat of simplification in the interpretation of atomic spectra is not a simple task, and the author is to be commended for the facility with which he carries through his plan.

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## AN APPEAL FOR MATHEMATICAL UNDERSTANDING

*Mathematics for the Million.* By LANCELOT HOGBEN, F.R.S., London School of Economics. Illustrations by J. F. Horrabin. W. W. Norton Company, Inc., New York. xii + 647 pages. $3.75. 1937.

THE title might suggest that here is another "mathematics made easy," a short-cut course in technical tricks for the apprentice computer. On the contrary, this is a reasoned appeal for common sense and understanding on the part of educated readers for the application of the mathematical discoveries of the race toward the solution of present-day problems. The earlier British edition stirred wide interest. For the wealth of historical and social contacts, for the pervasive philosophical motivation, for the breadth of sympathy and vigor of attack upon entrenched apathy this book is outstanding. It is not designed to inform the specialist, since it contains little material on pure mathematical theory with which any competent instructor in college mathematics is not already familiar. No brief list of its twelve chapters can do the work justice. Perhaps the most unusual are Chapter III—"The Grammar of Size, Order and Number, or Translating Number Language," and Chapter XII—"Statistics or the Arithmetic of Human Welfare," which strike notes that traditional text-books seldom suggest. Undoubtedly even the little mathematical technique assumed will discourage or repel many scholarly persons. Yet the lively, informative and gracious style and suggestive illustrations will maintain the average reader's interest through its six hundred and fifty pages, leaving him eager for more, and thrilled with a new sense of the power and flexibility of mathematics as a method of thinking.

ALBERT A. BENNETT

# SPECIAL ARTICLES

## DIGITALIS AND CALCIUM SYNERGISM[1]

EXPERIMENTS were published by Gold and Edwards[2] in 1927, which showed that hypercalcemia resulting from the injection of calcium chloride or the parathyroid hormone rendered the normal dog more susceptible to the action of ouabain. This was confirmed by the experiments of Lieberman[3] in which another digitalis glucoside and calcium gluconate were used. That digitalis and calcium act synergistically in animal experiments has been known for a long time and observations have been published indicating a similar phenomenon in man (review of literature, Berliner, 1933).[4] Bower and Mengle[5] reported two cases in which patients under the influence of digitalis died after an intravenous injection of calcium gluconate. They ascribed this to synergism between the two drugs and performed experiments in dogs which led them to the same conclusion. Their animal experiments, however, are not very convincing because of the large doses of digitalis they injected, although their conclusions are in accord with the work of others.

A discordant note is struck in a more recent report by Nahum and Hoff,[6] who tested the effect of intravenous calcium chloride in rabbits which had received digitalis in the form of digifoline. A careful examination of their paper, however, shows that in those animals in which no additive effect was observed, there is reason to believe that the animals were no longer under the influence of digitalis, and furthermore, in those in which there is reason to believe that the animals were under the influence of digitalis, a very strong synergistic effect with calcium may have been present.

Two significant facts which Hatcher[7] demonstrated in 1912 appear to have escaped consideration, namely, (1) that the rabbit excretes digitalis with extraordinary rapidity and (2) that the rabbit is very tolerant to digitalis. In the experiments which we performed (see Table I), it was found that approximately three to seven times the largest doses of digitalis used by Nahum and Hoff were excreted completely or almost so within less than eight hours (experiments 4 and 5). It must be concluded therefore that in the eighteen rabbits in which these authors observed no additive action between digitalis and calcium, there was little or no digitalis present, because the dose (0.5 to 0.75 cat unit per kgm subcutaneously) was administered eighteen hours prior to the calcium, and the probability is that during that period most or all of it was excreted.

Another group of their animals was treated in a somewhat different manner. In addition to the subcutaneous dose of digitalis eighteen hours previously, they received a dose of 0.25 cat unit per kgm intravenously one half hour before the calcium. This treat-

[1] From the Department of Pharmacology of Cornell University Medical College, New York.

[2] H. Gold and D. J. Edwards, *Am. Heart Jour.*, 3: 45, 1927.

[3] A. J. Lieberman, *Jour. Pharmacol. and Exp. Therap.*, 47: 183, 1933.

[4] K. Berliner, *Am. Heart Jour.*, 8: 548, 1933.

[5] J. O. Bower and H. A. Mengle, *Jour. Am. Med. Assn.*, 106: 1151, 1936.

[6] L. H. Nahum and H. E. Hoff, *Proc. Soc. Exp. Biol. and Med.*, 36: 860, 1937.

[7] R. A. Hatcher, *Arch. Int. Med.*, 10: 268, 1912.

TABLE I
FATAL DOSE AND PERSISTENCE OF ACTION OF TINCTURE DIGITALIS IN RABBIT

| Rabbit no. | Weight kgm | Period of injection min. | M.L.D.* mgm per kgm | M.L.D. cat units | Remarks |
|---|---|---|---|---|---|
| 1 | 2.89 | 106 | 730 | 8.58 | |
| 2 | 2.98 | 61 | 408 | 4.8 | |
| 3 | 2.28 | 95 | 802 | 9.4 | Received 1.5 cat units per kgm (specimen A) daily for two days; on third day a similar dose 8 hours prior to final testing. |
| 4 | 2.57 | 95 | 708 | 8.3 | Received 2.5 cat units per kgm (specimen A) 8 hours prior to final testing. |
| 5 | 3.07 | 93 | 650 | 7.6 | Received 1.5 cat units per kgm (specimen A) daily for two days; on third day 5.5 cat units per kgm (specimen B) in two doses 5 to 7 hours prior to final testing. |
| 6 | 2.08 | .. | ... | 3+ | Survived 3 cat units per kgm (specimen B) in one injection. |
| 7 | 2.92 | .. | ... | 4–6 | Received 4 cat units per kgm (specimen B) in one dose and 2 cat units per kgm in a second injection 5 minutes later; caused death with ventricular fibrillation. |

* All these tests were made with specimen B, a tincture of digitalis with a cat unit potency of 0.85 cc. Specimen A was a tincture of digitalis with a cat unit potency of 0.75 cc. All injections were made intravenously. The doses in the table refer to the leaf.

ment caused the death of three of the five animals in four hours. These doses are extremely small for the rabbit. In our experiments (see table) the M.L.D. for the albino rabbit proved to be about eight times as much as that for the cat by the same method of slow intravenous injection.[8] Sudden intravenous injections of three and four units per kgm did not prove fatal. Accordingly, the subcutaneous doses which Nahum and Hoff gave eighteen hours prior to the calcium and which they referred to as 50 to 75 per cent. of the "calculated lethal dose" of digitalis, were in fact only about 6 to 9 per cent. of the lethal dose for the rabbit, and the additional intravenous doses (0.25 cat unit per kgm) were only about 3 per cent. of the lethal dose for the rabbit. In view of the rapid excretion of digitalis in the rabbit, the dose which proved fatal to three of five animals was only about 3 per cent. of the intravenous fatal dose when the animal was treated with calcium in the manner of their experiments.

Such facts constitute the standard evidence for the phenomenon of synergism. But the authors conclude: "In the normal unanesthetized rabbit heart the effects of calcium and digitalis are not additive." In view of the unusually high degree of synergism shown by the death of these three rabbits and the long interval before death, confirmation of these experiments would be desirable.

As matters stand, the synergism between calcium and digitalis remains an established fact. From the practical standpoint it needs to be borne in mind that the rapid intravenous injection of calcium is a dangerous procedure, and that the danger is greater when the subject is under the influence of digitalis.

HARRY GOLD
NATHANIEL KWIT

[8] The tincture of digitalis with the alcohol evaporated off was diluted five times with physiological salt solution and administered slowly intravenously so as to complete the injection in about ninety minutes, a method similar to that used in the cat method of assay.

## THE pH STABILITY RANGE OF THE ELEMENTARY BODIES OF VACCINIA

THE causative agents of known virus diseases range in size from the elementary bodies of the pox diseases, which are almost as big as the smaller microorganisms, downwards to particles comparable in weight with the larger protein molecules. Since it is now possible to obtain concentrated and purified preparations of both large and small virus particles, a comparison of their properties becomes one of the most immediately interesting problems in the study of viruses. Recently[1] we reported preliminary results of a comparison of the pH stability ranges of the virus activity of infectious papillomatosis in rabbits and of the molecules of the purified virus protein[2] of this disease. In this investigation it was found, by animal titration and by ultracentrifugal analyses, that the protein molecules were disrupted at exactly those pH's at which the virus activity was immediately lost. The present note records the results of a similar comparison of the pH stabilities of the virus activity of vaccinia and of its purified elementary bodies.

The vaccine virus employed was obtained as calf lymph from the North Carolina State Board of Health. This virus was passed repeatedly through rabbits by the methods of inoculating and harvesting described by Craigie.[3] The destruction of virus activity was determined by suspending the virus in 0.04M salt buffer mixtures and inoculating the suspensions intradermally into susceptible rabbits after standing in the buffer for an hour, a day and a week. The actual pH of each suspension was measured with a glass electrode. The resulting lesions were charted daily for eight days after inoculation. Three experiments of this kind yielded practically identical results.

[1] R. W. G. Wyckoff and J. W. Beard, *Proc. Soc. Exp. Biol. and Med.*, 36: 562, 1937.

[2] J. W. Beard and R. W. G. Wyckoff, SCIENCE, 85: 201, 1937.

[3] J. Craigie and F. O. Wishart, *Brit. Jour. Exp. Path.*, 15: 390, 1934; etc.