the operation or within a few hours afterwards, and most of the deaths in operation cases have been from this cause.

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SOME EXPERIENCES IN THE TESTING OF TINCTURE OF DIGITALIS.

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ATTENTION has recently been drawn to the importance of standardizing the drugs of the digitalis group, and as no chemical method of testing the strength of these drugs is at present available, attempts are being made to devise some reliable system of physiological testing. Of possible methods, two in particular have been suggested as of suitable application. By one of these the drug is injected in given amount into the circulatory system of a living animal, either frog or mammal, and the strength of the drug is shown by its capacity to cause death within a given time, death being brought about by arrest of the heart in so-called systole. Employing this method on frogs, and using "good average samples" of the drug, that is to say, samples prepared with all due precaution and known to produce certain well-recognized physiological effects, Dixon has worked out a standard unit for tincture of digitalis.¹ A tincture, before being injected into the dorsal lymph sac of the frog, is diluted with an equal amount of water, and if the tincture be of standard strength, 6 minims of this solution should kill a frog of 25 grams weight in one hour.

The other method of testing is to use in place of an intact animal an isolated heart, perfused with Ringer's or Locke's solution, the drug being in this case exhibited by introducing it diluted to known extent with the perfusing fluid. Then, as in the first method mentioned, the arrest of the heart within a given time may be taken as an indication of the potency of the drug, while during the course of the experiment observation can also be made of the effects produced before arrest takes place. In the experiments of which particulars are given below this latter method was used to test a number of samples of tincture of digitalis. It is thought that it may be of use to give an account of the results obtained, as the experiments made were sufficiently numerous to afford some basis upon which to discuss the advantages or the drawbacks of the method.

The mammalian heart was used, the animals selected being young rabbits weighing usually from 3 to 4 lb. The heart was perfused through the coronary vessels with a Ringer's solution, after the manner made familiar by Langendorff, Locke, and others, and the contractions were recorded.* The recording lever was connected with the right ventricle, and throughout the experiments by the expression "arrest of the heart-beat" is meant arrest of the contractions of the right ventricle. The procedure was in all cases the same. A steady heart-beat having been established and an even series of contractions recorded, the undrugged Ringer's solution was replaced by a supply of similar solution containing a given percentage of tincture of digitalis and this supply was maintained until the heart succumbed to the action of the drug.

The question of a suitable percentage is of some importance if manageable results are to be obtained. Low percentages, which would be suitable in a detailed study of the physiological effects of digitalis on the heart, are found to work too slowly for convenience where the object is to test the relative strengths of many different samples, the gradual dying out of the heart-beat being with low percentages often very protracted. After some preliminary trials the strength adopted in these experiments was 1 in 200. Usually three experiments were made with the

sample of the drug and the average time required to arrest the heart was taken to indicate the potency of the sample. When a number of samples had been tested the question arose as to how they should be rated; within what limits might one sample legitimately differ from another. In a preliminary review of results obtained with the first eighteen samples, these were arranged in tabular form according to their potency, beginning with the strongest, that is to say the sample which arrested the heart in the shortest average time. (See Table I.)

No. 13 was a tincture prepared with special care by an expert pharmacist,† and it is considered here as a "good average sample." Nos. 7 to 16 might be considered as approximately equal in strength to the good sample, the

TABLE I.—Showing the Average Time Required to Arrest the Heart in the Case of each Tincture, with Maximal and Minimal Times: also the Median Time of Arrest.

Tincture No.	Average Time of Arrest in Minutes.	Maximal Time.	Minimal Time.	Median Time of Arrest in Minutes.	
I. Strong.					
1	19	21	16	16	
2	19	26	13	19	
3 (x)	20	26	11	20	
4 (x)	20	30	10	22	
5	21	28	14	—	
6 (x)	23	24	21	23	
II. Average.					
7	26	36	19	23	
8	27	46	14	20	
9	27	32	25	25	
10	28	34	21	30	
11	30	38	19	32	
12 (x)	20	52	14	24	
13	33	42	25	31	
14	33	48	25	26	
15	27	46	24	41	
16 (x)	43	50	39	41	
III. Weak.					
17	?	Over 1 hr.	25	?	
18	?	Over 1 hr.	37	—	
X (17 expts.)	27	52	10	23	
19	26	33	13	32	Average.
20	23	28	15	25	"
21	48	54	40	49	Weak.
22	50	60	31	60	"
23	19	24	15	19	Average.
24*	27	33	22		"
25*	29	33	25		"
26*	23	21	24		"

* Are not included in the chart.

average time of arrest with all these tinctures being over twenty-five minutes and under forty-five minutes. This group is marked II in the table.

Samples 17 and 18 made a weaker group, marked III, as in some of the experiments with these tinctures the heart was not arrested within one hour, which was the limit of time adopted.

Samples 1 to 6 appeared to fall into a "strong" group, I, their average times of arrest being all under twenty-five minutes. But the placing of these six samples apart had been decided upon with hesitation. Judged by their short average time of arrest, they were "strong"; and a study of the column of maximal values showed that their maximal times also were shorter than any maximal time recorded for a sample under group II. In the minimal column, however, the distinction between "strong" and

* For a description of the apparatus see Report of Special Chloroform Committee, *BRITISH MEDICAL JOURNAL*, July 18th, 1903, p. cxlvii; and more fully in Thompson Yates Laboratories Report, Part I, 1903. "On the Dosage of the Mammalian Heart by Chloroform," Sherrington and Sowton.

† For this tincture I am indebted to the kindness of Mr. P. H. Marden, F.C.B., Lecturer in Pharmacy in the University of Liverpool.

Fig. 1.—Heart of young rabbit, perfused with Ringer's solution; in the interval marked by the arrow the normal Ringer's solution was replaced by a similar solution containing 1 in 200 of tincture of digitalis No. 14. The effect is shown at the end of the 1st minute, 3rd minute, and at other intervals after the onset of the drug. The beat is slowed, and first diminished, then increased in amplitude. Tonus is very markedly increased after the first half of the experiment.

Fig. 2.—Experiment as in Fig. 1. Effect of tincture of digitalis No. 10. The flow is increased by the end of the 1st minute, although the rate of beat is rather less. At the 3rd minute the amplitude of beat has increased, but this would not account for the large increase of flow. The rate of flow remains above the normal until the latter part of the experiment, when the tonus has risen considerably.

"average" was less clearly marked. Two tinctures in group II, Nos. 8 and 12, had wide ranges of values and showed each a minimal time of fourteen minutes—a figure that would appear more appropriately in the "strong" group. A doubt was, therefore, felt as to whether these first six tinctures were really stronger, and the grouping was adopted tentatively.

The sequel showed that the distinction made by this grouping was finer than the method would allow of. It appeared later that samples 3, 4, 6, 12, and 16 were all portions of the same tincture, or were in any case prepared from the same batch of leaves in precisely the same way; so that, according to the rating above adopted, portions of the same tincture had been considered to differ so much as to fall under distinct groups. Clearly, then, the separation of samples 1 to 6 from the "average" group was fallacious, and the difference observed, for instance, between the "strong" sample No. 3 and the "average" sample No. 16 was due, not to the drug, but to the condition of the test object, the heart.

Of the tinctures dealt with, therefore, if we except samples 17 and 18, all may be considered as of approximately equal strength in so far as the discriminating power of the method can show.

In regard to the sample which appeared under different numbers, and which may be designated as sample X, the experiments made with it are valuable, for the indication they give as to the limits of variation to be expected from the hearts when used in the manner here adopted. For the number of experiments made was large, no less than 17 hearts having been

treated with this same tincture at the same strength, involving a lavish expenditure of time and material that might not have seemed justifiable under other circumstances.

The average time of arrest in these 17 experiments comes out at twenty-seven minutes. The variation limits

are: maximal time of arrest, fifty-two minutes; minimal time, ten minutes; variation limits which agree nearly with those before noted for No. 12, where the maximal is fifty-two minutes and the minimal fourteen minutes.

In the last column of the table are given the median or central values of the times of arrest. But a clear idea of the outcome of the testings is perhaps best obtained when the results are expressed in a curve. In the chart is shown the time area within which arrest most frequently occurs when the experiments are taken as a whole, and also the degree to which each sample falls into or diverges from this area of greatest frequency. (See Chart.) Curve 1 (continuous line) expresses the results of the experiments made with all the samples. Curve 2 (broken line) shows the results of the 17 experiments made with sample X. It will be noticed that the two curves are very similar in form.

From the foregoing data it is judged that a good average sample of tincture of digitalis, exhibited at the strength here used (1 in 200 of Ringer's solution) should arrest the heart in an average time of not more than forty-five minutes. Out of the whole number of tinctures in the tables, samples 18, 21, and 22 are reckoned, therefore, as

Fig. 3.—Curves showing variations of flow in four experiments made with sample 19. In (1) (2) and (3) the drug was at the usual strength of 1 in 200; the curves show rapid undulations during the first three minutes, after which the flow diminishes and remains below the normal. In (4) the drug was weaker—1 in 1,000—there is a small preliminary rise lasting seven minutes, the flow then sinks below the normal and remains subnormal, although a minor increase occurs which culminates at the twenty-third minute. Normal flow: (1) 24 c.cm. per minute; (2) 30 c.cm. per minute; (3) 34.5 c.cm. per minute; (4) 32 c.cm. per minute.

CHART.—Along the abscissa are represented periods of five minutes up to sixty minutes. The ordinates indicate the frequency with which arrest occurs within any time area. According to the time of arrest in each experiment, it finds its appropriate place in one of the time divisions. Thus, beginning from the bottom of the chart and reading across the sheet: Of the experiments made with tincture 1 (marked "I"), two of them fall into the time area 15-20 minutes; the other two into the 20-25 minute area. In a line next above, reading always across the chart, the experiments with tincture 2 will be found distributed in four time areas. The whole of the experiments made with all the tinctures having been arranged in this manner, the number falling within each time area is counted, and a mark is placed at the centre of that area opposite to the corresponding number of the ordinate. Thus into the first area seven experiments fall. The curve starts, therefore, from the dot opposite 7. The next mark is at 10, because 10 cases fall into the 15-20 minute area. In this way is formed a curve which shows the time space within which arrest most frequently occurs when the experiments are taken as a whole, and the extent to which any individual tincture agrees with this kind of general average. The smaller curve, drawn with broken line, is the result of arranging the experiments of sample X in this manner.

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rather below the average in strength. No. 17 is doubtful as it had one case in which arrest was not complete within the hour, while, on the other hand, two of its cases came well within the time-area of greatest frequency. All the other tinctures examined were up to the average of strength.

So far the point considered has been the "brute strength," so to speak, of the tinctures examined, but an inspection of the records of the experiments suggests the question as to whether its sheer strength is the only thing which it is important to know about a sample; other differences of action appear in the tracings which may possibly be of some importance. For instance, Figs. 1 and 2 are records of experiments made with the tinctures marked 14 and 10 in the table; samples which may be considered as of practically the same strength as judged by the time taken to cause arrest of the heart. Yet, on comparing the orderly working of the heart in 1 with the delirious irregularities of 2, some hesitation may be felt in rating these two samples as equal. It is not, of course, suggested that a tincture of digitalis which produced delirium cordis on the isolated heart of the rabbit would of necessity have the same effect on the human subject

this kind is very much a question of strength of dose. Judging only from indications given in the experiments here considered this does not appear to be the case with all samples. Among the tinctures dealt with, about half gave no trace of delirium even at the high strength used in these experiments, namely, 1 in 200. Sample 14 (see Fig. 1) gave no irregularity of either kind. No. 13, the "good average" sample, caused no delirium. (It gave "A" irregularity in one experiment.) The other samples which gave no delirium were Nos. 5, 9, 19, 20, 23, and perhaps 18. On the other hand, most of the tinctures which gave delirium showed also occasionally the "A" irregularity. With sample X, out of the 17 hearts on which it was tried, 16 showed absolutely no sign of delirium. The seventeenth had towards the end of the experiment a delirious interlude which lasted seventy-five seconds, after which the heart resumed its former even contractions. On one occasion this tincture was used at a strength of 1 in 100, arrest was rapid (occurring in six or seven minutes), but no delirium was observed. The "A" irregularity was, on the other hand, often very marked with this tincture, so marked in one case as to produce quite early in the experiment an effect resembling vagus arrest.

Fig. 4.—Curves showing the variations of flow in the three experiments made with sample 10. In each case the flow increases in a marked way, and remains above the normal during the first half of the experiment. Later, tonus is increased and the flow diminishes. Normal flow: (1) 18 c.cm. per minute; (2) 24 c.cm. per minute; (3) 34 c.cm. per minute.

when absorbed from the alimentary canal, but, comparing these experiments with one another, it does appear that the various samples used differ in their capacity for producing disorganization of the heart's rhythm, and such differences may possibly prove to be useful means of analysis.

Two types of irregularity were noticeable in the course of the experiments. Of these, one is characterized by a dropping out of ventricular beats. It occurred with many of the tinctures, and was sometimes very marked, so that on direct inspection of the heart as many as eight or ten beats of the auricle to one beat of the ventricle might be counted, while on the tracing (a ventricular record) appeared a series of widely-spaced contractions. As it is not desirable here to discuss any theory of the causation of this well-known phenomenon, it will be referred to simply as "irregularity A."

The other form of irregularity of the heart's rhythm which was observed is that known in its fully developed state as delirium cordis "D"; hurried and uneven movements arise in different parts of the heart, interfering with each other and producing a confused activity impossible of analysis, and impotent for the work of the circulation. An example of this kind of irregularity has been given in Fig. 2. It is, we believe, a generally received opinion that the production of delirium in digitalis experiments of

Accompanying the two types of irregularity which have been noticed were differences in the rate of flow through the coronary vessels. Throughout the experiments the coronary flow was measured by means of the little see-saw instrument devised by Schäfer. The movements of the instrument were recorded below the heart tracing by electric signal.

Sample 14, though showing no irregularity of either kind, gave the characteristics of flow associated with the "A" type, and may be contrasted, therefore, with Tincture 10, which represents the "D" type. In the three experiments made with sample 14 the flow diminished at once, and remained below the normal throughout each experiment, the always subnormal but undulating curve being curiously similar in all three cases. Tincture 19, another sample of this type, behaved in a like manner, but gave more marked undulations during the first three minutes (see Fig. 3). In the figure a fourth curve shows the variations of flow in an experiment in which the same tincture was used weaker—namely,—at a strength of 1 in 1,000. In this instance the sharp early undulations are almost obliterated; the flow rises slightly, and is maintained above the normal for some time; after the seventh minute there is a rapid fall. A minor increase, which culminates at the twenty-third minute, corresponds to the rise occurring in the other

cases at from six to nine minutes. Curve 4 has points of correspondence with the other three curves, but the variations occur in more elongated form. These constitute one type of effect.

With tincture 10, on the other hand, excepting for an immediate and short-lasting drop in one case, the flow rises with the onset of digitalis, and is maintained at a rate above the normal during the first half of the experiment, until the tonus of the heart has begun to rise in a marked degree, when the flow falls below the normal (Fig. 4). This marked increase of flow cannot be due to a rise of pressure, seeing that the pressure of the fluid entering the coronary vessels is in these experiments kept constant throughout their course. Nor can the greater flow be attributed wholly to increase in rate and strength of beat; variations of heart-beat may influence to a certain extent, but will not wholly account for the variations of flow which have been recorded. This can be shown from many experiments; to give one instance—the normal rate of beat was 200 per minute, the rate of flow 25 c.cm.; two minutes after the onset of digitalis the rate of beat was 196, the force being also diminished, but the flow was 31½ c.cm. per minute; six minutes later the rate of beat was 108 and the flow 40 c.cm. per minute. The only conclusion to be drawn is that a direct action on the coronary vessels had taken place.

In dwelling upon the differences observed between the action of tincture of digitalis from sample to sample, examples have been chosen from among the best-marked cases. With some tinctures these differences do not come out clearly; the samples cannot be said to belong to either "type."

To what the differences of action are due, and whether they are of importance from the point of view of practical testing—whether, for instance, an observed tendency in a tincture to produce delirium cordis should be held to detract from the value of that tincture—are questions at present difficult to answer. Further investigations might throw light on the causes of the variations observed. To hazard a conjecture, it seems possible that the constituent glucosides of digitalis may affect differently or in different degrees the various properties of the heart, and a preponderance of one glucoside over another in a tincture may give different results on that account. It would be useful to test reliable preparations of digitoxin and its fellows in the same way that these tinctures have been tested, with a view to tracing to its source each variety of effect.

The slowing of the heart-beat, which is so characteristic a feature of digitalis action, occurred with most of the samples tested. Fig. 1 is a good example. In some of the experiments, however, a correction has to be made for changes of temperature, and at present the amount of the necessary correction cannot be estimated.

The strength at which the drug was used (for reasons already mentioned) is less favourable to the demonstration of slowing effects than are weak solutions, such, for example, as those employed by Dixon² and Haynes.³ In testing the later samples, an experiment with the tincture at 1 in 1,000 was made, in addition to two or three experiments with the 1 in 200 solution, in order to bring out more clearly these effects.

In conclusion, it may be said that by the method here adopted it is possible to ascertain with regard to a tincture (1) its "strength"; (2) its capacity for producing "therapeutic results"—for example, slowing of the heart's beat and increase of its amplitude; (3) its tendency to cause disorganization of the heart's rhythm. It may be stated here that great care was taken to keep the conditions of experiment as constant as possible, much trouble being expended in securing animals of approximately similar age and weight. The number of experiments made amounted in all to 98.

It has not at present been shown whether very small differences in alcoholic strength, such as may exist between one fresh tincture and another (the samples used were all fresh) could modify their action on the heart when the tinctures are used at a strength of 1 in 200. Such differences in the samples so far examined should be very small. It would be desirable, however, to make some experiments with a view to possible fallacies in this direction, especially since it has recently been shown by Dixon⁴ that very small amounts of alcohol in

Ringer's solution affect the calibre of mammalian blood vessels.

The inquiry was undertaken in the first instance at the suggestion of Messrs. Evans, Sons, Lescher, and Webb. I have to thank them for supplying a great part of the material and a number of the various samples tested.

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ON MIGRAINE.*

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You may remember the advice given by Gobind the One-eyed to the author of *Life's Handicap*, when asked by the latter (as to the art of telling tales) "in what manner is it best to set about the task, O chiefest of those that string pearls with their tongue?" and Gobind replies, "Do thou this: tell them first of those things that *thou* hast seen and *they* together. Thus will their knowledge piece out thy imperfections."

And thus it is that I have chosen migraine as the subject of this short paper, seeing that we have all met with numerous cases, and also as I have had an intimate, if unwilling, acquaintance with this interesting disorder. I hope that you, with your knowledge, will piece out my imperfections.

DEFINITION.

The word, of course, is the shortened form of hemi-crania, and represents a definite entity, and must not be used, as it so often is, for headaches from whatever cause.

We call migraine a functional disease (thereby meaning that as yet we have discovered no organic basis), which is characterized by paroxysmal attacks of headache, usually one-sided, and which may be associated with sickness, peculiar affections of sight, and various mental symptoms.

If each disease could have its description written by one who has himself suffered, we should have truer and more graphic accounts to read, and our textbooks would be far more interesting.

ETIOLOGY.

We must look upon migraine as hereditary to a large extent. Perhaps one should say that the tendency to suffer from a neurosis is hereditary, but that the neurosis may appear in one generation as migraine, in another as spasmodic asthma, etc.

A patient who suffers from migraine generally has one parent gouty or a sufferer from migraine. The age of onset is variable, most cases begin about puberty, and on the other hand most cases improve about the age of 60.

Women are said to suffer more than men; but in my experience there has been a preponderance of men. Goodhart speaks well of us, he says, "migrainous subjects mostly come from the ranks of the temperate livers, who often work their brains to exhaustion."

As to the primary cause of the disease, at present we can only say that there is an hereditary predisposition to a brain storm. When we come to the immediate and exciting causes, one generally finds that mental or bodily fatigue, worry, or eyestrain are responsible. Typical causes are a cinematograph exhibition, a tour round a picture gallery, and prolonged microscopical work. I have never noticed in my own case, or in those of my friends, that errors in diet have produced a migrainous attack. It is often stated to the contrary in the textbooks, but so much the worse for the textbooks. A fatiguing journey, followed by a full meal taken on a hungry stomach, may predispose to an attack, but I am inclined to blame the fatigue and not the food.

SYMPTOMS.

May I begin by describing an attack of which I was the victim a few weeks ago? In the morning, while visiting a patient, I noticed that the lady's nose had become luminous and was trembling, and I knew that I was in for an attack. The area of disturbance was just below the central point of vision. Of course both eyes are equally

* A paper read before the North Lancashire and South Westmorland Branch.