end), and any bubbles are broken as before and a cover slip dropped on it.

The same process is repeated, one part of the unknown being used and nine of the Type II, which after being mixed is placed in a drop of saline on the opposite end of the same slide. The agglutination is observed with the low power of the microscope and is complete in ten minutes, sometimes in a much shorter time.

An agglutination at only one end means a Type I or Type IV, the latter if nine of the unknown agglutinates the known II, Type I if nine of the known II agglutinates the unknown.

No agglutination on either end of the slide commonly means a Type II; but there is an exception to this, as will be shown below, and agglutinations at both ends indicate a Type III with the following exception: Some Type IV bloods possess such high agglutinating power that the one tenth amount causes agglutination in the nine tenths of the Type II, giving agglutinations at both ends of the slide. It so happens that the agglutination occurring in this manner is generally somewhat weaker or less pronounced at one end than at the other, but this is not always the case. It is therefore customary in this laboratory to verify all Type III agglutinations with a known Type III, and also to corroborate the result further by agglutinating with known Types I and IV.

The exception to the statement that no agglutination on either end of the slide indicates a Type II is due to the fact that some bloods are apparently lacking in some substance or agent which, in a manner similar to the action of complement in fixation reactions, causes or permits the agglutination to proceed. When two bloods in both of which this ingredient is wanting are brought together, no agglutination results regardless of the type they may be. The accidental occurrence of such phenomena on several occasions in this laboratory has led us to confirm all results which indicate Type II by agglutination with a known Type IV.

NOTES ON DIGITALIS MEDICATION

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I. THE RATE OF DISAPPEARANCE OF DIGITALIS FROM THE BODY

When we try to maintain a patient under the full therapeutic effect of digitalis, we have always been handicapped by the fact that we do not know the rate at which the body can dispose of this substance by excretion or destruction. It seems likely from recent researches by Hatcher and Eggleston that both of these processes occur.¹

The patient is either liable to pass gradually out from under the influence when too small a dose is given, or with overadministration of the drug to have a series of vomiting spells which give the impression that the patient is especially susceptible to the vomiting.

It is evident that animal experiment would not give a definite answer to the question of the rate of disappearance of the drug, because of the marked variations that were found between different species.

The question was therefore applied directly to the patients by the following method: The drug was given so as to produce one of the mild toxic symptoms and then stopped entirely for a number of days. It was then given again until the same toxic sign reappeared. The amount of the drug used in the second course, divided by the number of days between the two toxic points, would give the daily average of the drug that had disappeared from the body in the interval, assuming that there is no change in the patient's tolerance for the drug, a fair assumption, as will be pointed out later.

The initial course was given so that the toxic symptoms appeared in from two to six or eight days, usually starting with doses of 30 minims of the tincture every four hours, or even 1 dram for the first three doses, and continuing with 15 or 20 minims every four hours. The second course was usually given in a similar way, starting with large doses and continuing with 20, 15 or even 10 minims every four hours, or three times daily. The second course was completed in an average of six days, though in a few cases it was prolonged, by using smaller doses, to ten, fourteen or seventeen days.

SIGN FOR DISCONTINUING DRUG

Vomiting was the symptom that was most frequently used as a sign for stopping the drug, as it was felt that this was a quite definite end-point. In one case the appearance of dropped beats due to heart block was used, electrocardiographic records confirming the clinical diagnosis, and in two cases severe nausea without vomiting caused the stopping of the drug at the end of each course.

The patients included ten cases of chronic cardiac valvular disease, three cases of chronic myocarditis, and one case each of chronic adhesive pericarditis, chronic parenchymatous nephritis and chronic interstitial nephritis. At the time of the first course they all showed signs of a rather marked degree of heart failure, but by the time of the second course, most of them were in better condition. The same lot of tincture of digitalis was used throughout this series. It was standardized by the cat unit method through the kindness of Prof. R. A. Hatcher and was found to be about an average strength tincture, having 1.25 c.c. per cat unit.

The details and results of the administration of the test on twenty-two occasions are shown in Table 1. The figure that represents the average rate of disappearance of the drug from the body is 22 minims of the tincture per day. In half of the cases the figure was below this and in half above it, the maximum variations being from 55 per cent. below to 82 per cent. above the average. The rate of disappearance seems to be independent of the amount of digitalis present in the body at the time, for it does not vary with the number of days elapsing between the first and the second points of toxicity. Nor was any relation noted between variations in the rate of disappearance and either the weight of the patient, the size of the doses of the tincture at the time vomiting occurred, the rapidity of administration of the total dosage, or the degree of heart failure shown by the patient at the time of the test. Susceptibility of the patient to the drug did not appear to influence the result either, for the rate of disappearance of the drug bore no relation to the quantity of digitalis per pound which was required to produce toxic symptoms in the patient's first course.

1. Hatcher and Eggleston: J. Pharmacol. & Exper. Therap. 12: 405 (March) 1919.

In five cases (2, 4, 6, 8 and 9 in Table 1), the test was repeated after an interval and in one case twice repeated, so that we have a total of six repetitions. In three of these the difference between the first and the later figures is not great, but in one case it is 9 minims, in another 10 minims and in another 17 minims. This variation does not seem to depend on the dosage used or on the length of time elapsed between the days on which digitalis was stopped in the successive courses. It does, however, vary with the days of administration

TABLE 1.—THE RATE OF DISAPPEARANCE OF DIGITALIS FROM THE BODY

Patient	Condi- tion	Days Elapsed between Two Points of Stopping Digitalis	Minims, Total in Course	Days of Adminis- tration of Course	Dosage During Last Day	Minims per Day Disap- pearance
1	A	9	90	1	30 m q4h	10
2	C	17	260	17	10 m q4h	15.3
	C	13	160	13	20 m tid	12.3
3	C	6	105	6	10 m tid	17.5
4	B	18	240	4	20 m tid	13.3
	A*	39	1,170+	39	10 m tid	30 +
5	B	10	135	3	15 m q4h	13.5
6	B	20	280	6	10 m q4h	14
	B	13	235	7	10 m q4h	18
	A*	24	550+	18	10 m tid	23 +
7	B	18	310	10	10 m tid	17
8	C	6	140	4	20 m q4h	23.3
	C	20	360	2	20 m q4h	18
9	C	10	200	3	20 m q4h	20
	B	19	570	14	10 m q4h	30
10	C	8	180	3	20 m q4h	22.5
11	C	10	270	6	15 m tid	27
12	C	15	450	4	30 m q4h	30
13	C	15	460	6	20 m q4h	30.6
14	B	7	240	3	20 m q4h	34
15	B	13	520	6	20 m q4h	40
16	B	11	440	6	20 m q4h	40
Average.....		13		6		22

A indicates that the patient shows only slight signs of heart failure.
B indicates that the patient shows moderate signs of heart failure.
C indicates that the patient shows marked signs of heart failure.
* These two patients had not yet reached the toxic stage with the dose recorded.

of the last course, being higher in a given patient when the course covers a greater number of days. This variation is not proportional to the number of days, nor can any explanation for it be offered.

The results of this investigation resemble those of other work on digitalis in the variability of the figures, but nevertheless in eighteen of the twenty-two tests the result lay between 12.3 and 30.6 minims per day, while in eleven tests, half of the total, it was between 13.3 and 27 minims, the latter a total variation of only 62 per cent. of the average. It is evident from this that the average figure of 22 minims per day would afford a fairly satisfactory basis for long continued digitalis medication, since in only half of the cases would it be much more or much less than the patient's ability to dispose of the drug.

BEARING OF RESULTS OF INVESTIGATION ON ADMINISTRATION OF DIGITALIS

These results seem to have two important bearings on the administration of digitalis over long periods of time. They demonstrate the approximate efficacy of the dosage of 10 minims of tincture of digitalis twice daily, which has commonly been considered sufficient to maintain the digitalis effect which has been already produced by larger doses. Only after a considerable number of days will a patient on this dosage come to be much below the grade of digitalization at which he started, and only occasionally will this dosage lead to a

return of the vomiting. Ten minims of the tincture² three times daily will lead to vomiting in the majority of cases, since fifteen of our twenty-two tests showed a slower rate of disappearance than this. Our results also demonstrate a new phase of the variability, from one individual to another, in the action of digitalis, a variability in the rate of disappearance from the body.

II. THE THERAPEUTIC DOSE OF TINCTURE OF DIGITALIS

In the course of the previous work it was possible to determine the amount of digitalis that was necessary to produce those early toxic manifestations (nausea, vomiting or dropped beats due to heart block) which are commonly encountered when the drug is given in sufficient dosage to obtain a prompt therapeutic effect. Sixteen suitable cases were found, nine of which were included in the previous series also. There were seven cases of chronic cardiac valvular disease, two of chronic myocarditis, two of chronic adhesive pericarditis, two of chronic parenchymatous nephritis, and one each of chronic interstitial nephritis, acute fibrinous pleurisy and carcinoma of the mediastinal glands. The noncardiac cases were included for the purpose of comparison; and since they did not give figures at either extreme of our results, it was felt that this was evidence that the handling of digitalis is not essentially different in cardiac and noncardiac cases.

TABLE 2.—THERAPEUTIC DOSE OF TINCTURE OF DIGITALIS

No. of Patient	Diagnosis	Con- di- tion	Weight	Minims Total Dos- age	Days of Admin- istration	Minims Dosage During Last Day	Minims per Pound
9	Chronic myocarditis	C	150	320	3	20 m q4h	2.14
11	Chronic myocarditis	C	110	240	4	15 m tid	2.14
		B		420	9	15 m tid	3.8
6	Chronic adherent pericarditis	B	123	275	2	20 m q4h	2.23
22	Chronic valvular disease	C	125	283	3	30 m tid	2.24
1	Chronic valvular disease	B	115	260	6	15 m tid	2.26
16	Chronic valvular disease	C	130	420	6	15 m q4h	3.23
10	Chronic parenchymatous nephritis	C	130	430	8	15 m tid	3.3
21	Acute fibrinous pleurisy	A	126	390*	6	20 m tid	3.33+
23	Chronic pericarditis	B	190	640	7	20 m q4h	3.35
3	Chronic valvular disease	C	134	490	8	15 m q4h	3.58
2	Chronic valvular disease	C	100	360	6	15 m q4h	3.6
12	Chronic valvular disease	C	200	780	7	30 m tid	3.9
20	Carcinoma	A	154	620	8	20 m q4h	4.0
19	Chronic valvular disease	C	172	690	8	30 m tid	4.06
18	Chronic parenchymatous nephritis	C	160	750	7	30 m tid	4.7
24	Chronic interstitial nephritis	B	130	640	8	20 m q4h	4.9
Average.....			140	466	6		3.33
25	Chronic valvular disease	B	91	555	22	20 m tid	6.1
26	Chronic valvular disease	B	125	830	21	20 m tid	6.64

* Did not vomit after this dose.

THE AVERAGE PERIOD OF ADMINISTRATION

None of these patients had received digitalis previous to this experiment for a period of at least three weeks. The drug was given as previously described for the first course, the average period of administration being six days, never over eight days except on one occasion, which was a repetition of the test after a thirty day interval (Patient 11, Table 2).

In this repetition of the test we see the influence of a lengthened period of administration. The first test

2. It must be remembered that 10 minims is equal to from 19 to 25 drops of tincture of digitalis, according to the dropper used.

was complete in four days and the second in nine days. Allowing for a daily disappearance from the body of 22 minims of the tincture for each of the five extra days, the figure for minims per pound of body weight is reduced to 2.8 minims, which is not very different from the 2.14 minims of the first test in this case. The time factor has a much more evident effect in the last two cases in Table 2, neither of which are included in the average for the series. The figures of 6.1 minims and 6.64 minims per pound of body weight represent the amount of the drug given over periods of twenty-two and twenty-one days respectively. When these are corrected to allow for a daily disappearance of 22 minims per day for each day over the average time of administration for the series, namely, six days, they are reduced to 2.23 and 4 minims per pound, respectively, which makes them quite comparable with the rest of the series.

Table 2 gives the data for these experiments, the average for the seventeen courses being 3.3 minims per pound of body weight. The variation is from 36 per cent. below this to 50 per cent. above it.

The only work with which this may be compared is that done by Eggleston,³ who also found marked variations from the average dose of the tincture, variations from 38 per cent. below to 71 per cent. above the average. Since he used larger doses of the tincture, toxic effects appeared in his series after an average of only three days. His results, moreover, were reduced to a standard strength of tincture such that one cat unit equals 1.00 c.c., a stronger tincture than ours. If Eggleston's figure of 2.2 minims per pound of body weight is corrected for the difference in strength of the tinctures it is raised to 2.75 minims; and if further corrected for the three days longer that were required to produce toxic effects in our experiments, considering that 22 minims per day were disposed of and taking into account that the average weight of his patients was 140 pounds, the figure becomes 3.23 minims per pound, which is quite in agreement with our figure of 3.3 minims.

THREE IMPORTANT POINTS

Three things among these results seem to demand special mention. The importance of the period of administration is very great, for each day some of the drug is destroyed or excreted from the body. The average amount of tincture required to produce a full therapeutic or early toxic effect is found to be in agreement with Eggleston's figure, and the variations from one individual to another are of the same considerable magnitude that he found.

IMPORTANCE OF A KNOWLEDGE OF THE VARIABILITY OF THE INDICATED DOSE

This variability of the dose of digitalis for different individuals is of great importance in therapeutics. Realizing that a variability has also been found in the rate of disappearance of the drug from the body, it will be plain how complicated the problem of digitalis medication must be. Two things, however, are quite plain: when the patient has received enough digitalis for his own special organism he will show one of the early toxic effects, usually nausea or vomiting. If after this he continues nauseated while the drug is being given, it means that he is receiving too much, that is, an excess over his average daily rate of disap-

pearance. We must carry these facts of variable susceptibility and variable disappearance clearly in mind, and combine with them the fact that digitalis is continually being disposed of by the body even during the period of administration, in order to avoid two common errors of clinical observation which may arise when digitalis is given. When a patient does not react to a usual dose of tincture of digitalis, it does not necessarily mean that the tincture is weak. It is possible that the patient may have a high susceptibility, and may require perhaps 4 or 5 minims per pound of body weight instead of the usual 2 or 3 minims, or the drug may have been given at such a slow daily rate as to little more than keep pace with the disappearance. On the other hand, the reappearance of vomiting a short time after resuming digitalis does not mean that the patient is one whose stomach cannot tolerate the drug. The time that has elapsed since the last vomiting must be considered, as well as the daily dosage.

FACTORS MAKING FOR A LOW VENEREAL RECORD IN THE AMERICAN EXPEDITIONARY FORCES

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The venereal disease incidence in the American Expeditionary Forces is considered as probably much lower than that ever obtained in our own army or in any other army operating in Europe. This opinion is not susceptible of proof as regards the armies in Europe, as the methods of reporting cases and estimating rates are not comparable. In the American army, cases were found largely as the result of physical inspections held at least twice a month, while in most other forces only those cases in which excuse from duty was granted or hospitalization occurred became known.

THE VENEREAL DISEASE RATE

The American incidence rate, based on inspection and stated in annual rates per thousand, varied for the greater part of the time during which American troops were present in large numbers in France between 62 and 31, averaging in the neighborhood of forty-five cases per thousand men per annum. This rate was never before closely approached in the U. S. army. It rose rapidly as troops were being sent home, but this rise was partly fictitious, and the true rate at that time was undeterminable. The corresponding incidence rate in the United States was always reported as higher than in France, averaging above 60 even after the armistice. It is thought that this was an error, as there is no sufficient reason known to account for a higher rate in the United States. Ignoring that rate, however, and considering only the low rate in the American Expeditionary Forces, this appeared the more remarkable for the following reasons:

(a) Many men in the United States were sufficiently near their usual safe sources of sexual gratification, whether wives or mistresses, to enable them to indulge occasionally and so avoid the call set up by prolonged abstinence.

(b) One of the most potent influences affecting conduct is the public opinion of a home community. While

3. Eggleston, Cary: Digitalis Dosage, Arch. Int. Med. 16:1 (July) 1915.