pulse, no marked result should be expected to follow the administration of the drug.

What may be expected from the administration of digitalis in cases of cardiac failure unaccompanied by auricular fibrillation? Well, in exceptional cases auricular fibrillation develops during the administration of the drug, and then these cases respond in the same manner as do most of the other cases of auricular fibrillation. Apart from these exceptional cases, as a rule, though not in all cases, the beneficial results will be only moderate or slight, or none at all. And a very important point in this connexion is that, unlike cases of auricular fibrillation, the improvement can usually be maintained without continuing the drug.

Strophanthus and squills should be regarded as substitutes for digitalis. They may be tried when a patient is found to be peculiarly intolerant to digitalis. With regard to the so-called alleged active principles of digitalis, it is asserted by those most competent to judge that there is no pharmacological or clinical evidence that they are either pure substances or that different samples of them are uniform in their potency; and that there is no reason to believe that they are more reliable than, and possibly they are not so reliable as, different samples of the tincture of digitalis.

And, lastly, among the common beliefs which are held by the profession at large is the belief that the internal administration of digitalis increases the blood pressure in man by constricting the peripheral vessels. In two papers which I read at the annual meetings of the British Medical Association in 1912 and 1913, I showed from investigations that, judged by the methods in use for observing the blood pressure clinically, this is not true; and therefore there is no risk in employing the drug in cases of degeneration of the walls of the blood vessels or of supernormal blood pressure.

The subject of heart disease demands serious attention. In the *BRITISH MEDICAL JOURNAL* of February 7th, p. 335, reference was made to a paper by Dr. Karl Grassmann, in which it was pointed out that the death-rate from diseases of the circulatory system is high in all countries, and that heart disease causes a large amount of invalidity in all sections of the population. The subject is well worthy of your study, and I trust that the remarks which I have made during the limited time at my disposal will be of service to you in your private practice.

ON TINCTURE OF DIGITALIS (B.P.): ITS ACTIVITY AND STABILITY.

BY

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I.

INTRODUCTION.

THE subjoined observations deal primarily with the physiological activity, assayed on frogs, of a series of tinctures of digitalis, prepared according to the *British Pharmacopoeia* from leaves grown in the years 1911-1913 inclusive.

These tinctures, examined within a few days of manufacture, and repeatedly during the following months, showed marked variation not only in their initial activity but also in their stability. Many of them were in the first instance sent by the manufacturers to the Society of Apothecaries for physiological assay, and these were supplemented by samples purchased from wholesale firms of good repute. In comparison with the above there were also examined a small number of tinctures purchased from dispensing chemists and a few non-official solutions, including some prepared from so-called pure principles.

The mode of assay was based on the method practised by Houghton in 1895, and published three years later⁸—namely, that of injecting measured doses into a series of frogs and noting the smallest dose, in proportion to body-weight, which arrested the ventricle in systole. In the majority of initial assays only a single series of frogs was employed. Repetition of each assay would have

determined the "minimal lethal" dose with smaller error, but careful manipulation was found to yield such concordant results, and the variations found at the outset were so marked, that this appeared unnecessary, since it was of greater interest to test broadly the variability and stability of the whole series than to follow minutely the changes in a limited number of samples. The accuracy of the work was, however, controlled by occasional re-assays, after a few days' interval, on a fresh batch of frogs. The frogs employed (*R. temporaria*) were almost exclusively males, between 20 and 30 grams in weight. Within these limits the ratio of body-weight to body-surface is so nearly constant that no attempt was made to ascertain whether weight or surface is the better basis of dosage. Weight was chosen on account of its readier determination.

The activity of the tinctures is expressed in terms of the Dixon-Haynes standard²—that is, in terms of a tincture with a minimal lethal dose of 0.75 c.cm. per 100 grams body-weight. The number expressing activity is obtained from this by dividing 0.75 by the minimal lethal dose found in each case, and the latter (minimal lethal dose) is calculated as lying midway between the smallest dose that proved fatal, by arresting the ventricle in systole, and the largest that failed to kill. The alcohol of the tinctures was removed by distillation, *in vacuo*, at 40° C. In each initial assay the doses tested were six in number, ranging between 0.3 c.cm. and 1.0 (or 1.2) c.cm. per 100 grams body-weight. In early re-assays three doses were given—(1) the smallest dose that proved fatal at the preceding assay, (2) one larger, and (3) one smaller than the first. In re-assays of stale tinctures several series of frogs were at times necessary. The difference between consecutive doses was, at most, 0.2 c.cm. (per 100 grams), and no assay was taken as completed until at least one animal showed systolic arrest of the ventricle and unless the largest non-fatal dose was completely absorbed. Verification of absorption is a precaution of cardinal importance. A more detailed account of these procedures will be published elsewhere.

II.

INITIAL ACTIVITY OF THE TINCTURES.

Fifty-five tinctures were examined within a few days of manufacture, and are grouped according to their activity in Table I.

TABLE I.—Classification of Tinctures according to Initial Activity.

$$\text{Activity} = \frac{\text{Standard M.L.D.}}{\text{Observed M.L.D.}} = \frac{0.75}{x}$$

Group:	I.	II.	III.	IV.	V.
M.L.D. (c.cm. per 100 gm.)	1.3-1.0	0.9-0.75	0.7-0.6	0.55-0.45	0.4-0.3
Activity	0.6-0.75	0.8-1.0	1.1-1.25	1.4-1.7	1.9-2.5
Number of tinctures	2	9	12	18	14
Percentage	4	16	22	33	25

The distribution of the tinctures among the above groups in the three years taken separately was strikingly different. This matter is, however, of pharmaceutical rather than of clinical interest, and will be dealt with in detail in another publication.

A similar examination of twenty-three British tinctures, by Dr. Alexander Goodall,³ published in 1912, showed equally great variation. Classified as above, they were as follows:

In Group I	5 (22 per cent.)
„ Group II	12 (52 per cent.)
„ Group III	1 (4 per cent.)
„ Group IV	3 (13 per cent.)
„ Group V	2 (9 per cent.)

Within the same range, therefore, there was a much higher percentage of weak, and a much lower percentage of the very strong, samples than was found in the present work.

Taken broadly, the tinctures of Groups II and III may all be regarded as "standard" and make up (in Table I) between one-third and one-half of the total. Only 3 to 4 per cent. were much below standard. More than one-half of the total number (Groups IV and V) was very much above standard.

Five samples, obtained from dispensing chemists, were assayed in comparison with these. Three of them were approximately standard (Group II), and reacted consistently on repetition of the test. The remaining two were very weak (Group I) and reacted in every way like stale samples (*vide infra*).

Variability in tincture of digitalis is an old story. From it arose the practice of physiological assay, as far back as 1895. Since the adoption of physiological assay in this country, some nine years later, several accounts of variation have appeared. Barger and Shaw,¹ in a set of weak samples, found a range of activity from 100 to 150. Dixon and Haynes,² in mixed commercial samples, not all of recent manufacture, described variations from 100 to 280. Their samples were also very weak. Variations also appeared in a series tested by Miss Sowton,¹⁴ by perfusion through the mammalian heart. Goodall's results (*loc. cit.*) have already been quoted in detail. Gordon Sharpe and Lancaster⁶ found cases of pronounced weakness. Later, Gordon Sharpe and Branson⁵ described higher and more uniform activity. Elsewhere⁴ Gordon Sharpe characterizes some samples as no more toxic—that is, active—than tap-water. Wide variation has also been recorded by Martindale.¹²

The variation seems attributable to the leaf rather than to the process of manufacture. Climate, soil, weather, etc., cannot be without influence on the metabolism of the plant; and autolytic changes, in gathered leaves, are well known.

Professor Cushny, to whom the development of physiological assay is largely due, has found of late only small variations in different samples obtained from the same source. He finds, however, in common with others, that samples from different sources show wide variations.

It is a reasonable supposition that the increasing cultivation of digitalis, which during recent years has led to higher average activity of the leaf, will, in conjunction with more uniform drying and storing, tend gradually towards greater uniformity in the strength of its products.

III.

STABILITY OF THE TINCTURES.

The tinctures were stored in a dark cupboard, on a low shelf, in a room of which the temperature varied during the year from 13° to 23° C.

The temperature in the cupboard would presumably be lower and less variable than in the body of the room. These conditions are probably better than those in a retail pharmacy, though not so favourable as those in a wholesale store. Most of the bottles were corked, and the samples in these proved, on the whole, no more unstable than those in stoppered bottles.

It is obvious that quality of storage is of importance for all unstable preparations. And quality of storage is not without influence on the activity of these tinctures. Comparison of a few samples, fresh from the cellars of the Society of Apothecaries, with samples of the same preparations kept at the university, has consistently shown the former to be the better. But the difference has not been great, and good storage, though it retards, does not prevent deterioration (*cf. Houghton, infra*).

The most stable tincture was one of those initially in Group I. Fourteen months after manufacture it showed no definite signs of deterioration (*vide Fig., Curve III*). In this it was unique. Of the remaining tinctures, tested twelve months after manufacture, more than four-fifths had lost a large fraction of their initial activity.

Table II, a monthly digest of the activity of those samples which were initially up to (or above) standard, shows that deterioration may be found even during the first month. The first column of the table (signifying little or no change), at the third month, contains only one-half of those tinctures whose activity was then known. At the sixth month the corresponding proportion is one-fourth. But such figures must not be interpreted too literally, for not all the tinctures were examined each month, and the variations in stability were great. In all cases it may be said that weak tinctures (whether weak *ab initio* or by deterioration) change slowly. Tinctures, not weak in the first instance, after a variable period of inappreciable change, deteriorate more or less rapidly until they reach a stage of comparatively constant weak-

TABLE II.—Showing, Month by Month, the Number of Tinctures known to have Undergone Specified Deterioration. (Tinctures Initially Below Standard not Included.)

Age in Months.	Deterioration in Terms of Initial Activity.				Age in Months.	Deterioration in Terms of Initial Activity.			
	0-10%	20-30%	40-50%	60-70%		0-10%	20-30%	40-50%	60-70%
1	20	4	—	—	7	1	4	6	5
2	17	9	1	—	8	1	4	6	5
3	14	10	3	—	9	1	4	7	6
4	13	8	3	—	10	1	3	8	10
5	9	8	4	—	11	—	1	8	11
6	6	8	5	5	12	—	5	13	13

ness, in the neighbourhood of one-half standard. These points are illustrated by the results of repeated tests on four tinctures shown in the accompanying chart.

Ordinates = activity of tinctures. Abscissae = age of tinctures in months. The upper curve (circular black discs) shows (1) a prolonged period of unchanging activity, (2) deterioration, (3) sustained weakness. The second curve (circles) shows earlier deterioration, followed by prolonged constant weakness. The third curve (re-cumbent crosses), confluent with the second, shows sustained weakness throughout. The fourth curve (erect crosses) shows sustained weakness, during the second year, of a tincture not tested until one year after manufacture.

The following tables give three-monthly statements of activity in terms of the standard. Tables III and IV deal individually with different groups; conjointly, with all the samples not below standard.

TABLE III.—Showing Deterioration of the Tinctures initially in Groups II and III.

Age in Months.	No. of Tinctures Examined.	No. of Tinctures in Group I.	No. of Tinctures in Groups II and III.
0	21	0	21
3	14	1	13
6	9	3	6
9	7	4	3
12	9	9	—

TABLE IV.—Showing Deterioration of the Tinctures initially in Groups IV and V.

Age in Months.	No. of Tinctures Examined.	No. of Tinctures in Group I.	No. of Tinctures in Groups II and III.	No. of Tinctures in Groups IV and V.
0	32	0	0	32
3	22	—	9	13
6	25	1	17	7
9	19	3	16	—
12	25	13	12	—

From these it appears that, six months after manufacture, approximately two-thirds of the first set (Groups II and III) and nearly all of the second (Groups IV and V) are still of standard or higher activity; and that, at twelve months, all examined of the first set, and about one-half of those (examined) of the second set, are much below standard.

The assay of stale tinctures is more troublesome and less precise than that of recently prepared samples. Stale tinctures appear to react less rapidly than fresh ones. Certainly, the effect of the injections is later in onset, and less closely proportional to dose. As many as four (or more) series of frogs are not infrequently necessary to give consistent results.

The total toxicity of a tincture does not diminish *pari passu* with its cardiac activity. There has, indeed, appeared to arise in some old samples an increased toxicity to the central nervous system. A fresh tincture rarely displays a dead frog with a beating ventricle—that is, a frog killed other than by ventricular arrest. With old tinctures the phenomenon is more frequent. Hence, unless the frog be examined soon after abolition of the corneal reflex, there is a danger of classing as primarily cardiac a death due to failure of the nervous system. For the heart of a frog, under digitalis, will cease beating more nearly in systole than in diastole, by whatever means the frog is killed. The error of observation is, therefore, in the direction of overrating the cardiac activity of an old tincture, and deterioration tends to be underrated. This consideration is of importance, as the deterioration described above is earlier in onset or greater in degree than that recorded by some other observers.

Dixon and Haynes² found no loss of activity in standard samples in six months.

Houghton,⁹ on the other hand, finds deterioration to be recognizable "from month to month, even though the preparations are stored with exceeding care." But the degree of his deterioration is small. A low standard (1.5 c.cm. per 100 grams) and good storage may account for this (*cf. supra*).

Martin¹¹ (standard=0.75 c.cm. per 100 grams) describes "no appreciable loss" in nine months, but finds "practically inert" preparations after two years. He, however, does not make it clear whether his method would show, for example, a 20 to 30 per cent. loss or a 20 to 30 per cent. residue of activity.

Goodall⁸ (standard=0.83 c.cm. per 100 grams) found three samples (out of twenty-three) "unchanged" in one year. Later (one and a half to three years) he found a loss of activity ranging from 33 per cent. or less to 66 per cent. or more. This deterioration is comparable in degree with, though later in onset than, that found in the present inquiry. It is unfortunate that so small a proportion of the total number was tested at the end of the first year.

Gordon Sharpe and Branson⁵ (standard=0.75 c.cm. per 100 grams) found seven out of nine samples up to standard, and the remaining two doubtful, after twenty months' storage. Eight months later only one of the nine was standard. The percentage deterioration was not tested. A tincture may lose 60 per cent. of its initial activity or more, and yet be of standard activity.

Deterioration has also been found by Hale,⁷ who describes loss of activity amounting to less than 20 per cent. per annum. But his most active tincture (minimum lethal dose = 1.6 c.cm. per 100 grams) was initially less than half standard.

Summary of Results as to Deterioration.

The results of the present work in this direction may be summed up as follows:

1. Weak tinctures show little or no change in a year or more. Active tinctures deteriorate much more rapidly.
2. Of those initially within 25 per cent. of standard, all were more than 25 per cent. below standard after a year's storage.
3. Of those initially more than 25 per cent. above standard only one-half were within 25 per cent. of standard after one year's storage, and these had lost 20–70 per cent. of their original activity.
4. In a few samples deterioration was recognizable one month after manufacture.

Table V records duplicate assays of a series of tinctures after a year's storage, and serves to check the consistency of the foregoing results. One set of bottles was stored in the university laboratory, and the previous history of each was known at the time of assay. The second set was stored in a pharmaceutical laboratory, and was assayed without knowledge of the individual samples. Two (or more) series of frogs were employed for each individual sample.

TABLE V.—Showing Consistency in Re-assay of Two Sets of the Same Series of Tinctures after a Year's Storage.

No.	Initial Activity.	Activity after a Year's Storage.		No.	Initial Activity.	Activity after a Year's Storage.	
		At the University.	In a Pharmaceutical Laboratory.			At the University.	In a Pharmaceutical Laboratory.
I	1.7	0.7	0.8	VIII	1.1	0.6	0.6
II	1.4	0.8	0.7	IX	0.9	0.5	0.6
III	1.4	0.8	0.7	X	2.0	1.1	1.1
IV	1.7	0.7	0.7	XI	1.7	0.7	0.8
V	2.1	1.0	0.9	XII	1.4	0.8	0.7
VI	1.1	0.65	0.7	XIII	1.5	0.8	1.25
VII	0.9	0.7	0.7				

The only noteworthy discrepancy is shown in No. XIII. This may be due, in part, to difference in storage, in part to the inconsistency met with in stale samples. The effect is, at most, to make it uncertain in which of the two standard groups the sample should be placed.

Of interest also was the repeated assay of a tincture, reputed to be twelve years old, of which the initial activity was not known. At the first test it showed clearly an activity in excess of standard (1.2), and six months later appeared to be unaltered. After another five months it was slightly below standard (0.9), a second supply proving however, to be rather higher (1.1). A third supply, a month later, failed to yield a definite minimum lethal dose, though tested with three series of frogs. It seems possible that repeated admission of air to the bottles had accelerated the deterioration, previously arrested by prolonged non-disturbance. This factor may have contributed to the discrepancy between the two samples of No. XIII (Table V).

IV.

NON-OFFICIAL PREPARATIONS.

The following were examined:

Fluid Extracts of Digitalis, U.S.P., and other Concentrated Alcoholic Preparations.

These were eight times as concentrated as the B.P. tincture. When diluted to correspond with the tincture, they appeared as follows:

A sample of U.S.P. extract, some months old, was three-fourths standard. After one year's further storage it became one-half standard. A second sample of the same class (U.S.P.), four months old, was between 1.25 and 1.5 times standard, and did not deteriorate during the succeeding six months. A similar preparation at the time of manufacture was 1.7 times standard. Seven months later it was 1.2 times standard, and eleven months after manufacture it was slightly below standard, but still in Group II. Both in initial activity and in stability it agreed with a B.P. tincture prepared from the same batch of leaves.

Such preparations are economical. In them the yield of the leaf is apparently as great as in the tincture (Martindale, *loc. cit.*), and the cost of the alcohol one-eighth as much. In stability they resemble the B.P. tincture.

"Non-alcoholic" Preparations.

A "non-alcoholic" tincture proved to possess less than one-half of the standard activity. A concentrated "non-alcoholic" solution, when appropriately diluted, was no more active. The age of these preparations was not known. A glycerine extract, at the time of manufacture, was one-fifth standard, when diluted in accordance with its concentration. A year later it had deteriorated about 25 per cent. A fourth sample, freshly prepared from a concentrated alcoholic extract, was above standard

(Group III) when manufactured. Its keeping qualities, after removal of the alcohol, have not been tested.

There is no obvious *raison d'être* for preparations of this type, even when the freshly-prepared officinal infusion is not available, since large doses of digitalis can be given, in the concentrated extracts mentioned above, with a negligible amount of alcohol.

A Tincture Prepared from Green (Undried) Leaf.

This preparation, allowing for its concentration, was 4.5 times standard when manufactured. After lapse of a year it was still over 1.6 times standard. Although more active, it was not more stable than most officinal tinctures.

Crystalline Digitaline (French).

Digitoxin (German).

Four samples of a French commercial solution, all from the same manufacturer, have been subjected to examination. The reputed dose of these, 18 minims per diem, is rather less than that of the *B.P.* tincture. These solutions are said to be physiologically tested. Two of the samples (of recent manufacture) were of high activity—1.25 to 1.5 times that of a standard tincture. The third sample (over one year old) and the fourth (three years old) were about 0.8 standard. In activity these samples were, on the whole, well up to standard, and in stability proved superior to the *B.P.* tincture. Supplement of the physiological tests by precise physiological standardization* would render such preparations of still greater value.

The stability of the crystalline substance was further tested on solutions in 60 per cent. alcohol, prepared in the laboratory. Two samples of crystalline French digitaline, from different sources, showed little deterioration in sixteen months, and a sample of German digitoxin proved equally stable.

Soluble Constituents of Digitalis Leaf.

Comparison was made of three solutions from the same manufacturer. These are issued in ideal form, namely, in sealed glass "ampoules," containing 1 c.cm. of "sterile" solution, which is said to correspond, in activity, to an equal volume of the officinal tincture. The activity of this solution on the frog is about one-half that of the standard tincture. For administration by the mouth it is, therefore, not economical, except where it proves to be qualitatively superior—for example, in tolerability—to the pharmacopoeial preparation.

It offers, however, the advantage that it can be given by intravenous injection. Observations on the cat¹⁵ have shown that, administered in this way, it can be relied on to produce characteristic digitalis effects. Experiments by Moore¹⁵ on the rabbit—an animal relatively insensitive to digitalis—point in the same direction.

In the matter of stability, it has resembled a weak tincture, showing little or no change in six months, and a loss of not more than 30 per cent. in a year and a quarter. This may be due to good bottling (sealed ampoule) rather than to intrinsic stability of the solution.

Comparison of the above solutions of "pure principles" with the *British Pharmacopoeia* tincture is of some importance. It is beside the mark to dilate on the chemical impurity of the "principles" in question. It seems fair to presume that they are all mixtures, in which either the less soluble or the more soluble glucosides are the predominant constituents. In either case solutions are obtainable which in stability are superior to the average tincture. How far, in clinical work, such solutions can replace the officinal preparation cannot be shown by laboratory experiment. A fresh tincture differs from them, in that it contains the soluble and insoluble glucosides in more nearly equal proportions, and may, on this account, have a value not possessed by any solution of a so-called "pure" product.

V.

CRITICISM OF RESULTS.

It must be emphasized that the assays under consideration are not merely measurements of general toxicity. Properly carried out, and controlled by prompt *post-mortem* examinations, they are measurements of the

cardiac activity of the preparations. For it is on the heart itself that the effect of the injections is seen. Moreover, they are measurements made via the normal body fluids of the animal. This is of importance, for the body fluids, by their well known reaction with the saponins and by their ability to dissolve the less soluble therapeutic glucosides, materially influence the action of a tincture. For these reasons lymph sac injections are preferable to saline perfusions of the isolated heart as quantitative gauges of digitalis activity. Further, their consistency, *inter se*, is incomparably greater.

It may be admitted that such injections tend to exaggerate, though less than perfusions, the activity of drugs which have to be given by the mouth. For they determine total activity (that is, activity of less stable as well as that of more stable constituents), and the nett activity of such mixtures as the *British Pharmacopoeia* tincture (that is, activity of absorbed constituents) is not a constant fraction of the total. Hence in the present work Houghton's method has not been utilized to its full capacity. What has been attempted is a classification in groups so broad as to possess unquestionable significance.

From what has been stated above, it follows that clinical effects are rarely, if ever, closely proportional to the assay value of the tinctures. Some digitalis glucoside is passed, unchanged, in the faeces; and some is lost by hydrolysis, in the alimentary canal. Presumably some is similarly hydrolyzed in the medicine bottle. Hence there is a tendency towards equalization of the effects of unequally active tinctures. Minute adjustment of clinical dosage to total physiological activity is therefore impracticable, and the implication that so complex a mixture as tincture of digitalis will yield to the heart substantially "x" tonic units per cubic centimetre swallowed is largely illusory. But, broadly treated, physiological assay may fairly be termed indispensable. For the variations found are so great that approximately equal effects cannot reasonably be expected from equal doses of different samples.

The solutions of the so-called pure principles are less complex than the officinal tincture, and detailed standardization might profitably be carried out. It does not follow that the simpler solutions would, in every case, be as valuable as the more complex, but they would offer, if properly standardized, a degree of uniformity that is otherwise unobtainable. For this reason, as well as on account of its great stability, a standardized solution of crystalline French digitaline (or of digitoxin) would be a valuable addition to the *British Pharmacopoeia*.

No observations have been made in the course of the present inquiry on the keeping qualities of the digitalis leaf. Other workers (Gordon Sharpe and Lancaster⁶) have stated that when properly dried and properly stored it retains considerable activity for several years. And longer storage than one year is unnecessary. If this be granted, the foregoing results suggest that digitalis treatment could be materially assisted, at all events in hospital practice, by the following procedure:

1. Annual purchase of (cultivated) leaf.
2. Physiological assay of the leaf by means of a freshly prepared tincture. This assay would appear to hold good for the leaf for one year, and should ensure uniform activity in all freshly prepared tinctures, infusions, and pills from the same leaf during that year.
3. Manufacture of fresh tincture at least twice (preferably thrice) a year.
4. Assay of each tincture three months after manufacture.

Where these safeguards are possible the need for the "pure" preparations is reduced to a minimum. In private practice uniformity is less certainly assured. But physiologically assayed leaf and tincture are readily obtainable, and if purchased from wholesale stores in small quantities (that is, at sufficiently frequent intervals) should afford some security for uniformity. In such cases the solutions and pills of French digitaline (German digitoxin) and of the soluble digitalis glucosides offer assistance when the local supply of galenicals proves uncertain.

SUMMARY.

To sum up, not a single sample of tincture of digitalis could fairly be termed inert. Very few of the (fresh) samples were initially weak, but most of them became weak within a year. Interpretation of this deterioration

* By standardization is meant adjustment of the concentration of the solution to yield a minimum lethal dose of the same value in all samples. Such adjustment of officinal preparations is obviously precluded, and, even if admissible, would in the case of tincture of digitalis be heavily discounted by deterioration.

is necessarily somewhat speculative. There is, however, evidence, particularly in the recent work of Kraft,¹⁰ that one of the most active water-soluble glucosides is strikingly unstable. And the present inquiry has shown that alcoholic solutions of the less soluble active glucosides are more stable than the official tincture. It appears from these considerations that the deterioration of a tincture may chiefly be due to loss of its water-soluble glucosides. If this is correct, a fresh tincture is equivalent to a (moderately) stale sample *plus* a quantum of fresh infusion, and the supplementing of a weak tincture by a fresh infusion might prove more serviceable than heavy dosage with the tincture alone. It may be anticipated that the former course would yield earlier digitalis effects with less risk of cumulation.

My thanks are due to the Science Committee of the British Medical Association for a grant towards the expenses of this research.

CONCLUSIONS.

1. Few tinctures of digitalis are, initially, below standard.
2. Tinctures, not below standard, vary 200-300 per cent. in initial activity.
3. All such tinctures, after a variable period of constant activity, undergo deterioration, which may commence

within a month of manufacture, and may amount, in a year, to 70 per cent., or more, of their initial activity.

4. Concentrated alcoholic extracts of digitalis leaf compare favourably with, and behave as, the *British Pharmacopoeia* tincture.

5. Solutions of crystalline French digitaline (German digitoxin) are more stable than the above.

6. Commercial "non-alcoholic" tinctures, and allied preparations, are not trustworthy.

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- ¹⁴ Sowton: *BRITISH MEDICAL JOURNAL*, 1908, i, p. 310.
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A CASE OF ACUTE RHEUMATIC HEART-BLOCK.

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THE chief interest in this case lies in the number of electro-cardiographic and polygraphic records taken before, during, and after the occurrence of acute partial heart-block in a rheumatic child.

S. P., a boy aged 12, had occasional sore throats up to the age of 10 years, when he was admitted to the London Hospital with pericarditis and acute rheumatism. In the following year, 1913, he was again admitted for a much milder attack of acute rheumatism. On discharge he was transferred to the Cardiac Department under Dr. James Mackenzie. He complained frequently of precordial pain as an out-patient, and two months later, February 16th, 1914, he was again admitted as the precordial pain had become more severe. He then had rheumatic nodules and mitral and aortic regurgitation; on deep inspiration the sternum was held down and there was slight sinking of the epigastrium suggesting pericardial adhesions. On the fifth day after admission he developed tonsillitis which lasted five days. Following this

For a fortnight after admission his *a-c* interval, the measure of the time taken for an impulse to pass from auricle to ventricle, was normal—that is less than $\frac{1}{2}$ second, as shown by daily polygraphic tracings. On the electrocardiogram the *P-R* interval, the electrocardiographic equivalent, approximately, of the polygraphic *a-c* interval, was also less than $\frac{1}{2}$ second. The *a-c* interval then increased beyond $\frac{1}{2}$ second and remained prolonged for ten days before dropped beats resulted. The dropped beats only occurred on two days, though the degree of block on these days reached the ratio (auricle to ventricle) of 2 to 1 (see tracing). On the day before the dropped beats commenced the pulse-rate was 106, on the two days during which dropped beats occurred it was 75 and 74, and on the following day it was again 104. These pulse-rates were counted on the polygraphic tracings taken at approximately

the same hour each day. The drop in the rate was due to the falling out of ventricular contractions. Electrocardiograms at this time showed a prolonged *P-R* interval, and a block varying in ratio of auricle to ventricle as 3 to 2 or as 2 to 1. For another week the *a-c* interval remained increased beyond $\frac{1}{2}$ second, during which time the *P-R* interval was also well over $\frac{1}{2}$ second; it then returned to normal.

Chart showing the pyrexia accompanying the heart-block.

mal and, except on one day, remained normal for the remaining three weeks of his stay in hospital. The block had lasted for eighteen days. When examined ten days after discharge the *a-c* interval was still normal.

Polygraphic tracing showing an irregularity of the pulse caused by "dropped beats" in heart block. The block varies between 3 to 2 and 2 to 1.

attack he had slight irregular pyrexia for nearly four weeks. During the later part of this period he developed the heart-block (see Chart).

It is interesting to note that except for pyrexia there were no symptoms referable to the block, and without