gence but proudest of their wealth," but rather a place where a moral conscience grew amongst a whole people, where a sense of the majesty of *Maat* or right became pervasive.

It was a professor in another state university in this region who said that institutions have to be created as systematic reminders of good ideas. Conservation is not only a good idea; without it there will cease to be an America as we know it. When and if that time comes it will not be the Mississippi that will be to blame or a change of climate or European wars. It will be man—the men and women of America—you and I—who created the problems where once there was bounty and balance in nature. The structure that we have met to dedicate symbolizes an idea, a morality, a common good, right. Though time crumble its walls, if the idea of common good survives, the purpose of the building will have been fulfilled. Backed by a passion for human welfare, its staff will reach out into every part of the state to earn dividends upon the public investment which it represents.

According to Livy it was an ancient Roman custom to enclose any place that had been struck by lightning and keep it inviolate ever after. In such a place a stone was buried to represent the lightning. The enclosure was called a "puteal" and it was sacred. This building may be called a modern form of puteal. It represents interest in the forces of nature, forces unbalanced by man and now striking back with lightning effect. It is a place inviolate from those who talk freedom and are silent about the common good. Our puteal may last like that watering trough at Wolfeboro for 150 years, or like the sense of *Maat* in Egypt for a thousand years, according to the will and the conscience and the intelligence of the people of Illinois at work upon their own problems and, like the men of the Plymouth Plantation, forever intent upon the changing question of their better ordering and preservation.

STATUS OF BIO-ASSAY OF THE DIGITALIS GROUP[1]

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THE bio-assay of digitalis is made necessary by the fact that pure principles are not generally available, and most of the practice is confined to the use of crude material or mixtures of glucosides. There are no satisfactory chemical methods for their estimation. Numerous methods have been suggested for the assay of digitalis, embracing a wide variety of animals and techniques.

The U. S. Pharmacopeia has taken a hand in the problem with the view of providing digitalis of uniform potency. Every specimen labeled U.S.P. digitalis is compared with a standard digitalis powder on a qualified batch of frogs. All digitalis labeled U.S.P. is supposedly of the same strength within the limits specified, namely, ± 20 per cent.

TABLE 1

TINCTURES OF DIGITALIS ASSAYED BY THE FROG METHOD IN 1907 BY EDMUNDS

No.	Toxic dose (cc)	Origin of plant
1	.08	From German leaves.
2	.11	From English leaves.
3	.12	From leaves obtained from manufacturer of tincture No. 5.
4	.13	
5	.15	Physiologically assayed.
6	.16	From physiologically assayed leaves.
7	.175	Physiologically assayed.
8	.18	
9	.18	From German leaves.
10	.19	
11	.20	From English leaves.
12	.21	
13	.26	"German tincture."
14	.27	
15	.28	
16	.29	From English leaves.

Table 1 shows how variable digitalis was before the pharmacopeia described a method of assay. These data were used in 1907 by Edmunds[2] in support of his recommendation for the inclusion of the frog method into the pharmacopeia. He assembled a number of preparations of digitalis and assayed them by a frog method. He found the strongest about three times as potent as the weakest. Since then a fairly large literature has accumulated on the subject of digitalis assay, and statistical refinements have been introduced into the treatment of assay data for the purpose of improving the accuracy of the methods.[3, 4]

About six months ago we assembled a number of the outstanding brands of tincture of digitalis, labeled U.S.P., supposedly of similar potencies. We assayed them by the cat method,[5] and the results are presented

[1] Based on an address given before the Cornell University Medical College Research Society, November 7, 1940. Part of the material represents work carried out at the Beth Israel Hospital, and the Hospital for Joint Diseases, New York City, in collaboration with Dr. Nathaniel T. Kwit and Dr. Milton Kramer, later to be published *in extenso*.

[2] C. W. Edmunds, *Jour. Am. Med Asn.*, 48: 1744, May 25, 1907.

[3] C. W. Chapman and C. A. Morrell, *Jour. Pharmacol. and Exp. Therap.*, 46: 229, October, 1932.

[4] L. C. Miller, C. I. Bliss and H. A. Braun, *Jour. Am. Pharm. Asn.*, 28: 644, October, 1939.

[5] The technique employed in this laboratory involves intravenous injection, either continuously or in equal fractions at 5-minute intervals, until death in an average period of between 60 and 90 minutes in the cat under very light ether anesthesia.

in Table 2. The strongest tincture is nearly three times as potent as the weakest.

TABLE 2
POTENCY OF TINCTURES OF DIGITALIS (U.S.P. XI)

	Specimen	Cat unit potency cc of tincture
1	John Wyeth	0.35
2a	Parke Davis	0.36
2b	Parke Davis	0.46
3	Squibb	0.58
4a	Digitol (Mulford)	0.58
4b	Digitol (Mulford)	0.86
5	Lilly	0.60
6	"Tr. Digitalis U.S.P. XI"	0.96

It seems, therefore, that we are in need, not merely of improvement in the method of assay, but that we are in need of a method of assay.

Various complaints have been lodged against the animal assay methods. One favorite objection is that they measure the toxic action of digitalis glucosides, not a therapeutic action: systolic standstill of the frog's heart, or fibrillation of the ventricles in the cat. The therapeutic action is a difficult matter to get at directly, representing, as it does, the increased force of the heart's contraction.

The search for a therapeutic end-point for the assay of digitalis in animals doesn't seem to be very important, however, because the therapeutic and toxic effects of digitalis are due to the same action, and there is no good evidence for a significant difference in the ratio of the doses exerting toxic and therapeutic actions.

The literature on this matter is limited, and most of it is not convincing. The experiments of Visscher and his collaborators[6] have aroused a good deal of interest. They concluded that digilanid C has 30 times as great a ratio of the toxic to the therapeutic dose as digilanid B. To obtain this figure, they related the concentration in the heart-lung preparation of a dog to the intravenous fatal dose for the cat. Without going into an evaluation of this method, suffice it to state that there are reasons for believing that for a valid ratio of toxic to therapeutic dose, it is necessary to compare these doses in the same test object.[7]

We studied this problem[7a] in the laboratory by means of the papillary muscle technique[8] which was described before this society last year. You may recall that when the papillary muscle of the cat's ventricle is made to record its tension developed during systole by means of an isometric lever, we obtain a record such as this (Fig. 1). When the muscle begins to fail under the unfavorable circumstances of the environment, a digitalis glucoside restores the systolic tension. After a time the muscle begins to fail again, and we

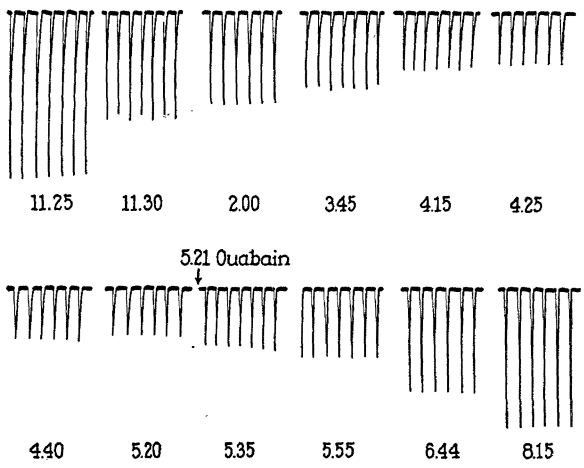

FIG. 1

found that the length of time elapsing before the muscle fails with toxic doses is dependent on the potency of the preparation. The next chart (Fig. 2)

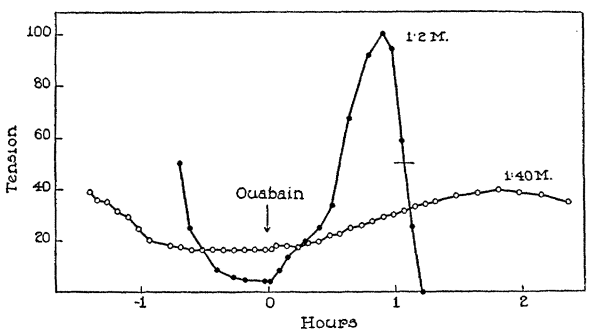

FIG. 2

shows the appearance of the record when one compares a 1:40 million solution of ouabain with a 1:2 million solution. You will note that the time from the application of the drug to the depression to half-tension is much shorter with the stronger solutions. Using this papillary muscle technique, we related the minimal dose which causes a rise in systolic tension, which we call the therapeutic dose, to the dose which causes the toxic effect. We compared a variety of preparations in this way and found that ouabain, digitoxin-like materials,[9] and lanatoside A, B and C (Sandoz), widely different digitalis glucosides, show no significant differences in the ratio of the toxic to the therapeutic dose.

An attempt was made to secure some information about this ratio from experiments on humans by determining the incidence of poisoning when a full thera-

[6] G. K. Moe and M. B. Visscher, *Jour. Pharmacol. and Exp. Therap.*, 64: 65, September, 1938.

[7] McK. Cattell and H. Gold, *Jour. Pharmacol. and Exp. Therap.*, 66: 7, May, 1939.

[7a] McK. Cattell and H. Gold, *Jour. Pharmacol. and Exp. Therap.*, 71: 114, February, 1941.

[8] McK. Cattell and H. Gold, *Jour. Pharmacol. and Exp. Therap.*, 62: 116, January, 1938.

[9] The preparations of digitoxin-like materials we used were Digitaline Nativelle and Digitoxin (Merck).

peutic dose is given, and comparing that with the incidence of poisoning when the full therapeutic dose is doubled. In this way we compared digitalis leaf with the digitaline and with lanatoside C. Table 3 shows

TABLE 3

RATIO OF TOXIC TO THERAPEUTIC DOSE IN MAN

Preparation	Number of full therapeutic doses	Number of cases	Incidence of toxicity (per cent.)
Digitalis	1	82	3.7
	2	125	38.4
Digitaline (Nativelle)..	1	24	8.3
	2	13	46.0
Lanatoside C	1	26	7.6
	2	16	50.0

the results. The ratios are of the same general order for the three preparations. Nearly half of the patients develop toxic symptoms when the therapeutic dose is doubled.

Therapeutic or toxic end-points, therefore, serve equally satisfactorily for assay purposes.

The real problem seems to be that when two preparations of digitalis are compared by different methods or in different animals, different answers are obtained. In Table 4 there are some illustrations of this. Here

TABLE 4

RELATIVE POTENCY OF DIGITALINE (NATIVELLE) AND LANATOSIDE C BY VARIOUS METHODS

Test method	Digitaline (mgm)	Lanatoside C (mgm)
Cat assay	1	0.7
Papillary muscle	1	10
Oral therapeutic (man)	1	12
Intravenous therapeutic (man)	1	1.5

are two glucosides of digitalis, the potencies of which are compared by different methods. When the digitaline or digitoxin (Merck) and lanatoside C are injected intravenously into cats until death occurs by the method of the cat assay, lanatoside C is found to be a little stronger than the others. However, when one compares these preparations on the isolated papillary muscle, one obtains a very different answer, and in the reverse direction. Instead of lanatoside being stronger than the digitoxin-like materials, it is now found to be 1/10 as strong. In the cat method of assay the whole body is exposed to the digitalis glucoside, whereas in the papillary muscle technique only the heart muscle is exposed to it. The question arises whether the reversal in order of potency may not be due to differences in the fixation of the drugs by other body tissues, or possibly chemical alteration by the tissues. When one compares digitaline and lanatoside C by intravenous administration in man, they are found to be nearly of the same potency, but the digitaline is about 12 times as strong as lanatoside C by oral administration. It is clear that one of the chief factors in this difference is the degree of absorption from the gastrointestinal tract.

All this, by way of illustration of the fact that different methods of assay yield different results with respect to the relative potencies of two preparations of digitalis glucosides. The question then arises, which of the known methods yields the correct answer? Which gives results valid for humans?

The two methods with which most of the work has been done are the cat method of Hatcher and Brody, and the one-hour frog method of the U. S. Pharmacopeia.

When the tincture of digitalis ages it grows weaker by the frog method, but its potency changes little by the cat method.[9a, 10] The explanation may lie partly in the fact that the frog method involves absorption from the lymph sac, whereas the cat method involves no absorption, since here the drug is injected directly into the circulation.

Recently the government seized a tincture of digitalis because they found it only about ½ as potent as U.S.P. digitalis. But when we tested this tincture by the cat method, we found it to possess the expected potency of a U.S.P. tincture, namely, 0.67 cc per cat unit. This tincture also proved to have full potency in man. A similar discrepancy in the results by the cat and frog methods was obtained with the present specimen of digitalis which has proved entirely satisfactory in the 60 member clinics of the New York Heart Association. By the frog method, 2.6 mgm of this digitalis equals 1 mgm of U.S.P. reference powder, whereas by the cat method only 1.6 mgm of this digitalis equals 1 mgm of the reference powder.

Each of the two methods has its own group of supporters, but there have been no satisfactory experiments in humans to show which gives results that are valid for man. We have made some studies bearing on this problem. In these it is essential to compare the different specimens in the same individual and to select such doses as fall in the critical range of sensitivity for the given individual.

We have made comparisons using as criteria of effects the ventricular rate changes in patients with auricular fibrillation and T-wave changes in patients with regular sinus rhythm. Both methods give the same answer. Both reveal the full therapeutic action of digitalis.[10a]

Fig. 3 is an example of the type of experiment made in a comparison of two preparations. The patient entered the hospital with auricular fibrillation and a

[9a] F. Wokes, *Quart. Jour. Pharm. and Pharmacol.*, **2**: 48, 1929.

[10] C. C. Haskell, *Jour. Am. Pharm. Asn.*, 14: 492, June, 1925.

[10a] H. Gold and McK. Cattell, *Arch. Int. Med.*, 65: 263, Feb., 1940.

rapid ventricular rate. He was put to bed and the routine examinations necessary for a complete diagnosis were made, including urine and blood examinations, electrocardiograms and x-rays. While the patient lay quietly in bed, a one-minute apex count was made with the stethoscope at least three times daily, during the control period of seven days or longer. The average rate for the day is represented by one point on the curve. The full dose of digitalis was given at one time. The apex count was then made in the same manner every hour throughout the day. In the succeeding days, the record was obtained in the same way as in the control period. When the rate returned to a level approximately that of the control, as was the case in two or three weeks, the second specimen of digitalis was given in the same way, and a similar record was

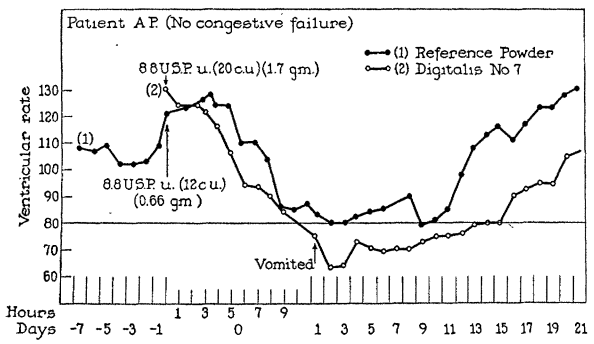

FIG. 3

made. The sensitiveness of the method was determined in several experiments in which different doses of the same preparation were given. The order in which the different doses and different preparations were given was varied so as to be certain that the effect of the second dose did not represent the summation of effects. The results in Fig. 3, which are typical of a group of experiments, show that the one-hour frog method of the U. S. Pharmacopeia is misleading. A dose of 8.8 U.S.P. units of one preparation of digitalis leaf produced satisfactory digitalization, while the same number of U.S.P. units of another preparation produced a lower rate as well as symptoms of poisoning in the same person. When the foregoing doses of the two preparations are expressed in cat units, the one which produced the smaller effects represents only 12 cat units, whereas the one which produced poisoning represents 20 cat units.

It appears from these results that the cat method may be better than the frog method for digitalis in that the intensity of the effects seems to follow in a more direct relationship to the number of cat units. However, there is evidence that the cat method, when applied to purified glucosides, is also misleading. Fig. 4 shows a comparison of the effects of cat units of the digitaline with cat units of digitalis by oral administration. Note that 3 cat units of the purified material produces the same effects as 20 cat units of digitalis. It would prove disastrous to give a patient the same

Comparative Effects of Cat Units of Digitaline Nativelle and Digitalis by Oral Administration

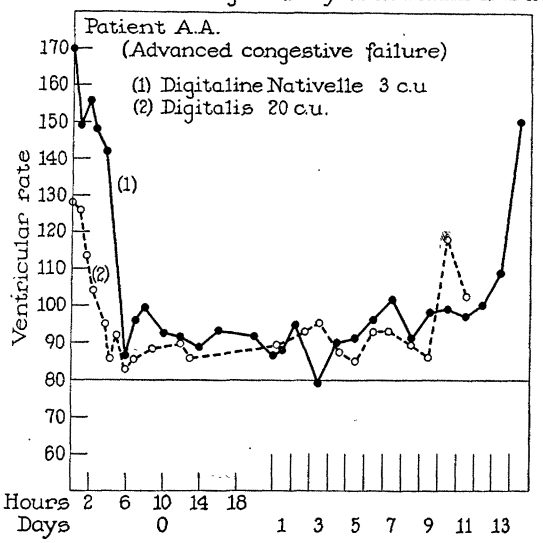

FIG. 4

number of cat units of digitoxin or digitaline as of digitalis.

Digitoxin-like materials are well absorbed,[11, 12] whereas in all probability only the digitoxin-like frac-

Comparative Effects of Digitaline Nativelle by Oral and Intravenous Administration

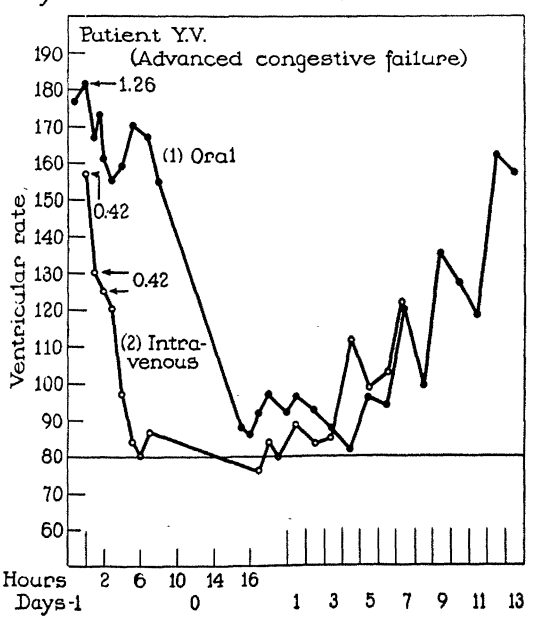

FIG. 5

[11] R. A. Hatcher, *Jour. Am. Med. Asn.*, 75: 460, August, 1920.

[12] C. Eggleston, *Jour. Am. Med. Asn.*, 75: 463, August, 1920.

tion in digitalis is absorbed under ordinary conditions, representing only a portion of the activity of digitalis. Thus a difference in absorption may explain the fact that a cat unit of the purified material which we used is about seven times as potent in man by mouth as a cat unit of digitalis. Fig. 5 shows that the dose (1.26 mgm) of digitoxin-like material by intravenous injection is the same as the dose by oral administration. In the case of digitalis, there is a wide spread between the dose by intravenous injection and by oral administration.

Differences in absorption, however, are not the only factors that bring the cat method into question. Several years ago Wyckoff and Goldring[13] made a study at Bellevue Hospital on patients with auricular fibrillation. They gave 0.1 mgm of ouabain intravenously every half hour and found that by the time 1 mgm was given, full effects had developed. In some of our recent experiments with the digitaline we found that the full dose of this material when given by intravenous injection is also between 1 and 1.26 mgm (see Fig. 5). The milligram of ouabain, however, represents 10 cat units, whereas the 1.26 mgm of the digitaline represents only 3 cat units. Since they were both given intravenously, absorption can not be responsible for the difference. The phenomenon must be due to a difference in the way in which the cat and man utilize the two glucosides.

The indications are that neither the frog nor the cat method overcomes all the obstacles to uniformity among digitalis preparations. From the practical standpoint what we need to know is the potency of digitalis preparations in man.

The foregoing observations indicate that the final evaluation of the potency of a preparation of digitalis must be based on determinations in man. We have made experiments[14, 15] which indicate that digitalis can be adequately assayed on humans. The T-wave changes of the electrocardiogram run parallel with the therapeutic actions of the drug and in suitable individuals, with or without heart disease, differences as small as 30 per cent. in the dosage of digitalis can be detected by unequivocal changes.

A more satisfactory solution is the use of purified digitalis glucosides which do not require bio-assay. It appears that there are digitalis glucosides which are well absorbed from the gastrointestinal tract and which can be extracted with reasonable uniformity.

[13] J. Wyckoff and W. Goldring, *Arch. Int. Med.*, 39: 488, April, 1927.

[14] H. Gold, N. T. Kwit and McK. Cattell, *Jour. Pharmacol. and Exp. Therap.*, 69: 177, July, 1940.

[15] N. T. Kwit, H. Gold and McK. Cattell, *Jour. Pharmacol. and Exp. Therap.*, 70: 254, November, 1940.

OBITUARY

FRANK CRAIG JORDAN

THE tragedy which cost the lives of Dr. Frank C. Jordan and his wife, Harriet Roy Jordan, shocked an unusually wide circle of friends and acquaintances.

Frank Craig Jordan was born at Cordova, Ill., on September 24, 1865; the son of John Henry and Louisiana Craig Jordan. Marietta College granted him the following degrees: B.Ph. in 1889; M.A. in 1892, and the honorary degree Sc.D. in 1929. In 1914 the University of Chicago granted him the earned degree Ph.D. His thesis, "The Color Changes of Certain Variable Stars of Short Period," is still an important document for all who are interested in these stars.

Following a number of years spent as instructor in astronomy and mathematics, he received a fellowship at Yerkes Observatory in 1905. He joined the staff of the Allegheny Observatory in 1908 where he was professor of astronomy in the University of Pittsburgh, assistant director, and since 1930, director.

Dr. Jordan's scientific work was divided between radial velocities of early type stars and the photometry of short period variable stars. Fifteen major articles dealing with stellar spectra, including eleven orbits, are found in the Publications of the Allegheny Observatory. One volume of these publications is devoted entirely to Jordan's observations and light curves of twenty-nine Cepheid variables and sixteen eclipsing variables. A number of light curves of additional variables await publication; for still other stars the data are not sufficient to permit the derivation of definitive light curves. These data will be made available to astronomers in a memorial volume.

Dr. Jordan had a number of interests. He was a faithful worker in his church and other community activities. Until recently he engaged in such athletics as swimming and tennis; more recently in golf; he played the organ with fervor and took great delight in music. But of all his interests he found the greatest enjoyment in observing with the telescope, in which occupation none excelled him either in enthusiasm or expertness. In the first decade of the work of the Thaw Refractor the exposures were short and the time required to change from one object to another was of importance. In this period 35,000 plates were secured, 12,000 by Jordan. On the basis of the average of other observers his share would have been 9,000. His great number of plates was not due so much to the enthusiasm with which he watched for breaks in the clouds as to the remarkable efficiency of his unhurried speed.

The American Association for the Advancement of