criteria of improvement, can be produced by daily repetition of a relatively small dose of the drug that can then be continued as the daily maintenance dose without producing toxic symptoms. As is well known such results cannot be obtained with such small doses in the average patient with far advanced congestive failure; the larger daily doses usually required in these cases cannot be long continued without producing toxic symptoms.

3. In the average ambulatory cardiac patient there is a wide margin between the minimum dosage that produces full therapeutic results and the maximum that can be tolerated without toxic symptoms. This margin is frequently smaller in patients with far advanced failure and the latter often require the largest dosage that can be tolerated in order to produce the best results.

4. It is the accepted practice to use relatively larger doses of digitalis to produce the full therapeutic effects and then relatively smaller daily ones in order to maintain these results for long periods of time. The usual explanation is that the smaller doses are necessary in order to maintain the high "effective concentration" of the drug produced by the larger ones. Evidence has been set forth proving, however, that the "effective concentration" of the drug within the body necessary to maintain the full effects is usually much lower than that required to produce them in the beginning.

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## THE THERAPEUTIC VALUE OF DIGITALIS IN PNEUMONIA *

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The work of Cohn and Jamieson [1] definitely established that there is a digitalis action on the heart in lobar pneumonia. In an address given in 1916 on the use of digitalis in pneumonia, Cohn [2] concluded that this drug did no harm and might be life saving. He suggested that it might be given to all patients as a routine, and explained the method of dosage in operation at the Hospital of the Rockefeller Institute. This extremely careful work and these conservative suggestions naturally influenced medical thought throughout the country, so that during the next ten years the routine giving of digitalis to patients with lobar pneumonia became a not uncommon procedure in many clinics, including Bellevue Hospital and most of the other large hospitals in New York.

However, during the period in which digitalis was given, no studies of comparative mortality were made between groups of patients with pneumonia receiving digitalis, and others from whom it was withheld. In Bellevue Hospital the study by the Columbia, Cornell and New York University Medical Divisions in the cases of lobar pneumonia with reference to specific antipneumococcus therapy by the control method provided a machinery that could readily be adjusted to include an investigation of the effects of the use or nonuse of digitalis as routine therapy in this disease as well. It seemed, therefore, an ideal time to investigate the action of the drug in cases of pneumonia, through the opportunity to use methods more favorable to constructive conclusions than had hitherto been employed.[3]

### METHOD

In other studies of the value of digitalis in pneumonia there were none in which simultaneous observation under identical conditions were made on similarly selected groups of patients treated with digitalis and patients from whom digitalis was withheld. If sound conclusions are to be drawn, it is essential that both groups of patients, those receiving digitalis and those from whom digitalis is withheld, be selected similarly and simultaneously.

The analysis of hospital records of previous years with the study of digitalis untreated and treated groups does not constitute a properly controlled series. As a rule, under these circumstances, digitalis was not given in the milder cases of pneumonia, while it was thought necessary in the more severe cases and the patients were given it. This fact is well brought out by Randolph [4] in his analysis of 100 consecutive cases at the George Washington University Hospital, by Cohn and Jamieson [1] in their study of 105 cases at the Rockefeller Institute, and by Burrage and White [5] in their analysis of 221 cases during a five year period at the Massachusetts General Hospital. A further method of selection of controls, as done by Hart [6] in his study of influenzal pneumonia, in which a considerable number of controls "were selected at random from time to time," does not seem satisfactory. Nor yet does the comparison of untreated cases observed during one period of time with cases treated with digitalis during another period seem justified, as was done by Stone, Phillips and Bliss,[7] and later again by Stone,[8] since other methods of treatment as well as virulence of infection differ greatly from time to time.

In the present study it was decided that patients should be selected for the digitalis or nondigitalis groups in the following way: Patients were received into the "pneumonia series" according to the date and hour of admission, and alternate patients were treated with serum. The combination of serum and digitalis therapy led to the grouping of patients into four classes, selected only by the time of admission, and termed arbitrarily A, B, C and D. The treatment of the patients in these four classes was as follows:

Class A received neither serum nor digitalis.
Class B received serum only.
Class C received digitalis only.
Class D received both serum and digitalis.

This system of classification operated in each ward independent of other wards, so that factors of general care and nursing might be the same for each class of treatment.

* Read before the Section on Pharmacology and Therapeutics at the Eighty-First Annual Session of the American Medical Association, Detroit, June 25, 1930.

* From the First (Columbia), Second (Cornell), and Third (New York University) Medical Divisions of Bellevue Hospital, and from the Departments of Medicine of Columbia, Cornell and New York University.

1. Cohn, A. E., and Jamieson, R. A.: The Action of Digitalis in Pneumonia, J. Exper. Med. **25**: 65-81 (Jan.) 1917.

2. Cohn, A. E.: The Use of Digitalis in Pneumonia, New York M. J. **105**: 234 (Feb.) 1917.

3. The committee for the study of digitalis in pneumonia is composed of Drs. Norrie and Woodruff of the First (Columbia University) Medical Division, Drs. Du Bois, Niles and Eggleston of the Second (Cornell University) Medical Division, and Drs. Wyckoff and DeGraff of the Third (New York University) Medical Division of Bellevue Hospital.

4. Randolph, B. M.: The Cardiovascular Problem in Pneumonia, Arch. Int. Med. **43**: 248-266 (Feb.) 1929.

5. Burrage, W. S., and White, P. D.: Digitalis in Pneumonia, Am. J. M. Sc. **174**: 260-264 (Aug.) 1927.

6. Hart, T. S.: The Heart in Bronchopneumonia: Observations on the Activity of the Heart and Its Response to Digitalis Made During the Recent Epidemic, Am. J. M. Sc. **158**: 649-658 (Nov.) 1919.

7. Stone, Willard; Phillips, B. J., and Bliss, W. P.: A Clinical Study of Pneumonia Based on 871 Cases, Arch. Int. Med. **22**: 409-439 (Oct.) 1918.

8. Stone, W. J.: The Heart Muscle Changes in Pneumonia with Remarks on Digitalis Therapy, Am. J. M. Sc. **163**: 659-668 (May) 1922.

Criteria of diagnosis were those ordinarily used to establish the diagnosis of lobar pneumonia; namely, typical history, physical observations, characteristic sputum, pneumococcus typing and fluoroscopic examination, verified whenever possible by postmortem examination. In the first year of the digitalis study (1927-1928), all cases of lobar pneumonia were included in the series regardless of the duration of the disease on admission or of general complications. In the second year (1928-1929), cases with history of onset more than eight days previous to admission or with general system disease were excluded from the digitalis-serum series; but of the cases thus excluded, any that showed evidence of cardiocirculatory disease were studied in the digitalis series as extra cases and were treated with or without digitalis according to the time of their admission, with reference to the regular A, B, C and D grouping.

In a large, active service such as that at Bellevue Hospital, it is difficult under ordinary circumstances to be certain that medications are always given exactly in the form and at the hour ordered, but in this special study every precaution was taken to know precisely how and when the digitalis was administered. The "digitalizing dose" for each patient was put in a small cardboard box labeled with the patient's name and given to the nurse in charge of the ward. The order for digitalis was written both in the ward and in the order book and on a manila tag fastened securely to the patient's bed. When the nurse gave the digitalis, she initialed the tag and wrote on it the exact hour of administration. These tags, later collected, constituted a permanent record.

Identical observations were made on patients who received digitalis and those from whom digitalis was withheld. The usual clinical and laboratory observations were taken, such as temperature, pulse, respirations and blood pressure, urinalysis and Wassermann reaction, and frequently morphologic and chemical examination of the blood. In addition, every patient was electrocardiographed daily during the febrile period, and every other day thereafter. A control tracing was taken on all digitalis-treated patients before any digitalis was administered. A total of 2,668 electrocardiograms were taken in the first year, and 3,369 in the second. Of the 835 patients studied in both years, 625 were electrocardiographed three or more times, 153 had one or two tracings, and 57, or less than one tenth, died before any tracings were taken at all.

A special staff was appointed to carry out the work along the method outlined. A full-time fellow was in resident charge of the work each year,[9] and was assisted by an electrocardiographic technician and a diener. This staff was working in addition to the staff then studying the serum treatment, and to the regular intern staff of the hospital.

## DIGITALIS

Previous to the beginning of the investigation, different preparations of digitalis had been used in the three services. In the Columbia University service, the regular Bellevue Hospital preparation of digitalis was used. In the Cornell University Service, a preparation which we will call B was in use. This had been standardized by the manufacturer and was said to have a potency of 66 mg. equivalent to one cat unit by the cat unit method of Hatcher. In the New York University Division a preparation standardized by the manufacturer was in use which was said to have a potency of 100 mg. equivalent to one cat unit. These preparations had been in routine use in the wards and at this time there was no reason to doubt the reliability of the standardization. However, as it was desired to use a standardized preparation in all three services it was decided to discontinue the use of the unstandardized hospital digitalis in the Columbia Division and to use in its stead on this as well as in the Cornell Service preparation B, and to use in the New York University service a preparation which we will call A.

On its being noted that there was a high incidence of toxic signs for patients treated with the B preparation, it was found that this specimen of digitalis was approximately twice as active as the manufacturer had stated, in terms of cat unit potency. Reports dealing with the standardization of this preparation have been published.[10] When the error in standardization had been proved, a third noncommercial standardized preparation of digitalis was administered to patients in all divisions. This preparation, designated preparation G, had a potency of 100 mg. equivalent to one cat unit. While this occurrence resulted in unfortunately high dosage to a number of patients, it enabled us to study three groups: patients receiving too little dosage, optimum dosage (as far as could be determined) and high dosage.

## DOSAGE

It was realized that in acute disease such as pneumonia, patients have to receive their digitalis rapidly. At the same time it was felt that the production of toxic effects should be prevented if possible. For this reason it was decided to give the digitalis in divided dosage, in no case giving a patient a digitalizing dose of more than the amount of 0.15 cat unit per pound of body weight, and to stop the administration of the drug on the appearance of any suggestive toxic symptom even though the full calculated amount had not been given. During the first year the dose was divided into parts approximating 30, 30, 15, 15 and 10 per cent of the estimated dose and these were given at intervals of six hours, the last dose (when given) being given about twenty-four hours after the first. As it was deemed unwise and unnecessary to weigh these patients, they were divided roughly into three groups, those who appeared to weigh less than 125 pounds (56.7 Kg.), those weighing between 125 and 175 pounds (79.4 Kg.) and those weighing over 175 pounds.

Because of the incidence of toxic signs, especially vomiting and the higher grades of heart block, in the digitalis-treated cases before the specimens were restandardized, it was decided, in the second year of the investigation, to reduce the dosage. Patients were then divided into two weight groups instead of three, those weighing above and below 150 pounds (68 Kg.). The lighter weight group received a total digitalizing dose of ten cat units, or 1 Gm., and the heavier 12.5 cat units, or 1.25 Gm. This was administered in three doses, the first 50 per cent of the total, the second 25 per cent, given twelve to eighteen hours after the first, and the third dose, 25 per cent, given after another interval of from six to eight hours. This dose compares closely with that given by Cohn and Jamieson.[1] They

9. The Fellows in Medicine in immediate charge of the digitalis investigation were J. Allen Yager, M.D., during the first year; Janet G. Travell, M.D., the second year and Margery Shearer, M.D., during the third year. The authors wish to express their appreciation for the invaluable services rendered by the Fellows.

10. Wyckoff, John; and Gold, Harry: A Dangerous Preparation of Digitalis, J. A. M. A. **94**: 626 (March 1) 1930. Wyckoff, John; Gold, Harry; and Travell, Janet G.: The Importance of Differences in the Potency of Digitalis in Clinical Practice, Am. Heart J. **5**: 401-411 (April) 1930.

had observed with 0.8 Gm. definite digitalis effects on the electrocardiogram in pneumonia, and their usual dosage [2] was between 1 and 2 Gm. Hart [6] also used a similar dosage in the treatment of influenzal pneumonia, giving 25 minims (1.5 cc.) of the tincture every four to six hours for six doses, or a total of the equivalent of 1 Gm. in twenty-four hours, and 24 minims daily thereafter, or the equivalent of 0.3 Gm. Stone [8] used a dosage of 4 cc. of tincture digitalis given every four hours for six doses, or a total dose the equivalent of 1.6 Gm. of powdered leaf in twenty-four hours, and no daily maintenance dose.

In our investigation, a daily maintenance dose of two cat units was given in both years. This was administered in a single dose each morning, and was discontinued when the temperature became normal or if toxic signs developed.

It was particularly difficult to determine proper dosage from the experience of others because most investigators either used no standardized preparation of digitalis, or, if a standardized preparation were used, the fact that it had been standardized was noted without estimation of its potency.

TABLE 1.—*Comparative Mortality of Digitalis Untreated and Treated Patients for the First and Second Years of the Investigation* *

| | No Digitalis | | | Digitalis | | | |
|---|---|---|---|---|---|---|---|
| Year | Number of Patients | Number Died | Mortality, per Cent | Number of Patients | Number Died | Mortality, per Cent | Difference in Mortality |
| 1..... | 197 | 68 | 34.5 | 158 | 67 | 42.4 | 7.9 |
| 2..... | 207 | 68 | 32.9 | 180 | 73 | 40.6 | 7.7 |
| 1 and 2..... | 404 | 136 | 33.7 | 338 | 140 | 41.4 | 7.7 |

* In tables 1, 2, 3, 4 and 6, patients discharged at their own risk, patients in the C and D (digitalis treated) series who received no digitalis, and deaths within twenty-four hours after admission have been excluded.

In all, 834 cases were studied. A few of these patients were discharged from the hospital at their own risk on the request of responsible relatives; several others in the groups scheduled to receive digitalis, through error, received none. These, and all patients dying within twenty-four hours after admission, were excluded from the tabulations. There remained 742 patients.

Table 1 shows the gross results of the study. It must be remembered that a difference of 7.7 per cent in a mortality of 33.7 per cent means an increase in mortality of more than one fifth. The mortality of the digitalis group and the group receiving no digitalis is consistent for both years. This is particularly noteworthy because during the second year the dose was greatly reduced, as has been stated. A later study, however, shows that this high mortality occurs in patients getting the larger doses, even in the second year.

TABLE 2.—*Mortality of Males and Females for Digitalis Untreated and Treated Patients*

| | No Digitalis | | | Digitalis | | | |
|---|---|---|---|---|---|---|---|
| Sex | Number of Patients | Number Died | Mortality, per Cent | Number of Patients | Number Died | Mortality, per Cent | Difference in Mortality |
| Male..... | 357 | 123 | 34.5 | 299 | 125 | 41.8 | 7.3 |
| Female..... | 47 | 13 | 27.7 | 39 | 15 | 38.5 | 10.8 |

The sex distribution was preponderatingly male for the series, but table 2 shows that the sex ratio was consistent both in the group receiving digitalis and in that from which the drug was withheld. The female series is so small that it is doubtful whether the difference of 3.5 per cent greater mortality among the women receiving digitalis is of significance.

TABLE 3.—*Mortality of Age Groups for Digitalis Untreated and Treated Patients*

| | No Digitalis | | | Digitalis | | | |
|---|---|---|---|---|---|---|---|
| Age Group in Years | Number of Patients | Number Died | Mortality, per Cent | Number of Patients | Number Died | Mortality, per Cent | Difference in Mortality |
| 10 to 29 | 94 | 15 | 16.0 | 73 | 19 | 26.0 | 10.0 |
| 30 to 39 | 109 | 30 | 27.5 | 76 | 25 | 32.9 | 5.4 |
| 40 to 49 | 99 | 40 | 40.4 | 99 | 44 | 44.4 | 4.0 |
| 50 plus | 102 | 51 | 50.0 | 90 | 52 | 57.8 | 7.8 |
| Totals..... | 404 | 136 | 33.7 | 338 | 140 | 41.4 | 7.7 |

Table 3 shows age distribution in the groups receiving and not receiving digitalis. The distribution is extremely consistent in the patients who did not take this medicine; in the group which did receive digitalis there are about 6 per cent more over the age of 40 than under. Brooks [11] advises routine digitalis therapy in older patients. In this series, digitalis did not reduce the mortality in the older age groups; the patients over 50 receiving digitalis showed a mortality of 7.8 per cent higher than patients in the same age group not receiving the drug.

It is known that the mortality in pneumonia is different in the various types. Patients with type I pneumonia have a relatively low mortality and those with type II a very large mortality. Table 4 compares the type incidence in the two groups. It is shown that it is consistent in both, and that the difference in mortality in the group receiving and not receiving digitalis cannot be due to a preponderance of a low mortality type such as type I or of a high mortality type such as type II occurring in one of the two groups. It shows that the mortality is always higher in the group receiving digitalis except for type II; patients in type II receiving digitalis actually had a mortality of 2.3 per cent lower than patients not receiving it.

TABLE 4.—*Mortality of Pneumococcus Types for Digitalis Untreated and Treated Cases*

| | No Digitalis | | | Digitalis | | | |
|---|---|---|---|---|---|---|---|
| Type | Number of Patients | Number Died | Mortality, per Cent | Number of Patients | Number Died | Mortality, per Cent | Difference in Mortality |
| I..... | 98 | 22 | 22.4 | 66 | 23 | 34.8 | 12.2 |
| II..... | 130 | 62 | 47.7 | 108 | 49 | 45.4 | —2.3 |
| III..... | 28 | 9 | 32.1 | 25 | 12 | 48.0 | 15.9 |
| IV to XIII and unclassified.. | 135 | 33 | 24.4 | 128 | 50 | 39.1 | 14.7 |
| Miscellaneous.. | 13 | 10 | .... | 11 | 6 | .... | .... |
| Total..... | 404 | 136 | 33.7 | 338 | 140 | 41.4 | 7.7 |

We have been unable to explain this inconsistency in otherwise consistent results. Our type II patients had similar age distribution in the two groups and the group receiving digitalis received it in the same dosage as did the patients having other types of pneumonia.

Our cases were carefully watched and toxic symptoms, such as vomiting, second, third or fourth stage

11. Brooks, Harlow: The Treatment of the Patient with Lobar Pneumonia, Internat. Clin. 4: 201-215 (Dec.) 1927.

heart block and coupled rhythm, occurred to some degree in 75 of the 338 cases. As might be expected, 65 of these were noted in the 142 patients receiving digitalis B (the improperly standardized preparation), and in only 5 patients of the 93 receiving digitalis A, and in 5 of the 109 patients receiving digitalis G. These facts will be discussed later.

It was pointed out by Cohn and Jamieson [1] that, in auricular fibrillation and flutter, greatest benefit could be expected from digitalis therapy in pneumonia. Table 5 shows that in 835 cases there were 33 cases of either auricular fibrillation or flutter. Seventeen patients received no digitalis and 16 received it. Of the patients who received no digitalis, 9 died, a mortality of 52.9 per cent. Of the 16 patients who received digitalis, 14 died, a mortality of 87.5 per cent. In this

TABLE 5.—*Mortality and Incidence of Auricular Fibrillation and Flutter* *

| Auricular Fibrillation and Flutter | No Digitalis (429 Patients) | Digitalis (406 Patients) | Total All Patients (835 Patients) |
|---|---|---|---|
| Number of patients | 17 | 16 | 33 |
| Incidence in series | 4.0% | 3.9% | 4.0% |
| Number died | 9 | 14 | 23 |
| Mortality | 52.9% | 87.5% | 69.7% |

* The average dose of digitalis per patient for the digitalis treated group was 1.17 Gm.

paper these facts are simply being presented. A more detailed analysis of these cases and those now being studied will be presented at a later time.

Stone, Phillips and Bliss [7] discuss the necessity of considering separately patients the course of whose disease is associated with pneumococcal complications such as empyema, endocarditis, pericarditis, arthritis and meningitis from those not so associated. In order that we might do this, table 6 was prepared. This table shows that 27 of the digitalis treated patients had such complications; 19 died, a mortality of 70.4 per cent. There were 24 patients not receiving digitalis;

TABLE 6.—*Mortality of the General Series Except Patients with Pneumococcal Complications for Digitalis and No Digitalis Groups*

| | No Digitalis | | | Digitalis | | | |
|---|---|---|---|---|---|---|---|
| Group | Number of Patients | Number Died | Mortality, per Cent | Number of Patients | Number Died | Mortality, per Cent | Difference in Mortality |
| General series | 404 | 136 | 33.7 | 338 | 140 | 41.4 | 7.7 |
| Pneumococcal complications | 24 | 14 | 58.3 | 27 | 19 | 70.4 | 12.1 |
| Series excluding patients with pneumococcal complications | 380 | 122 | 32.1 | 311 | 121 | 38.9 | 6.8 |

14 died, a mortality of 58.3 per cent, a difference in mortality of 12.1 per cent in favor of patients not receiving digitalis.

A further study along this line is shown in table 7, which compares the mortality of patients with negative and with positive blood cultures. Of 53 patients with positive blood cultures who received digitalis, 42 died, a mortality of 79.2 per cent. Of 54 patients with positive blood culture who did not receive digitalis, 43 died, a mortality of 79.6 per cent, a difference of only 0.4 per cent in patients having positive blood cultures. On the other hand, of 116 patients having negative blood cultures and receiving digitalis, 40 died, a mortality of 34.5 per cent, while of 124 patients with negative blood cultures who did not receive digitalis, 25 died, a mortality of 20.2 per cent. This shows a 14.3 per cent lower mortality for those who did not receive digitalis.

TABLE 7.—*Comparative Mortality of Patients with Negative and Positive Blood Cultures for Digitalis and No Digitalis Groups* *

| | No Digitalis | | | Digitalis | | | |
|---|---|---|---|---|---|---|---|
| Blood Culture | Number of Patients | Number Died | Mortality, per Cent | Number of Patients | Number Died | Mortality, per Cent | Difference in Mortality |
| Positive | 54 | 43 | 79.6 | 53 | 42 | 79.2 | —0.4 |
| Negative | 124 | 25 | 20.2 | 116 | 40 | 34.5 | 14.3 |

* Patients discharged at their own risk, and patients in the C and D (digitalis treated) series who received no digitalis have been excluded.

Table 8 compares the mortality of patients receiving the three preparations of digitalis and of patients taking none. It will be seen that the average cat unit dose of preparations A and G was 18.4 and 10.4, respectively, while that for preparation B, the misbranded one, was 31.3. It shows that the mortality rate of groups A and G are almost identical, 36.7 and 37.7 per cent, respectively, and that the mortality rate for patients receiving digitalis B is approximately 10 per cent higher, 47.2 per cent.

TABLE 8.—*Comparative Mortality of Patients Receiving Digitalis A, B and G and of Patients Receiving No Digitalis*

| Digitalis | Average Cat Unit Dose | Number of Patients | Number Died | Mortality, per Cent |
|---|---|---|---|---|
| Specimen B | 31.3 | 142 | 67 | 47.2 |
| Specimen A | 18.4 | 90 | 33 | 36.7 |
| Specimen G | 10.4 | 106 | 40 | 37.7 |
| No digitalis | .... | 404 | 136 | 33.7 |

We expected an analysis of the latter group to show that the high mortality was due to the toxic effect of digitalis as shown by other evidences of digitalis toxicity, in which case, as is obvious, all patients receiving the drug in toxic dosage should not be considered in the investigation. Much to our surprise, however, we found that the highest mortality came in the group of cases that did not show any of the known toxic symptoms of digitalis but who had received large dosage of the drug. In fact, the analysis of table 9 shows that

TABLE 9.—*Mortality of Toxic and Nontoxic Cases*

| Toxic | Number of Patients | Number Died | Mortality, per Cent | Average Cat Unit Dose |
|---|---|---|---|---|
| Specimen B | 61 | 15 | 24.6 | 32.2 C. U. |
| Specimen A | 5 | 2 | 40.0* | 17.4 |
| Specimen G | 4 | 2 | 50.0* | 8.0 |
| All preparations | 70 | 19 | 27.1 | |
| Nontoxic | | | | |
| Specimen B | 81 | 52 | 64.2 | 30.6 C. U. |
| Specimen A | 85 | 31 | 36.5 | 18.5 |
| Specimen G | 102 | 38 | 37.3 | 10.5 |
| All preparations | 268 | 121 | 45.1 | |

* Numbers too small to be of any significance.

patients developing signs of digitalis toxicity had not only a lower mortality (27.1 per cent) than patients receiving digitalis and developing no toxic signs (45.1 per cent), but even a lower mortality than patients receiving no digitalis whatever (33.7 per cent).

The possibility was considered of having included in the group receiving a large dosage of digitalis a number of patients who had actually received insufficient dosage of digitalis; in table 10 the nontoxic cases are further divided into those which showed positive digitalis effects on the T wave or the P-R interval in the electrocardiogram and those which showed no such effects. This table shows definitely that the higher mortality in the nontoxic digitalis group cannot be attributed to insufficient digitalis, because in the twenty-two patients who did not receive enough digitalis to produce an effect in the electrocardiogram, the mortality is low.

TABLE 10.—*Mortality According to Digitalis Effect All Preparations—Nontoxic Cases*

| | Number of Patients | Died | Mortality |
|---|---|---|---|
| Digitalis effect..... | 246 | 115 | 46.7% |
| No digitalis effect..... | 22 | 6 | 27.3% |

Because different preparations were given at various periods of the year and in different wards we have in table 11 compared the mortality rates of patients treated with each preparation of digitalis with those of the untreated patients for the same periods and on the same divisions. Thus the digitalis A cases are compared with the nondigitalis cases in the Third Medical Division up to Jan. 31, 1929, the digitalis B cases with nondigitalis cases of the First and Second Medical Divisions up to Jan. 31, 1929, and cases treated with digitalis G with the nondigitalis cases in all medical divisions after Jan. 31, 1929.

In this table an arbitrary grouping of the nondigitalis groups shows a range in the mortalities of these samples of from 30.8 to 36.4 per cent, a range of 5.6 per cent. The patients in the group receiving digitalis specimen A have a 0.3 per cent higher mortality, those receiving digitalis specimen G 6.9 per cent higher mortality and those receiving digitalis specimen B a 13.3 per cent higher mortality than a group treated under identical conditions and time, but receiving no digitalis.

TABLE 11.—*Comparative Mortality of Digitalis Untreated and Treated Patients According to Preparation Used*

| | No Digitalis | | | Digitalis | | | |
|---|---|---|---|---|---|---|---|
| Period | Total | Died | Mortality | Preparation | Total | Died | Mortality |
| Divisions I and II; until Jan. 31, 1929 | 177 | 60 | 33.9% | Specimen B | 142 | 67 | 47.2% |
| Division III; until Jan. 31, 1929 | 110 | 40 | 36.4% | Specimen A | 90 | 33 | 36.7% |
| Divisions I, II and III; after Jan. 31, 1929 | 117 | 36 | 30.8% | Specimen G | 106 | 40 | 37.7% |
| Entire period..... | 404 | 136 | 33.7% | All preparations | 338 | 140 | 41.4% |

## COMMENT

In the tables presented, in all categories except patients with type II pneumonia there was an increase in the mortality among patients receiving digitalis as contrasted with those who did not receive the drug. When these tables are reanalyzed, the patients receiving digitalis being grouped into those who received toxic dosage of the drug, those who received a digitalis effect but no toxic dosage, and those who showed no evidence of digitalis effect, it would appear that patients receiving enough digitalis to produce an effect on the electrocardiogram but not enough to produce toxic signs had an increased mortality, but on still further analysis it was shown that the increased mortality occurred in that group which received the largest amount of digitalis, irrespective of whether or not they showed toxic digitalis signs. Furthermore there is no evidence, even among the group who received what might be termed optimum dosage, that routine digitalis therapy could reduce mortality. This was true even among a small group of patients with auricular fibrillation who were studied.

In the giving of digitalis to patients with congestive heart failure in organic heart disease there are three guides useful in controlling medication: first, certain actions on cardiac mechanism, as shown clinically by ventricular slowing, or graphically by an increased P-R interval or changes in the T wave; second, the clearing up of signs of heart failure, and, third, the appearance of certain mild toxic phenomena. In pneumonia, on the other hand, except for the lowering of rate in patients who have developed auricular fibrillation there are practically no signs of digitalis effects other than those described in the electrocardiogram by Cohn and Jamieson [1] and toxic effects. The clearing up of signs of heart failure can never be used as a guide.

Since in the congestive heart failure of heart disease untoward effects are rarely if ever seen in patients who have not first developed mild symptoms of toxicity, it had previously been our belief that in patients with pneumonia receiving digitalis careful observation would give evidence of mild toxic digitalis effect before any damage could be done by the drug. This does not seem to be true in the light of our experience. In our cases there is a definite increase in the mortality of patients who received large doses of digitalis but who had none of the clinical symptoms of either early or late digitalis toxemia. May it not be that because of the effects of pneumonia toxin digitalis may produce death not infrequently without any warning signs of the usual clinical manifestations of mild or profound toxicity? If this is true, extraordinary care should be used in the giving of digitalis in pneumonia, for the dose cannot be guided except by an arbitrary limitation of the total dosage.

## SUMMARY

There is no evidence that routine digitalis therapy in lobar pneumonia results in a lowered mortality.

In pneumonia patients with sinus rhythm the only consistent evidences of digitalis effect are electrocardiographic changes and mild toxic effects.

About 95 per cent of patients have sinus rhythm throughout the course of lobar pneumonia.

Clinical symptoms of digitalis toxicity are not a sufficient guide in digitalis therapy in lobar pneumonia to prevent increase in mortality when the drug is used. The amount of the drug given is a better guide.

When given in dosage too small to show any effect, it causes no changes in mortality. When given in dosage comparable with the amount usually needed in the treatment of heart failure, it produces effect on the P-R interval and T wave of the electrocardiogram but causes little change in mortality.

Digitalis may perhaps be life saving in an occasional patient in whom there is auricular fibrillation or auricular flutter.

Auricular fibrillation and auricular flutter occur rarely, in less than 5 per cent of all cases. Patients developing this condition frequently recover without digitalis.

It is believed by us that the routine giving of digitalis to patients with lobar pneumonia is dangerous.

## ABSTRACT OF DISCUSSION

### ON PAPERS OF DRS. GOLD AND DEGRAFF AND DRS. WYCKOFF, DU BOIS AND WOODRUFF

DR. FRANK N. WILSON, Ann Arbor, Mich.: There has been a considerable difference of opinion among cardiologists regarding the advisability of giving digitalis in a routine manner to patients with pneumonia. Those who favored its administration advanced the following arguments: Digitalis has the same effect on the T-wave and the P-R interval of the electrocardiogram in pneumonia that it has in heart disease and in health (Cohn); consequently, pneumonia does not prevent it from producing its characteristic effects on the heart muscle. Auricular fibrillation is not uncommon in pneumonia. The response to digitalis is the same as in fibrillation due to other causes (Cohn). This disturbance constitutes an extra hazard which may be greatly diminished or eliminated by the routine administration of the drug. Roentgen studies have shown that the heart dilates in pneumonia. The dilatation is prevented or diminished by giving digitalis (Levy). The dilatation suggests that the heart muscle is weak; digitalis apparently improves its condition. Those who opposed the routine administration of digitalis in pneumonia did so on the ground that it had not been clearly shown that cardiac weakness played an important rôle in the mortality rate and that, as a general principle, drugs should not be given as a routine but only when the need for them became apparent. Those who favored giving the drug had, perhaps, a little the best of the argument; there was, however, something to be said on the other side. In view of the work which Drs. Wyckoff, Du Bois and Woodruff have reported, it is difficult, so it seems to me, to escape the conclusion that the routine administration of digitalis in pneumonia is dangerous. I should like to ask the authors their opinion regarding patients who have some measure of cardiac failure before they develop pneumonia; whether or not they advocate the giving of digitalis to these. If I understood Drs. Gold and DeGraff correctly, they dealt exclusively with patients who had auricular fibrillation. In such patients digitalis has a profound effect on the heart rate. This effect, which is a very important one in these patients, is due chiefly, not entirely, to the effect of the drug on vagal tone. In patients with normal rhythm, this effect is negligible. It is not known that the vagal and muscular effects of the drug are always parallel. Consequently, conclusions based on the effect of digitalis in one group of patients cannot, so it seems to me, be applied to the other without reservations.

DR. A. A. HEROLD, Shreveport, La.: In 1909 I read a paper before our state society in which I advocated the use of digitalis in pneumonia based on the fact that in numerous autopsies we found dilatation of the heart the cause of death in pneumonia. My plea at that time was to give the digitalis and feel the way both by blood pressure readings and by pulse rate, and give it, as Dr. Wilson brought out in summarizing the arguments pro and con, before it is too late, because if one waits for the fibrillation or the dilatation to start or what not and then starts digitalis, there will not be time to get the digitalis effect. That is a point which I would like to ask the authors to bring out in closing. How can a quick digitalis effect be obtained in those cases in which it is indicated if it is not going to be given in a routine manner?

DR. HAROLD E. B. PARDEE, New York: Drs. Gold and DeGraff have added an important fact to the knowledge of digitalis: the dose to maintain an effect need not be as large as the dose which was necessary to produce that effect. However, in its application to the therapeutics of digitalis, I do not believe that this is so important as it is from the point of view of pharmacology. In treating patients one is usually concerned with maintaining effects against rather considerable odds, and I would feel that in treating a patient it would always be necessary to give the patient the dose which would be close to his therapeutic limit before I would be sure that I had produced the best results of which the drug was capable. In the interpretation of the heart rate of patients with auricular fibrillation, certain sources of error arise, and these have a bearing on the conclusions of Drs. Gold and DeGraff. The chief source of error is that certain patients may have the same heart rate at rest and yet after exercise the heart rate will be increased differently, thereby indicating a different degree of digitalis effect. This may be in part due to an idiosyncrasy of the patient but it depends also on the degree of the digitalis effect. If a patient should be found with a heart rate when at rest of 75, which went up to 110 after a certain amount of effort, that patient given more digitalis might still have a heart rate when at rest of approximately 75, and yet after the same effort the rate would increase only to 90. Obviously the patient is in a much better physiologic condition when his heart rate goes only to 90 after exercise than he is when it goes to a higher rate, because exercise occurs constantly in his daily life. The heart rate cannot, of course, be taken as an indication of the degree of cardiac reserve. I believe that these two things also are so independent, in a considerable number of patients, that one must be wary how one draws conclusions from the heart rate as to the degree of cardiac reserve. Therefore, to maintain a constant heart rate when at rest does not necessarily men that cardiac efficiency is being maintained at a constant level or that the same therapeutic effect of digitalis is being obtained.

DR. OSCAR W. BETHEA, New Orleans: I was interested to note that the work on auricular fibrillation substantiated the work of the English physicians in which Lewis, following McKenzie, grouped the auricular fibrillation cases into four divisions: those that would remain normal when reduced to normal, without digitalis; those in which small doses of digitalis would maintain the effect; those in which large doses of digitalis were necessary to maintain the effect, and those in which no dose of digitalis would maintain the effect. I sometimes feel that we of this generation think that we discovered the large dose of this drug. I was interested recently to note that the elder Wood thirty odd years ago, in the United States Dispensatory, spoke of a patient that had received a teaspoonful of tincture of digitalis three times a day for a long period of years and had been maintained apparently in a state of perfect health. With regard to the treatment of pneumonia, I was highly delighted to note the trend of the statistics that were presented to us, particularly as in my paper tomorrow on the treatment of pneumonia, I protest most earnestly against the routine administration of digitalis.

DR. HARRY GOLD, New York: In reply to Dr. Wilson's remarks, I wish to say that we used only patients with auricular fibrillation in our study. Slowing of the heart rate in these patients is not due solely to stimulation of the vagus center. The evidence for that was presented many years ago by the results obtained after paralysis of the vagi by atropine in digitalized patients. Furthermore, slowing of the heart rate is only one element in the action of digitalis, and improvement that results in patients with auricular fibrillation is not due merely to slowing of the heart rate. The work of recent years has shown beyond a shadow of doubt that there is no fundamental difference between patients with a regular sinus rhythm and those with auricular fibrillation in the response of their congestive heart failure to digitalis. This suggests that the principles laid down in this study should apply to patients with a regular sinus rhythm. We were studying the response of heart failure to digitalis. Changes in the heart rate, however, yield the most striking graphic representation of the results and that is why we used the heart rate in our illustrations. We stated throughout that these patients improved as completely as possible and that when we gave them twice as much digitalis as they had at the beginning they did not show any greater improvement. I do not know what else one can do to ascertain that the full therapeutic effects of digitalis have been produced. Dr. Pardee's remarks on the relation between dosage and the response of the heart rate to effort are not supported by any evidence based on controlled studies. If a patient is given 3 grains (0.2 Gm.) of digitalis daily and marked improvement in the symptoms and signs of failure results, and if he is then given 6 grains (0.4 Gm.) daily with no signs of greater beneficial effects, it is probable that he does not need the 6 grains, but that 3 grains is sufficient. Dr. Pardee states that he prefers to give the larger doses. It is not justifiable to give patients twice as much digitalis as they need as a matter of personal preference, especially since we do not know what other actions, harmful or otherwise, the drug may exert in the body.

DR. JOHN HENRY WYCKOFF, JR., New York: In reply to Dr. Wilson's query about patients who have congestive heart failure or have heart failure before they develop pneumonia, I think that such patients should be treated as any other patients with congestive heart failure; they should be given digitalis. Dr. Herold asked how patients might be rapidly digitalized if such was necessary when routine digitalis therapy was not used. In cases of sudden death in pneumonia it seems to me that it is doubtful whether digitalis medication would ever be of value; for example, such a condition as ventricular fibrillation. But when heart failure does occur, as in the presence of auricular fibrillation, digitalis is probably indicated. Such an effect can be obtained by giving it by mouth in six to eight hours, or in one or two hours by the intravenous use of ouabaine. As to the value of digitalis in preventing cardiac dilatation, if digitalis does prevent such dilatation it should have had that effect in patients treated in this series as digitalis medication was begun as soon as possible after admission.

## THE DRINKER RESPIRATOR

### ANALYSIS OF CASE REPORTS OF PATIENTS WITH RESPIRATORY FAILURE TREATED FROM OCTOBER, 1928, TO JUNE, 1930 *

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In a series of papers published in THE JOURNAL [1] and elsewhere [2] we have given a description of the construction, operation and application of an electrically driven device for the prolonged administration of artificial respiration. As the result of considerable experience in the use of the apparatus in certain hospitals in Boston, New York and Philadelphia, various technical improvements have been made and a small respirator has been developed especially for the initiation of respiration of babies who breathe either with difficulty or not at all at birth. Both types of respirator, in their latest form, are shown in the accompanying illustrations.

Essentially, the respirator consists of a sheet metal tank equipped with a comfortable bed and mattress. The patient's head protrudes through a flat soft rubber diaphragm or collar attached to the body of the respirator, the rubber collar making an air-tight seal about the patient's neck. The diameter of the collar is adjustable, and thus excessive tension on the neck of the patient is avoided.

By means of electrically driven blowers and an appropriate valve arrangement, the air pressure within the tank is changed alternately from a few centimeters negative pressure to normal atmospheric pressure. The negative pressure induces inspiration—the chest and diaphragm of the patient expand and air is inhaled. The return to atmospheric pressure allows the normal tone of the respiratory muscles to cause expiration. Both the size and the rate of breaths taken are under control of the attendant and can be measured (or recorded) by means of a suitable U-tube manometer, filled with colored water and connected by rubber tubing to the body of the respirator.

In general, negative pressure of about 12 to 18 cm. of water suffices to maintain adequate ventilation in an adult or child with complete respiratory paralysis. In the case of new-born babies in which respiration does not begin within a few minutes after birth, lower negative pressures (from 8 to 10 cm.) have been found adequate.[3] Our experience indicates that the negative pressure used should be sufficient merely to prevent cyanosis or obvious respiratory distress—nothing is gained by using excessive negative pressures for long periods, while we have reason to believe that such pressures actually do harm to the lung tissue, particularly in the case of infants whose lungs may be atelectatic.[4]

Without having the pump stopped, the patients can eat, drink and sleep while in the respirator. A bed pan can be passed through one of the port-holes, enemas can be given, and rectal drips can be administered in deglutition cases. The noise of the machinery, although not excessive, is sufficient to prevent the use of a stethoscope in chest and heart examinations. We have taken roentgenograms of patients' chests both while the respirator was running and when the bed was pulled out and the pump stopped.

### ANALYSIS OF CASE REPORTS

At this writing, June, 1930, twelve adult-sized respirators are in use in New York hospitals and two in Boston hospitals. One child's and three infant's respirators are in the Children's and Lying-In hospitals in Boston and two infant's respirators are in use in the University and Lying-In hospitals in Philadelphia. In all, approximately forty adult patients have been treated in New York; six adults, six children and about twenty-five infants (full-term and premature) in Boston, and three infants in Philadelphia. As the result of the simplification of the apparatus, treatment in the respirator has become more or less routine hospital procedure and does not require specialized attention on our part. It has therefore become increasingly difficult to obtain complete records of all cases treated. Our analysis consists of a brief summary of cases in which we have complete information and which we believe to be of interest to the medical profession.

*Acute Anterior Poliomyelitis:* Of seven desperate cases of respiratory failure treated, four have been described in THE JOURNAL.[1] Of the final recovery of one of these, B. H.,[1] Dr. Frank R. Ober, consulting orthopedic surgeon to the Peter Bent Brigham Hospital, Boston, May 24, 1930, writes:

It is impossible to say about B. H.'s ultimate recovery. When I first saw him on Sept. 26, 1929 [thirteen days after admission to the Peter Bent Brigham Hospital] he had a paralysis of practically every one of his skeletal muscles including the

* Read before the Section on Preventive and Industrial Medical and Public Health at the Eighty-First Annual Session of the American Medical Association, Detroit, June 27, 1930.

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2. Drinker, Philip; and Shaw, L. A.: An Apparatus for the Prolonged Administration of Artificial Respiration: I. A Design for Adults and Children, J. Clin. Investigation **7**: 229-247 (June 20) 1929. Shaw, L. A., and Drinker, Philip: Ibid. **8**: 33-46 (Dec. 20) 1929.

3. Murphy, D. P., and Coyne, J. A.: The Use of a Modified Drinker Respirator in the Treatment of Asphyxia Neonatorum, J. A. M. A. **95**: 335 (Aug. 2) 1930.

4. Murphy, D. P.; Farber, Sidney; Drinker, C. K., and Drinker, Philip: Unpublished data.